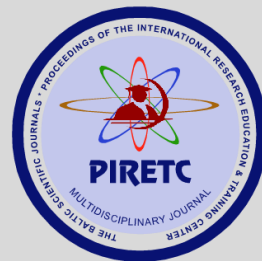


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The beautiful thing about learning is nobody can take it away from you—B. B. King

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MANIFESTATION OF KEY ISSUE PECULIARITIES OF THE INFLUENCE OF ETIOLOGICAL FACTORS ON PERIODONTAL HEALTH AND DENTAL HEALTH CARE

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ABSTRACT

The aim of the research was to study and analyze the manifestation of key issue peculiarities of the influence of etiological factors on dental health. Many disease classifications have been made in periodontology over the years. They share a common application of the concept of natural health and define periodontal health as the absence of any clinical manifestation of a current or past disease. The American Academy of Periodontology has defined health as the condition of a functioning patient with no evidence of disease or abnormality. Applied specifically to a periodontal structure, this definition predicts the absence of signs and symptoms of devastating periodontal and gum disease or a tissue condition outside of the normal range. Periodontal diseases are among the most common diseases in children and adolescents. These include gingivitis, aggressive localized or generalized periodontitis (or early periodontitis, which includes prepubertal generalized or localized periodontitis and juvenile periodontitis), and periodontitis associated with systemic disorders. The best approach to treating periodontal disease is prevention, followed by early diagnosis and treatment. The term "periodontitis diseases" includes all diseases of individual tissues of the periodontium, which are accompanied by inflammatory atrophic or dystrophic changes. The importance of the problems of periodontal diseases is explained, first of all, by their significant distribution in the world. That is why a large number of dentists are working on a deeper and thorough study of this pathology. The main role in the development of periodontal disease is played by local and general factors, or their combined effects. As a result, this idealistic demand for a flawless periodontium somehow disgusts. The proposed model of periodontal health is unrelated to disease processes as it is a paradigm for maintaining periodontal health. Explain the factors that influence periodontal health (function, comfort, stability and well-being). Comfort, function and positive well-being are defined and expressed by the patient; However, periodontal stability requires observation by the dentist. Essentially, a stable periodontium is one in which the level of attachment has not changed, as measured clinically with a periodontal probe. Although there are many limitations in using

clinical levels of attachment to determine periodontal stability, it is currently the gold standard used to determine changes in the periodontal attachment apparatus. A multifactorial genetic effect in their etiology is more common in periodontal diseases. A further complication of the relationship between genes, environment and disease is that environmental genetic influences are necessary to maintain periodontal health. In addition, epigenetic changes in the environment also affect periodontal health. It is clear that many genetic traits (eg, type and quality of bone around the tooth root) and epigenetic changes in the oral cavity are important factors in determining the host's response to potential injury and conferring periodontal predisposition.

The importance of personal oral hygiene for supragingival plaque removal is a central paradigm in periodontal management. Periodic patient extractions are important because dental bacterial biofilm is the most important modifiable risk factor for periodontitis. Therefore, there is strong evidence that mechanical removal of dental biofilm (eg, brushing, flossing) can significantly affect periodontal tissue stability. Good oral hygiene requires highly motivated and trained individuals with adequate manual dexterity, effective cleaning equipment, chemotherapy drugs to remove plaque, and proper oral hygiene instructions.

Keywords: Manifestation, key issue, features, influence, etiological, factors, dental health.

Introduction

Many people use the word "health" casually when talking about illness, without any frame of reference. Commonly used health-related terms include 'medical services', 'health promotion', 'preventive health', 'health care', 'health insurance' and 'oral hygiene'. Of course, the word "health" means different things to different people in different situations. An epidemiologist may use mortality data to study the "health" of a population, an economist may discuss the "health" of the economy in terms of sustained GDP growth, a stressed-out dental student may wonder whether his final exams will affect his "health". ". . . " is probably your common sense, and periodontists measure bone and bonding levels when looking for information about periodontal "health." Obviously, these professionals use the same word, but with very different meanings. Etymologically, the word "health" " " comes from the Old English "hale", meaning "healthy", "reasonable" or "good". In general, the original and broad connotation of the word prevailed, but in a modern context.

While the original Old English meaning of "health" has survived through the ages, the concept of "health" in the 21st century is much more confusing than we might imagine. What we consider healthy has evolved from definitions of health that have changed over time as public understanding of disease and health has been influenced by a growing scientific knowledge base and by our cultural, social and individual values. Despite ever-evolving pretexts, the definition of health is important because it provides a common reference point for identifying recurring signs and symptoms that fit within a reasonable standard definition of normal. So instead of trying to define a set of periodontal diseases whose etiology we cannot easily explain, it would be better to define what periodontal health actually is and what can influence it. The purpose of this article is to present a framework for periodontal health that can be useful for clinical decision-making.

All medical practices, including dentistry, focus on one aspect of health. How would you define health? The preamble to the Constitution of the World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". The preamble goes on to say that "one of the fundamental rights of every human being is the maintenance of the highest attainable standard of health". Therefore, WHO global health is

an important and desirable visionary goal for individuals and society. Health is not the meaning of life, but the source of everyday life. In short, health is characterized as a positive concept that emphasizes social and personal resources in addition to physical capabilities. It is clear that the WHO definition is neither useful nor functional in everyday life, as it is difficult to obtain. Moreover, questions about the meaning of "perfect physical and mental health" and "free from disease or infirmity" have not been satisfactorily answered and probably never will be. Therefore, the researchers presented their conceptual interpretation of health, which can be divided into two broad categories: 1) the concept of natural health and 2) the concept of holistic health. The concept of natural health assumes that a person is healthy only when all their organs are functioning within certain limits in a statistically normal environment. A disease is a dysfunction of one or more organs. In this model, health and disease are mutually exclusive; In other words, a person is healthy when he is not sick. Determining whether a person is healthy or ill relies primarily on information from actuarial records and/or clinical studies.

The concept of holistic health states that a person is healthy if they can achieve all-important goals under normal conditions. Default conditions should not be confused with normal conditions but in reference to a cultural norm. Therefore, a person is considered healthy if they have had high blood pressure for a long time, but continues to perform all desired daily activities. Taking only the example of the tooth, a person with stable gingival recession, who can chew effectively and without pain and without aesthetic problems is considered periodontally healthy.

Objectives

The aim of the research was to study and analyze the manifestation of key issue peculiarities of the influence of etiological factors on dental health.

Methods

The material of the article was the data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. use the following databases (for extensive literature searches to identify the manifestation of key issue peculiarities of the influence of etiological factors on dental health.): pubmed, web of science, clinical key, tomson reuters, google scholar, cochrane library, and elsevier foundations. national and international policies and guidelines were also reviewed and as well as grey literature.

Results and discussion

Periodontal diseases are among the most common diseases in children and adolescents. These include gingivitis, aggressive localized or generalized periodontitis (or early periodontitis, which includes prepubertal generalized or localized periodontitis and juvenile periodontitis), and periodontitis associated with systemic disorders. The best approach to treating periodontal disease is prevention, followed by early diagnosis and treatment.

The term "periodontitis diseases" includes all diseases of individual tissues of the periodontium, which are accompanied by inflammatory atrophic or dystrophic changes. The importance of the problems of periodontal diseases is explained, first of all, by their significant distribution in the world. That is why a large number of dentists are working on a deeper and thorough study of this pathology.



The main role in the development of periodontal disease is played by local and general factors, or their combined effects.

Periodontal evaluation was based only on various physical measurements such as: attachment height, probing depth, bone loss, mobility, recession, degree of inflammation, etc. Periodontal health was often taken for granted and defined simply as the absence of signs and symptoms of periodontitis. Because of this, these strict and sometimes differing definitions of periodontitis have led to the idealistic necessity of a pristine periodontium for the periodontal health that affects us all in one way or another. In addition, potentially questionable recommendations were made in the absence of a realistic definition of health. The purpose of this manuscript was to assess the biological, environmental, sociological, economic, educational, and psychological relationships relevant to the development of a paradigm for defining periodontal health using a modified model of well-being. The paradigm includes four key characteristics such as dental function, pain-free dental function, periodontal stability, and psychological and social well-being of the individual. Finally, strategies and guidelines for periodontal health promotion were evaluated.

Many disease classifications have been made in periodontology over the years. They share a common application of the concept of natural health and define periodontal health as the absence of any clinical manifestation of a current or past disease. The American Academy of Periodontology (AAP) has defined health as "the condition of a functioning patient with no evidence of disease or abnormality." Applied specifically to a periodontal structure, this definition predicts the absence of signs and symptoms of devastating periodontal and gum disease or a tissue condition outside of the normal range. As a result, this idealistic demand for a flawless periodontium somehow disgusts us.

When it comes to the periodontium, wellness is a dynamic situation that changes from day to day. Each person will have an individual interpretation of periodontal wellness (i.e., health) based on their personal values and cultural orientations. Such a definition of periodontal health differs markedly from the traditional biomedical (i.e., natural) approach, which defines periodontal health as the complete absence of signs of disease. Using our current knowledge base as well as cultural norms and values, the proposed definition of a healthy periodontium in wellness should encompass simple and consistent characteristics to enable the individual to achieve positive goals. Life. These simple characteristics of periodontal health include four key elements. They form the basis of a proposed model of periodontal health that includes aspects affecting the health-disease continuum.

The proposed model of periodontal health is unrelated to disease processes as it is a paradigm for maintaining periodontal health. Explain the factors that influence periodontal health (function, comfort, stability and well-being). Comfort, function and positive well-being are defined and expressed by the patient; However, periodontal stability requires observation by the dentist. Essentially, a stable periodontium is one in which the level of attachment has not changed, as measured clinically with a periodontal probe. Although there are many limitations in using clinical levels of attachment to determine periodontal stability, it is currently the gold standard used to determine changes in the periodontal attachment apparatus.

Microbial biofilms cover the human skin, intestines, urogenital system, nasopharynx and mouth. The bacterial composition of these biofilms is characteristic of the habitat, diverse and stable for the parent species. Together with the environment of their habitats, biofilms form dynamic ecosystems. They contribute significantly to homeostasis and tissue health, but in severe

conditions they can contribute to or cause pathology. Maintaining balanced ecosystems has been proposed as a disease prevention strategy.

Mental stress is thought to be a contributing factor to several diseases including depression, cardiovascular disease and asthma to name a few. It is known that chronic stress can compromise the immune system and wound healing and contribute to pathogenic infections that can lead to periodontal destruction in susceptible patients. Unfortunately, the complex biological nature of stress makes it difficult to understand how it affects periodontal health in conjunction with many environmental factors (eg, biofilm, hygiene, diet, smoking). Although there is currently no full understanding of how stress can alter susceptibility or progression to periodontitis, how we manage stress can play an important role in our periodontal health.

Among the local causes, first of all, we should mention the infectious factor. Gingivitis is a typical inflammatory reaction of the connective tissue in response to plaque microflora that causes damage to the dentin-gingival epithelium. If treatment is not carried out, then gingivitis as a primary disease progresses and turns into periodontitis. Gingivitis is more often of infectious origin, where anaerobes and actinomycetes predominate in the local microflora.

There are different definitions of "plaque", but the most commonly used term is "plaque". The majority of researchers explain the development of inflammatory processes in the periodontium by the influence of the tooth buckle. It contains a large number of microbes; one milligram of dental plaque contains 100 to 300 million microbes. The growth of the tooth buckle directly depends on the amount of carbohydrates in the food. The growth of dental plaque under the gum causes tissue irritation due to microorganisms and their toxins, which leads to damage to the epithelium of the gum pocket and inflammation of the surrounding tissues.

In periodontology, attention is paid to non-mineralized plaques, tooth buckle, soft dental plaques, as well as supragingival and subgingival calculus formed from mineralized dental plaques. Thus, tartar is formed at the expense of plaque mineralization. Tartar formation is influenced by the presence of alkaline phosphatase and aldolase in the bacterial plaque, as well as the high ATP content of dental plaque and saliva. Dark and pale calculus differ morphologically and biochemically. Light-colored tartar is considered the initial stage of stone formation, and dark - the final stage.

The condition of periodontal tissues is affected by the products of microbial vitality - toxins. Exotoxins do not have a pronounced pathogenic potential. The formation of dental plaque is influenced by the alkaline phosphatase and aldolase present in the bacterial plaque, as well as by the high ATP content in dental plaque and saliva. Dark and pale calculus differ morphologically and biochemically. Light-colored tartar is considered the initial stage of stone formation, and dark - is the final stage.

In the immunological aspect, Saliva from the mumps salivary gland contains antibodies that destroy oral bacteria. According to some authors, salivary peroxidase from the salivary gland plays an important role in the ecology of the tooth buckle. Mixed saliva contains two peroxidases that can stop bacterial growth. At the same time, salivary peroxidase has an antibacterial effect on lactobacilli and streptococci.

The role of all these enzymes in the development of periodontal disease is not completely certain. The condition of periodontal tissues is affected by the products of microbial vitality - toxins. Exotoxins do not have a pronounced pathogenic potential, while endotoxins show resistance to temperature effects, stimulate the activity of antibodies, cause vasomotor changes, disrupt cell turnover, which is accompanied by hyperglycemia with subsequent hypoglycemia and necrosis.



In periodontology, attention is paid to tooth buckle formed from non-mineralized plaques, soft dental plaques and also supragingival and subgingival calculus formed from mineralized dental plaques. Thus, tartar is formed at the expense of mineralization of the plaque. The formation of dental calculus is influenced by the alkaline phosphatase and aldolase present in the bacterial plaque, as well as by the high ATP content in dental plaque and saliva. Dark and pale calculus differ morphologically and biochemically. Light-colored tartar is considered the initial stage of stone formation, and dark - the final stage.

The condition of periodontal tissues is affected by the products of microbial vitality - toxins. Exotoxins do not have a pronounced pathogenic potential. The contact between dental floss microbes and periodontal tissues leads to autoimmune processes that determine a chain reaction, and the latter is accompanied by progressive alteration in the periodontal tissue. That is why the microbial flora of the tooth-gum pocket, the possibility of microbial allergy of the body and the development of autoimmune reactions will be widely studied.

A number of authors indicate that the microflora and its enzymes can cause allergy in the oral cavity and cause Artius and Schwartzman's allergic-type phenomenon. Polymorphonuclear leukocytes and lysosomal enzymes take part in the pathogenesis of the latter. In the gingival tissue damaged by endotoxins, the degranulation of polymorphonuclear leukocytes was observed with the help of an electron microscope, with the release of the accompanying lysosome from the cell. Enzymes and other products of lysosomal origin enter into interaction with the surrounding structures, which leads to disruption of histohematal barrier penetration. It should be noted that as a result of the increased penetration of the histohematal barrier, bacterial antigens pass through the epithelial attachment, which appears to be a serious tissue barrier.

Enzymes produced by the mycobacteria of the bacterial loop provide the alteration changes that ultimately contribute to the formation of the periodontal pocket. In the exudate of the gingival pocket, factors have been found that lead to the attachment of epithelial cells and the disintegration of damaged leukocytes. Local changes can also be accompanied by general immunological changes.

The majority of authors believe that polymorphonuclear leukocytes, with the help of a chemotactic reaction, ensure the gathering of immunocompetent cells that produce antibodies in the area of damage. An important role is played by complement, which is the leading mediator in the inflammatory process. To date, it is known that the complement binding reaction occurs as a result of the stepwise interaction of 9 separate components. However, the final stage of these reactions is the lysis of erythrocytes of microbial cells. It is during this process that important side products are formed that have a direct relationship with inflammation.

Increased permeability of blood vessels, change in the chemotactic reaction of polymorphonuclear leukocytes, and swelling of the gums contribute to the accumulation and implantation of dental plaque bacterial antigens, which affect the body's immune system.

Chemotaxis is induced by the bacterial cell, as well as the antigen-antibody and complement system reaction mechanism. Cellular and humoral mechanisms are involved in this reaction. The most significant antigens are cell membrane mucoproteins of gram-positive bacteria and lipopolysaccharides of gram-negative bacteria. Proteins produced by bacteria can also function as antigens. The immune mechanism of action of the bacterial ingredients of the buckle is complex and has not been conclusively studied.

Of the local factors, special importance is given to saliva. It should be noted that enzymes have a great role in the development of inflammatory-dystrophic processes in periodontal tissues. About

30 enzymes have been found in mixed saliva: amylase, lipase, acetylcholinesterase, pseudocholinesterase, catalase, peroxidase, anhydrase, aldolase, succindehydrogenase and others. Examination of enzyme activity showed that the main amount of amylase is in the liquid fraction. This fact is explained by the fact that salivary glands are the source of amylase, lysozyme and peroxidase; lactate dehydrogenase-emigrated leukocytes; In case of protease and phosphatase, gingival epithelium and oral mucosa. During periodontal disease, amylase activity increases in saliva, along with lactate dehydrogenase, acid and alkaline protease, RNase and peroxidase activity in both salivary fractions. It is worth noting the action of the protective system of salivary glands during periodontal diseases.

According to saliva immunoglobulin, which is adsorbed on the bacteria in the oral cavity, acts on the principle of antigen-antibody. Saliva from the mumps salivary gland contains antibodies that destroy oral bacteria. Salivary peroxidase from the salivary gland plays an important role in the ecology of the tooth buckle. Mixed saliva contains two peroxidases.

Microcirculatory disorders are known that the development of dystrophic processes plays an important role in the pathogenesis of periodontal disease. Hypoxia plays a major role in the genesis of dystrophy itself. The authors have identified a sharp decrease in the oxygen level in the initial stage of periodontosis. Disruption of oxygen supply and its utilization during periodontosis is primarily related to disturbances in the microcirculation ring. In the initial stage of periodontitis, changes are most pronounced in the capillary, precapillary and arterial rings of microcirculation, which leads to the development of hypoxia and metabolic disorders, while the generalization of the process is due to the presence of numerous anastomoses. When we talk about microcirculation disorders, we should take into account the increased permeability of the blood vessel wall and the fact that the dynamic activity of platelets and the state of permeability of the capillary wall of the gums are closely related. Factors that affect the functional capacity of platelets contribute to a decrease in capillary permeability.

The traumatic factor plays an important role in the development of periodontal disease. The latter is caused by the effect of poor-quality orthopedic constructions, hanging edges of teeth, orthodontic equipment, and others on periodontal tissues. We should also mention the anatomical features of the teeth, their incorrect location in the tooth row and carious damage, that is, the factors that contribute to the appearance of dental plaque. The reasons listed above can cause: papillitis, gingivitis, less often other deeper damage to the periodontium. In addition, the damage has a local character.

Overloading of periodontal tissues leads to pathological changes in periodontal tissues. The latter can be caused by occlusal anomalies, early loss of molars and premolars, extraction of many teeth, incorrect determination of the indication of a bridge prosthesis, improper formation of the oral cavity, and others. The increase in the adaptive capacity of the periodontium may lead to the disruption of blood supply and subsequent resorption of bone tissues.

Overloading of periodontal tissues affects the bone tissue. In an experiment on dogs, resorption of the alveolar ridge, extraction of the apex of the tooth root and destruction of nerve cells of the periodontium were found. During periodontal trauma, clinical and radiological changes are observed.

Periodontal congestion is always accompanied by hemo- and lymphostasis, violation of histochemical barrier penetration, perivascular edema, diapedesis of blood-shaped elements, erythrocyte aggregation, embolism, and blood vessel thrombosis. All this affects the structure of periodontal tissues.



As it is known, teeth loosening develops because of disruption of the function of collagenous and elastic fibers of the periodontium. Later, their destruction is observed, the integrity of the epithelial layer is broken, a pathological pocket is formed, and then an inflammatory process develops because of the infection. Subsequently, inflammatory destructive processes lead to the resorption of bony ridges between the teeth.

Functional failure is one of the causes of periodontal disease and the functional failure of the chewing apparatus. Currently, inflammatory changes of periodontal tissues develop most often. It is worth noting the type of functional failure that develops during occlusal anomalies, for example in the case of open occlusion. Failure of chewing function is a characteristic of modern civilization. Processed soft food prevents a full load of periodontium, as a result of which atrophic processes develop. It should be noted that inflammatory changes most often develop during chewing function failure.

General factors

Psychosomatic factors have the main role as stress and emotional factors in the etiology of periodontal disease is noteworthy. Based on the research, it was established that chronic psychoemotional stress affects periodontal tissues. A situation that leads to prolonged negative psychoemotional stress causes hemomicrocirculatory changes and trophic disturbances in the tissues around the tooth. The development of periodontitis during long-term psychoemotional stress intensifies fibrinolysis and changes in blood coagulation system indicators, which appear to be one of the reasons for the development of pathological determinants. Among the systemic factors, genetic disposition, sexual maturation disorders, structural changes of polymorphonuclear leukocytes are also important.

Avitaminosis is an important factor. Many authors believe that avitaminosis plays a major role in the etiology of periodontal disease, especially the deficiency of vitamins C, B, A, and E. During vitamin C deficiency, inflammatory-destructive changes are observed in the periodontium. It primarily affects collagen fibers. The formation process of the latter is disturbed, the tissues are stretched, and the permeability of capillaries and intercellular layers increases. During avitaminosis, the bone tissue formation process in the body is inhibited and the resistance of periodontal tissues to infection decreases.

In the case of avitaminosis, the barrier function of the gum decreases, which is followed by inflammation of the latter. Vitamin E deficiency causes dystrophic processes, affects cellular respiration and the structure of collagen and elastic fibers. Oxidative processes and blood circulation are disturbed in the periodontium during avitaminosis.

Atherosclerotic lesion factors define periodontitis as a dystrophic process that develops as a result of atherosclerotic changes in periodontal blood vessels. According to Evdokimov, the manifestation of periodontitis against the background of atherosclerosis of periodontal blood vessels is caused by osteodystrophy of the bone of the alveolar ridge of the jaw. Currently, the pathogenicity of the microflora of pathological pockets is increased and the activity of enzymes is changed. Atherosclerotic changes in periodontal blood vessels play a major role in the development of periodontal tissue dystrophy. It has been shown by many authors that patients with a dystrophic form of periodontal inflammation, against the background of general atherosclerosis, had a violation of lipid metabolism: hypercholesterolemia, hyperbetalipoproteinemia, a decrease in lecithin cholesterol ratio and lecithin level in blood.

During the narrowing of the lumen of the nutrient blood vessel, bone hardening (eburnation) or osteoporosis occurs. Clinical and morphological observations show that bone resorption is observed during periodontitis, the latter is explained by secondary inflammatory processes, therefore, against the background of primary dystrophy of already existing periodontal tissues, by inflammatory bone resorption. Bone resorption can be observed without sclerotic changes of bone tissue, which violates the monopoly of the term "periodontitis" and indicates a periodontal damage with mainly inflammatory-destructive changes.

The nervous dystrophic process is the atrophic degenerative process of the tissues depend on the nutritional disorder of the periodontal tissues developed by the blood supply disorder. Similar changes can develop when the tissue loses its ability to assimilate food substances. In such a case, we can talk about the nervous trophic factors of eating disorders. The essence of the trophic influence of the nervous system lies not only in the regulation of tissue metabolism, but also in the maintenance of their structure during the regeneration process. Violation of trophic function leads to such a pathological process as dystrophy. On the basis of many literary data, provided with the following scheme of the nervous dystrophic process:

1. Pronounced tissue hyperemia, which passes into congestion and stasis at the periphery.
2. Manifestation of edema.
3. Proper dystrophic manifestations.
4. Penetration of microbial flora into the tooth-gum pocket and progression of the inflammatory process.
5. A pronounced purulent inflammatory process.
6. Regenerative processes that are not completed by closing the defect and forming a scar.

Endocrine disorders are the relationship between the endocrine system and periodontal disease. As a result of clinical and experimental studies, the influence of the functional state of the thyroid gland on the periodontal tissues was confirmed. He also notes that thyrotoxicosis is characterized by a picture of generalized periodontitis, the formation of deep pathological pockets, the release of purulent exudate from them, and active resorption of the alveolar ridge. Periodontal disease with hyper- and hypofunction of the existing gland has been described by many authors. Changes in the periodontium have been studied in more detail. In 90-93% of diabetic patients, there are changes in the periodontium that have a generalized character. The main role in the pathogenesis of periodontal syndrome in diabetes is given to periodontal angiopathy, and in the genesis of damage to small blood vessels - dysproteinemia and mainly the increase of glycosaminoglycans in the blood. Pathomorphological changes of blood vessels are noted against the background of diabetes. Diabetic microangiopathy is based on plasmorrhagic processes that lead to primary damage to the basal membrane, subsequent wall sclerosis and hyalinosis. Hypoxia developed during diabetes causes a decrease in the stability of periodontal tissues, against the background of which the role of the microbial factor increases, and the increase in the concentration of glucose in the gum fluid and saliva contributes to the multiplication of microbes and the rapid formation of tartar.

Due to already existing metabolic disorders and against the background of increased permeability of the periodontal connective tissue structure, microflora of the gingival fissure causes inflammatory and destructive changes, and overloading of the periodontal tissues aggravates the existing condition. As can be seen from the literature, when the depth of the pathological pockets increases, the total number of neutrophilic leukocytes decreases. A sharp decrease in their phagocytic activity, a decrease in dystrophically changed neutrophils and epithelial cells and

glycogen and RNA in them. The deeper the form of diabetes, the more the reactivity of the periodontal tissues is reduced and the more severe their damage. Periodontal diseases are also described in diabetes insipidus.

Diseases of the blood and hemopoietic system-includes periodontal diseases, that are aggravated during anemia, in particular iron deficiency anemia. It was found that the oral mucosa of the patients was anemic, there were pathological pockets and bleeding from the gums. X-ray showed slight resorption of bone tissue. According to the blood plasma anticoagulant activity analysis, it is proved that patients have a longer coagulation time and an increased free heparin content. In addition, there is a tendency to decrease fibrin activity and sufficient enhancement of fibrinolysis. In the pronounced stage of periodontitis, hypocoagulation and hyperfibrinolysis are observed. Also, during the inflammatory-destructive form of this pathology, the development of thrombohemorrhagic syndrome is observed. These changes are caused by both functional and organic changes in the vascular system.

Diseases of the gastrointestinal tract contribute to the development of pathological processes in the oral cavity. A number of authors found periodontal diseases in 98% of patients with gastric and duodenal ulcers. According to their data, the damage of periodontal tissues during gastric ulcer is expressed in the area of the frontal teeth of the lower jaw. In the case of duodenal ulcer, periodontal disease is expressed in the area of the teeth next to the lower jaw.

The increase in morphometric index during periodontal disease was more pronounced in patients with duodenal ulcer than without background pathology. An increase in local cellular immunity in the gingiva expresses some pathogenic mechanisms that contribute to the development of inflammatory-destructive changes in the periodontium.

Blood serum phosphatase activity was examined in periodontal disease, ulcer patients, and the level was within the normal physiological range.

A number of authors, when explaining the development of pathological processes in the gums, attach importance to the biochemical changes in the blood, this is what the research points to. They noted an increase in blood histamine levels and a decrease in histaminase activity in patients with gastric and duodenal ulcers.

Pathological changes in the periodontium are accompanied by an increase in the level of histamine in the blood, and during the period of remission, its level is within the normal range. It seems that in the pathogenesis of periodontal changes in patients suffering from duodenal and gastric ulcers, the increase in the concentration of histamine in the blood has a certain importance. Therefore, local changes in the periodontium in people with ulcers are due to increased permeability of blood vessels.

It has been suggested that disruption of host defenses due to malnutrition can significantly alter the response of periodontal tissues to biofilm bacteria. Unfortunately, the precise role of diet in the initiation or progression of periodontitis in humans remains to be elucidated. Perhaps the clinical definition of severe vitamin C deficiency or scurvy was one of the first and best documented of all oral nutritional deficiencies. Therefore, an adequate intake of vitamin C is an important prerequisite for periodontal health. Like vitamin C, antioxidants are another potential dietary component that may be associated with periodontal health. A showed the relationship between serum levels of antioxidants and periodontal health. While good nutrition is important for a person's long-term survival, there is not enough scientific evidence to recommend specific micronutrients for oral health.

The importance of personal oral hygiene for supragingival plaque removal is a central paradigm in periodontal management. Periodic patient extractions are important because dental bacterial biofilm is the most important modifiable risk factor for periodontitis. Therefore, there is strong evidence that mechanical removal of dental biofilm (eg, brushing, flossing) can significantly affect periodontal tissue stability. Good oral hygiene requires highly motivated and trained individuals with adequate manual dexterity, effective cleaning equipment, chemotherapy drugs to remove plaque, and proper oral hygiene instructions.

The relationship between education and health status is well documented for a wide range of medical interventions. Mortality is inversely proportional to years of study, health problems and level of education. The relationship between education and health is complex and cannot be fully explained by income, labor market or marital status. Therefore, there are a variety of possible mechanisms that influence the relationship between education and health. Like systemic health, a person's periodontal health is positively correlated with education.

Although genetic factors are believed to play an important role in periodontal health and disease, the relationship between an individual's genetic makeup and periodontal health is complex. When it comes to diseases, the genetic contribution can be divided into two types of cures. In one case, the genetic influence on the etiology may be the driving force behind the disease phenotype. When this occurs, a significant change in gene function (i.e., mutation) results in the production of one or more proteins that characterize the disease phenotype. Such mutations are inherited according to Mendel's laws of inheritance. Unlike Mendelian diseases, another category of gene action involves complex or multifactorial genetic effects in a population. In particular, complex or multifactorial genetic conditions result from the influence of many genes, each contributing to a relatively small part of the etiology. These multiple genetic factors must act in conjunction with appropriate environmental factors (eg, microbes, smoking) to cause disease at a certain threshold of genetic and environmental factors. A multifactorial genetic effect in their etiology is more common in periodontal diseases. A further complication of the relationship between genes, environment and disease is that environmental genetic influences are necessary to maintain periodontal health. In addition, epigenetic changes in the environment also affect periodontal health. It is clear that many genetic traits (eg, type and quality of bone around the tooth root) and epigenetic changes in the oral cavity are important factors in determining the host's response to potential injury and conferring periodontal predisposition.

Conclusions

So gingivitis is believed to be a critical factor in the progression of the most devastating forms of periodontitis, not all forms of inflammation appear to be harmful. Acute periodontal inflammation is important for tissue protection or healing. Not every gingivitis turns into periodontitis, even if the chronic forms of gingivitis are taken into account. There are other paradoxical reports that the form of periodontitis develops independently of the clinical manifestations of inflammation. In addition, the doctor's ability to predict future loss of attachment around teeth based on a person's inflammatory state is low. Thus, the presence of inflammation does not necessarily represent a disease in itself, but rather a physiological adaptation of healthy tissue to genome-regulated biological injury. Indeed, chronic inflammatory mechanisms resulting from the interaction of environment (e.g. diet, stress, bacteria) and genetics (e.g. specific homeostasis repair mechanisms, tissue gene expression, inflammatory response) are complex dynamics of the state of dental health condition.



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THE MANIFESTATION ROLE OF ANTIOXIDANTS IN MAINTAINING CELLULAR REDOX HOMEOSTASIS DURING VARIOUS PATHOLOGICAL PROCESSES

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ABSTRACT

The purpose of the study was to study and analyze the manifestation role of antioxidants in maintaining cellular redox homeostasis. The review intentionally aims to highlight the anti-inflammatory and anti-allergic potential of some antioxidants. In addition, it also provides insight into how antioxidants modulate allergy-related inflammatory biomarkers and other allergy-related parameters, as supported by recent data. All information will be useful for scientists and researchers to study and develop new allergy drugs with modifications.

Most of the research on oxidative signalling pathways in allergic rhinitis has focused on finding potential dietary antioxidants as alternative pharmacotherapy options to combat this disease. Thus, the current literature is somewhat limited in defining the complex and diverse molecular pathways of specific oxidative stress in allergic rhinitis. Recent research on dietary antioxidants for the treatment of allergic rhinitis is discussed in detail, including the natural dietary sources of each antioxidant.

Antioxidants capture and release free radicals from the body and control lipid levels (especially cholesterol) in the blood. It has anti-cancer effect, stops the growth of cancer cells, and can also inhibit cancer cells. Stimulates and simultaneously activates the regeneration of normal and healthy cells. Supports normal platelet function and reduces blood viscosity. Provides free blood circulation in the vessels and promotes the elasticity of the vessels. Antioxidants have anti-inflammatory and antibacterial properties. Antioxidants keep the skin fair and supple and prevent premature aging. It has the ability to restore and regulate the growth of collagen fibers, restore youthfulness to the skin, anti-allergic by neutralizing the release of histamine, improve memory, increase the body's resistance to stress, and lower blood sugar levels.

Reactive oxygen species (ROS) are produced by living organisms as a result of normal cellular metabolism. At low to moderate concentrations, they are involved in normal cellular processes, but at high concentrations, they cause harmful changes in cellular components such as lipids, proteins, and DNA. The shift in the balance of oxidants/antioxidants in favour of oxidants is called oxidative stress. Oxidative stress contributes to the development of many pathological conditions, including cancer, neurodegenerative diseases, atherosclerosis, hypertension,

ischemia/reperfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, COPD, and asthma. Aerobic organisms have built-in antioxidant systems, including enzymatic and non-enzymatic antioxidants, which are generally effective in preventing the harmful effects of ROS. However, under pathological conditions, antioxidant systems can be overloaded. In this review, we summarize the cellular mechanisms of oxidants and antioxidants, as well as redox and redox regulation in health and disease. Taking into account the above properties of the zeolite mineral (clinoptilolite), the activated clinoptilolite 500 mg "Geomin Forte" developed by us is characterized by an antioxidant effect. Unlike traditional antioxidants, it stimulates the body's antioxidant system and is a direct antioxidant. The activated natural mineral zeolite (clinoptilolite) acts directly on the cell membrane as a surfactant, which is an electron donor. Geomin Forte is an antioxidant, 200 times stronger than vitamins C and E. This allows it to be used for poisoning (it is used as the best absorbent for food poisoning, infectious, occupational, chronic metal poisoning and chronic exposure). And also, against the background of the functional state of the immune system for a long time and to help with allergic diseases. GSH is present in all cellular compartments and is the main soluble antioxidant. The GSH/GSSG ratio is one of the main determinants of oxidative stress. GSH exhibits antioxidant activity in several ways. It neutralizes hydrogen peroxide and lipid peroxides through the action of GSH-Px. GSH donates its electron to H₂O₂ to be reduced to H₂O and O₂. GSSG is in turn reduced to GSH-by-GSH reductase, which uses NAD(P)H as an electron donor. GSH-Px is also important in protecting the cell membrane from lipid peroxidation. The reduced glutathione transports protons to membrane lipids and protects them from oxidative stress.

Keywords: Manifestation, role, antioxidants, drug, maintaining, cellular redox, homeostasis.

Background

The vitamin E family includes four tocopherols and four tocotrienols. α -Tocopherol (α T) is the predominant tissue form of vitamin E, and its deficiency causes immobility in humans. However, the results of several clinical trials do not support a protective role for α T in disease prevention in individuals with adequate nutritional status. On the other hand, recent mechanistic studies show that other forms of vitamin E such as γ -tocopherol (γ T), δ -tocopherol, and γ -tocotrienol have unique antioxidant and anti-inflammatory properties superior to α T in the prevention and treatment of chronic disease. These forms of vitamin E remove reactive nitrogen species, inhibit eicosanoid-catalyzed cyclooxygenase and 5-lipoxygenase, and reduce pro-inflammatory signaling such as NF- κ B and STAT3/6. Unlike α T, other forms of vitamin E are extensively metabolized to carboxychromanol by cytochrome P450 oxidation of the ω side chain. Long-chain carboxychloromannols, especially 13'-carboxychloromannol, are more potent anti-inflammatory agents than non-metabolizable vitamins and therefore may contribute to the beneficial effects of vitamin E forms in vivo. Consistent with mechanistic evidence, animal and human studies indicate that gamma-T and tocotrienols may be beneficial in diseases associated with inflammation. This review focuses on non- α T forms of vitamin E with respect to metabolism, anti-inflammatory effects and efficacy, as well as in vivo efficacy in preclinical models and human clinical trials.

Considering the above properties of the zeolite mineral (clinoptilolite), the activated clinoptilolite 500 mg "Geomin Forte" developed by us is characterized by an antioxidant effect. Unlike traditional antioxidants, it stimulates the body's antioxidant system and is a direct antioxidant. The activated natural mineral zeolite (clinoptilolite) acts directly on the cell membrane as a surfactant,

which is an electron donor. Geomin Forte is an antioxidant, 200 times stronger than vitamins C and E. This allows it to be used for poisoning (it is used as the best absorbent for food poisoning, infectious, occupational, chronic metal poisoning and chronic exposure). And also against the background of the functional state of the immune system for a long time And to help with allergic diseases.

As innate and adaptive immune cell types and cytokines have been identified as major asthma triggers, it is clear that definitions of endogenous asthma are changing and evolving. Given the availability of therapies targeting T2 cytokines and the identification of relatively simple biomarkers associated with T2 inflammation, the current approach is to categorize patients into high T2 and low T2 asthmatics. In severe asthma, fundamental questions remain unanswered due to an incomplete understanding of the inflammatory microenvironment of the lower respiratory tract and its contribution to the clinical manifestations of the disease. Recent advances have led to a better understanding of the molecular mechanisms underlying steroid resistance, tissue remodeling, and disease progression. This approach helped us understand the molecular mechanisms of low T2-weighted asthma. The chemosensory properties and airway remodeling recently reported in patients with asthma may be indicative of novel endotypes associated with low T2 patients. Accurate application of the results of these studies requires accurate clinical characterization for the design of clinical trials and the development of new biological therapies.

Natural forms of vitamin E are eight lipophilic molecules, including α -, β -, γ -, and δ -tocopherol (α T, β T, γ T, δ T) and α -, β -, γ -, and δ -tocotrienol (α TE, β TE, γ TE, δ TE). All forms of vitamin E have a chromanol ring and a unique 16-carbon side chain where tocopherols are saturated and tocotrienols have three double bonds. The various isoforms of tocopherols and tocotrienols differ in position 5 or 7 of the chromanol ring for the H or CH₃ group. Natural tocopherols have an RRR configuration at positions 2, 4' and 8', while tocotrienols have an R configuration at the second position.

An antioxidant is a molecule that prevents the oxidation of other molecules. Oxidation releases free radicals, which scientists believe cause many diseases. When the body receives enough antioxidants, it can fight free radicals on its own. In fact, the antioxidants, minerals, fiber, and other substances found in fruits, vegetables, and grains protect the body from disease, but taking large doses of additional antioxidants does not have much effect. Among the substances that act as antioxidants against harmful free radicals, the most common are vitamin A, vitamin C, vitamin E, selenium, flavonoids, lignan, and lutein. Sources of vitamin E are nuts, cereals, vegetables and vegetable oil. Sources of vitamin C include citrus fruits, tomatoes, green leafy vegetables, and strawberries. Sources of vitamin A include apricots, melons, broccoli, sweet potatoes, carrots, cabbage, and plums. Sources of selenium: nuts, fish, red meat, cereals, eggs, garlic and milk. Sources of flavonoids: soy, red wine, pomegranate, blackberry, currant and tea. Sources of lignans are flaxseed, barley, rye, whole grains, and oats. Sources of lutein: kiwi, spinach, Brussels sprouts, green tea and broccoli.

Antioxidants are substances that protect the human body from harmful particles and especially from free radicals. Free radicals are unstable, highly aggressive and active molecules that damage healthy cells and cause: frequent colds and flu, exacerbation of chronic diseases, premature aging of the body, the risk of atherosclerosis, heart attack, accidents, cerebrovascular diseases, cataracts and cancer. Antioxidants can be called the ecological side of the human body. These are "C", "E", vitamin A, lupine, lycopene, some amino acid complexes, the trace element selenium and some plant extracts. Plant foods are the main source of antioxidants. These are fruits, vegetables, herbs,



green tea and much more. These products also contain a large number of vitamins, minerals and other biologically active substances necessary to keep the body in good shape.

It is believed that vitamin A and the retinoic acid produced from it protect the body from surrounding carcinogens. Carotene is formed from vitamin A. American scientists have proven that foods rich in carotene protect against cancer. Colourful fruits and vegetables contain a lot of carotenes. With a sufficient amount of vitamin-A in the body, the skin becomes healthy and smooth, and the vessels remain elastic since this vitamin prevents the formation of loops in the vessels.

The activated mineral zeolite (clinoptilolite) 500 mg "Geomin Forte" developed and characterized by an antioxidant effect. Unlike traditional antioxidants, it stimulates the body's antioxidant system and is a direct antioxidant. The activated natural mineral zeolite (clinoptilolite) acts directly on the cell membrane as a surfactant, which is an electron donor. Geomin Forte is 200 times more antioxidant than vitamins C and E. Geomin Forte can be used for poisoning (used as the best food absorbent), infections, occupational poisoning, chronic metal poisoning and chronic exposure and also against the functional state of the immune system over time and in any case, with allergic diseases.

Vitamin E delays the oxidation of lipids (fats) and inhibits the growth of free radicals that destroy cells, prevents the formation of blood clots, has antitumor properties and strengthens the immune system. With a lack of vitamin E, fat metabolism is disturbed. For example, age spots on the hands are a sign of depletion of fatty acids. Vitamin E prevents the destruction of cells by roots, prevents the formation of blood clots, fights carcinogens and ensures proper muscle function. Sources include vegetable oils, green leafy vegetables, beans, egg yolks, soybeans, oats, milk, and wheat germ. Flaxseed, nettle and turmeric are also important sources of vitamin E.

One of the most powerful antioxidants is vitamin C (ascorbic acid). Vitamin E, which is assigned the role of a fat solvent, traps free radicals in the membrane, which consists of lipid molecules, and ascorbic acid performs this work in the water space between cells. Vitamin C also works in the circulatory system, protecting hemoglobin from oxidation, providing iron stores in the body, and regulating cholesterol levels. The human body can absorb 2-3 g per day, the excess is excreted by the kidneys. However, taking vitamin C in large quantities is not recommended, practice shows that this will not lead to anything good. High concentrations of vitamin C are found in asparagus, peas, beets, black currants, cabbage, cherries and strawberries.

Oxidative stress is a cause and effect of redox metabolism under various physiological and pathological conditions. Understanding the molecular mechanisms underlying oxidative stress and the role of antioxidants may be key to managing complications. Allergic rhinitis is a disease that impairs the daily functioning and quality of life of those affected and has a high prevalence and socioeconomic burden. Recent research has focused on the role of oxidative stress and antioxidants in allergy. The review discusses animal and clinical studies of oxidative markers and potential therapeutic antioxidants in the allergic diet. The complexity of each response and multiple physiological effects complicates clinical trials in the field of antioxidant drug therapy clinical trials. Thus, future research must take into account several confounding factors, including appropriate dose adjustments, and the search for more effective and potent natural biological compounds must continue. Based on these studies, long-term, randomized, placebo-controlled trials are needed to elucidate the role and effect of antioxidants in the clinical direction of pharmacological co-treatment of allergic diseases.

Objectives

The aim of the research was to study and analyze the manifestation role of antioxidants in maintaining cellular redox homeostasis.

Methods

The material of the article was the data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Use the following databases (for extensive literature searches to identify key points related to the manifestation role of antioxidants in maintaining cellular redox homeostasis): PubMed, Web of Science, Clinical key, Tomson Reuters, Google Scholar, Cochrane Library, and Elsevier Foundations. National and international policies and guidelines were also reviewed and as well as grey literature.

Results and discussion

Regulated physiological inflammation is a beneficial adaptive response that plays a role in defense against infection, tissue repair, and adaptation to stress or homeostasis. However, if left unchecked, it can become dangerous and manifest as tissue damage, septic shock, autoimmunity, fibrosis, metaplasia or homeostasis, and chronic autoinflammatory diseases. Whatever the cause, inflammation likely evolved as an adaptive response to maintain homeostasis. Many pathological and clinical features of allergic diseases reflect the long-term consequences of chronic allergic inflammation in the focus of prolonged or repeated exposure to allergens. An antioxidant is a molecule that prevents the oxidation of other molecules. Oxidation releases free radicals, which scientists believe cause many diseases. When the body receives enough antioxidants, it can fight free radicals on its own. In fact, the antioxidants, minerals, fiber, and other substances found in fruits, vegetables, and grains protect the body from disease, but taking large doses of added antioxidants does little. Among the substances that act as antioxidants against harmful free radicals, the most common are vitamin A, vitamin C, vitamin E, selenium, flavonoids, lignans, and lutein. Sources of vitamin E are nuts, cereals, vegetables and vegetable oil. Sources of vitamin C include citrus fruits, tomatoes, green leafy vegetables, and strawberries. Sources of vitamin A: apricots, melons, broccoli, sweet potatoes, carrots, cabbage and prunes. Sources of selenium: nuts, fish, red meat, cereals, eggs, garlic and milk. Sources of flavonoids: soy, red wine, pomegranate, blackberry, raisins and tea. Sources of lignans are flaxseed, barley, rye, whole grains, and oats. Sources of lutein: anemone, spinach, Brussels sprouts, green tea and broccoli [1].

Antioxidants are substances that protect the human body from harmful molecules, especially free radicals. Free radicals are unstable, highly aggressive and active molecules that damage healthy cells and cause: frequent flu and colds, exacerbation of chronic diseases, premature ageing of the body, risk of atherosclerosis, heart attack, accidents, cerebrovascular diseases, cataracts and cancer. We can say that antioxidants are an ecological door for the human body. These are "C", "E", vitamin A, lupine, lycopene, some amino acid complexes, the trace element selenium and some plant extracts. Plants are the main source of antioxidants. These are fruits, vegetables, herbs, green tea and much more. In addition, such products contain a large number of vitamins, minerals and other biologically active substances necessary to maintain the normal state of the body. Oxidative stress is a cause and effect of redox metabolism under various physiological and pathological conditions. Understanding the molecular mechanisms underlying oxidative stress and

the role of antioxidants may be key to managing complications. Allergic rhinitis is a disease that impairs the daily functioning and quality of life of those affected and has a high socioeconomic burden and prevalence. Recent research has focused on the role of oxidative stress and antioxidants in allergic rhinitis. The review discusses animal and clinical studies of oxidative markers and potential therapeutic antioxidants in the allergic rhinitis diet. The complexity of each response and multiple physiological effects complicates clinical trials of antioxidant drug therapy. Thus, future research should take into account several confounding factors, including appropriate dosage adjustments, and the search for more effective and potent natural biological compounds should continue. Based on these studies, long-term, randomized, placebo-controlled trials are needed to elucidate the role and effect of antioxidants in the clinical setting of pharmacological co-treatment of allergic diseases [2].

Reactive oxygen species (ROS) are produced by living organisms as a result of normal cellular metabolism and environmental factors such as air pollution or cigarette smoke. ROS are highly reactive molecules and can damage cellular structures such as carbohydrates, nucleic acids, lipids and proteins and alter their function. The shift in the balance between oxidants and antioxidants in favour of oxidants is called "oxidative stress". The regulation of redox and redox states is important for cell viability, activation, proliferation, and organ function. Aerobic organisms have built-in antioxidant systems, including enzymatic and non-enzymatic antioxidants, which are generally effective in preventing the harmful effects of ROS. However, under pathological conditions, antioxidant systems can be overloaded. Oxidative stress contributes to the development of many diseases and conditions, including cancer, neurodegenerative diseases, atherosclerosis, hypertension, ischemia/reperfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, COPD, and asthma. This review article summarizes cellular oxidative and antioxidant systems and discusses the cellular effects and mechanisms of oxidative stress [3].

Reactive oxygen species (ROS) are produced by living organisms as a result of normal cellular metabolism. At low to moderate concentrations, they are involved in normal cellular processes, but at high concentrations, they cause harmful changes in cellular components such as lipids, proteins, and DNA. The shift in the balance of oxidants/antioxidants in favour of oxidants is called oxidative stress. Oxidative stress contributes to the development of many pathological conditions, including cancer, neurodegenerative diseases, atherosclerosis, hypertension, ischemia/reperfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, COPD, and asthma. Aerobic organisms have built-in antioxidant systems, including enzymatic and non-enzymatic antioxidants, which are generally effective in preventing the harmful effects of ROS. However, under pathological conditions, antioxidant systems can be overloaded. In this review, we summarize the cellular mechanisms of oxidants and antioxidants, as well as redox and redox regulation in health and disease. ROS are formed from molecular oxygen as a result of normal cellular metabolism. ROS can be divided into 2 groups: free radicals and non-radicals. Molecules that contain one or more unpaired electrons that make the molecule reactive are called free radicals. When 2 free radicals share their unpaired electrons, a non-radical is formed. The three main ROS of physiological importance is superoxide anion (O_2^-), hydroxyl radical ($-OH$), and hydrogen peroxide (H_2O_2) [4].

A superoxide anion is formed when 1 electron is attached to molecular oxygen. This process is mediated by nicotinic adenine dinucleotide phosphate oxidase [NAD(P)H], xanthine oxidase, or the mitochondrial electron transport system. The main place of production of superoxide anions is

mitochondria, i.e. cellular machinery for the production of adenosine triphosphate. Normally, electrons are transported through the mitochondrial electron transport chain to reduce oxygen in water, but about 1-3% of all electrons leave the system to form superoxide. NAD(P)H oxidase has been found in polymorphonuclear leukocytes, monocytes and macrophages. During phagocytosis, these cells release peroxide, which causes a bactericidal effect. The peroxide is converted to hydrogen peroxide by the action of superoxide dismutase. Hydrogen peroxide easily diffuses across the plasma membrane and into peroxisomes due to the consumption of molecular oxygen in metabolic reactions. In a series of chemical reactions called the Haber-Weiss and Fenton reactions, H_2O_2 can decompose to OH in the presence of carrier metals such as Fe^{2+} or Cu^{2+} [5]. Other oxygen-derived free radicals are peroxy radicals ($ROO\cdot$). The simplest form of these radicals is the hydroperoxyl radical ($HOO\cdot$), which plays a role in the peroxidation of fatty acids. Free radicals can initiate lipid peroxidation chain reactions by removing a hydrogen atom from the methylene carbon of the side chain. The lipid radical then reacts with oxygen to form a superoxide radical. The peroxy radical initiates a chain reaction that converts polyunsaturated fatty acids into lipid hydroperoxides. Lipid hydroperoxides are very unstable and rapidly break down into by-products such as aldehydes (eg 4-hydroxy-2,3-nom) and malondialdehyde (MDA). Isoprostanes are another group of lipid peroxidation products resulting from the peroxidation of arachidonic acid, and their increased concentration has also been found in the plasma and exhaled air of asthmatic patients. Lipid peroxidation disrupts the integrity of cell membranes and leads to the remodelling of membrane structure. Hydrogen peroxide, superoxide radicals, oxidized glutathione (GSSG), MDA, isoprostane, carbonyl, and nitrotyrosine can be readily determined in plasma, blood, or bronchoalveolar lavage samples as oxidative biomarkers using standard assays [6].

Fat-soluble vitamin E is concentrated in hydrophobic cells within the cell membrane and is the main defense against membrane damage caused by oxidants. Vitamin E donates an electron to the superoxide radical formed during lipid peroxidation. α -tocopherol is the most active form of vitamin E and the main antioxidant associated with the cell membrane. Vitamin E activates the cell division of cancer cells and inhibits the formation of free radicals.

GSH is present in all cellular compartments and is the main soluble antioxidant. The GSH/GSSG ratio is one of the main determinants of oxidative stress. GSH exhibits antioxidant activity in several ways. It neutralizes hydrogen peroxide and lipid peroxides through the action of GSH-Px. GSH donates its electron to H_2O_2 to be reduced to H_2O and O_2 . GSSG is in turn reduced to GSH-by-GSH reductase, which uses NAD(P)H as an electron donor. GSH-Px is also important in protecting the cell membrane from lipid peroxidation. The reduced glutathione transports protons to membrane lipids and protects them from oxidative stress [7].

Carotenoids are pigments found in plants. Initially, β -carotene was found to react with superoxide ($ROO\cdot$), hydroxyl ($\cdot OH$), and superoxide ($O_2\cdot$) radicals. Carotenoids exhibit an antioxidant effect at low oxygen partial pressure, but may have a pro-oxidant effect at higher oxygen concentrations. Both carotenoids and retinoic acids (RA) can regulate transcription factors. Beta-carotene inhibits oxidation-induced activation of NF- κ B and the production of interleukin (IL)-6 and tumor necrosis factor- α . Carotenoids also affect cell proliferation. The antiproliferative effects of rheumatoid arthritis have been demonstrated in several studies. These effects on RA are mainly mediated by retinoic acid receptors and are cell type dependent. In breast cancer cells, the retinoic acid receptor has been shown to inhibit growth by causing cell cycle arrest, apoptosis, or both [8].



Oxidative stress occurs when the balance between antioxidants and ROS is disrupted, either due to a lack of antioxidants or due to accumulation of ROS. When oxidative stress occurs, cells attempt to neutralize oxidative effects and restore redox balance by activating or repressing genes encoding protective enzymes, transcription factors, and structural proteins. The ratio of oxidized and reduced glutathione (2GSH/GSSG) is one of the important factors that determine oxidative stress in the body. An increase in ROS production in the body can alter the structure of DNA, lead to changes in proteins and lipids, stress-induced activation of many transcription factors, and production of pro-inflammatory and anti-inflammatory cytokines [9].

Oxidative stress can result from an overproduction of ROS through metabolic reactions that consume oxygen and shift the oxidant/antioxidant balance in favor of oxidants. ROS are triggered by the metabolic activity of cells and environmental factors such as air pollution or cigarette smoke. Due to the unpaired electrons in their structure, ROS are highly reactive molecules and react with many biological macromolecules in the cell, such as carbohydrates, nucleic acids, lipids, and proteins, changing their functions. ROS also affect the expression of many genes by increasing redox transcription factors and chromatin remodeling by reducing histone acetylation/deacetylation. Regulation of the redox state is important for organogenesis, activation, proliferation, and organ function [10].

ROS can lead to DNA modifications in a variety of ways, including base degradation, DNA single- or double-strand breaks, purine-, pyrimidine-, or sugar-linked modifications, mutations, deletions or translocations, and cross-linking proteins. Most of these DNA changes are directly related to carcinogenesis, aging, neurodegenerative diseases, cardiovascular diseases and autoimmune diseases. Cigarette smoke, redox and non-redox metals such as iron, cadmium, chromium and arsenic are also involved in carcinogenesis and aging by forming free radicals or binding to thiol groups. The formation of 8-OH-G is the most well-known DNA damage due to oxidative stress and a potential biomarker of carcinogenesis [11].

Gene promoter regions contain homologous transcription factors. These transcription factor binding sites contain GC-rich sequences that are susceptible to oxidative attack. DNA synthesis of 8-OH-G at the transcription factor binding site can alter transcription factor binding and thereby alter the expression of associated genes, as shown for AP.1 and Sp-1 target sequences. In addition to 8-OH-G, 8,5'-cyclo-2'-deoxyadenosine (cyclo-dA) also inhibits cellular gene transcription when localized to the TATA domain. TATA-binding proteins initiate transcription by changing the bend of DNA. Binding to TATA-binding proteins can be disrupted by the presence of cyclo- α A [12].

Oxidative stress destabilizes microsatellite regions (short repeats). Redox-active metal ions and hydroxyl radicals increase microsatellite instability. Although single-stranded DNA breaks caused by oxidative damage are easily tolerated by cells, double-stranded DNA breaks caused by ionizing radiation can pose a serious threat to cell survival. CpG group methylation in DNA is an important epigenetic mechanism that can lead to gene silencing. Oxidation of 5-MeCyt to 5-hydroxymethyluracil (5-OHMeUra) can occur via disaggregation/oxidation reactions of thymine or 5-hydroxymethylcysteine intermediates. It appears that in addition to regulating gene expression, DNA methylation also affects chromosome organization. Aberrant DNA methylation patterns induced by oxidative stress also affect DNA repair activity [13].

ROS can induce lipid peroxidation and disrupt the assembly of membrane lipid bilayers, which can inactivate membrane-bound receptors and enzymes and increase tissue permeability. Lipid peroxidation products such as MDA and unsaturated aldehydes can inactivate many cellular

proteins by forming protein cross-links. Nominative 4-hydroxy-2 depletes intracellular GSH and induces superoxide production, activates the epidermal growth factor receptor, and stimulates fibronectin production. Lipid peroxidase agents such as isoprostane and thiobarbituric acid-reactive agents have been used as surrogate biomarkers of oxidative stress, with increased concentrations detected in exhaled air or lung or pulmonary lavage in patients with COPD [14].

ROS can cause peptide chain fragmentation, change in protein electrical charge, protein cross-linking, and oxidation of certain amino acids, leading to increased susceptibility to proteolysis by degradation by specific proteases. Cysteine and methionine residues in proteins are particularly vulnerable to oxidation. Oxidation of sulfhydryl groups or methionine residues in proteins causes conformational changes, protein cleavage and degradation. Enzymes that have metals at or near their active sites are particularly susceptible to metal-catalyzed oxidation. Oxidative modification of enzymes has been shown to inhibit their activity [15].

In some cases, selective oxidation of proteins may occur. For example, methionine can be oxidized to methionine sulfoxide and phenylalanine can be oxidized to o-tyrosine. Sulfhydryl groups can be oxidized to form disulfide bonds, and carbonyl groups can be inserted into protein side chains. Gamma rays, catalyzed metal oxidation, HOCl and ozone can lead to the formation of carbonyl groups [16].

ROS can induce the expression of many genes involved in signal transduction. A high GSH/GSSG ratio is important to protect cells from oxidative damage. Violation of this ratio activates redox-sensitive transcription factors such as NF- κ B, AP-1, activated T-cell nuclear factor, and hypoxia-inducible factor 1, which participate in the inflammatory response. Activation of transcription factors by ROS occurs through signal transduction cascades that transfer information from outside to inside the cell. Receptor tyrosine kinases, most growth factor receptors such as epidermal growth factor receptors, endothelial growth factor receptors and platelet-derived growth factor receptors, protein tyrosine phosphatases and serine/threonine kinases are targets of ROS. The extracellular signal-regulated kinases, JNK and p38, which are members of the mitogen-activated protein kinase family and are involved in many cellular processes, including proliferation, differentiation and apoptosis, can also be regulated by oxidants [17].

Under conditions of oxidative stress, cysteine residues in the DNA binding site of c-Jun, some AP-1 subunits, and inhibitory κ B kinase are reversibly S-glutathionylated. Glutathione and TRX have been reported to play important roles in regulating redox signaling pathways such as NF- κ B and AP-1, mitogen-activated protein kinase p38, and JNK. NF- κ B can be activated in response to oxidative stress such as ROS, free radicals, and UV exposure. Phosphorylation of I κ B releases NF- κ B and allows it to enter the nucleus to activate gene transcription. Many kinases phosphorylate I κ B at serine residues. These kinases are targets of oxidative signals for NF- κ B activation. Reducing agents increase NF- κ B binding to DNA, while oxidizing agents inhibit NF- κ B binding to DNA. TRX may have 2 opposite effects on NF- κ B regulation: in the cytoplasm, it prevents I κ B degradation and inhibits NF- κ B activation, but increases NF- κ B binding to DNA in the nucleus. Activation of NF- κ B through oxidative degradation of I κ B leads to the activation of many genes associated with antioxidant defense. NF- κ B regulates the expression of several genes involved in the immune response, such as IL-1 α , IL-6, tumor necrosis factor- α , IL-8, and several adhesion molecules. NF- κ B also regulates angiogenesis, cell proliferation and differentiation [18]. AP-1 is also regulated by redox status. In the presence of H₂O₂, some metal ions can activate AP-1. Increasing the GSH/GSSG ratio increases AP-1 binding, while GSSG inhibits AP-1 binding to



DNA. DNA binding of the Fos/Jun heterodimer is enhanced by a decrease in the conserved cysteine in the DNA-binding domain of each protein, while AP-1 DNA binding can be inhibited by GSSG in many cell types, suggesting that the formation of a disulfide bond with cysteine residues inhibits AP-1 DNA binding [19].

In allergic rhinitis, the role of thioredoxin-interacting protein (TXNIP) in oxidative stress was investigated. In a mouse model of OVA-induced allergic rhinitis, TXNIP expression in the nasal mucosa, MDA and SOD activity, and allergic rhinitis markers such as sneezing and nasal rubbing, OVA-specific IgE, and histamine were measured. Serum and specific IgE to OVA, IL-4, IL-5 and tumor necrosis factor (TNF)- α in nasal washings. Results were measured between mice treated intranasally with the TXNIP inhibitor resveratrol and untreated mice. In the untreated allergic rhinitis group, nasal symptoms, TXNIP and OVA-specific IgE levels, histamine and cytokine levels, and MDA and SOD levels increased, while those in the untreated allergic rhinitis group decreased. received treatment. In nasal tissues, epithelial cells and inflammatory cells were positive for TXNIP. This finding suggests that thioredoxin and TXNIP regulate transcription factors of oxidative stress pathways in allergic rhinitis, although a precise understanding of the signalling pathway between transcription factors and established markers of nasal symptoms remains to be determined [20].

Another transcription factor, NF- κ B, can also be activated in response to oxidative stress. Oxidation of H₂O₂ releases the inhibitory subunit NF- κ B (IKB). NF- κ B is then released and can enter the cell nucleus, where it acts as a transcription and expression factor for genes involved in the acute phase of the immune or inflammatory response. In allergic rhinitis, several recent studies have examined the function of the NF- κ B pathway in a mouse model of allergic rhinitis. Studies have shown that in an OVA-induced allergic rhinitis model, markers of oxidative stress such as MDA levels and the Nrf2 and NF- κ B pathways are elevated. They correlate with signs of inflammation such as cytokine levels and histopathological findings in models of allergic rhinitis. After treatment with the antioxidant mangiferin, the markers decreased [21].

In the pathogenesis of allergic rhinitis, antigen presentation by dendritic cells is the first stage of allergenicity. There are reports that disruption of the natural epithelium of the nasal epithelium may facilitate the absorption of allergens and harmful foreign particles in allergic rhinitis. Epithelial dysfunction with increased epithelial permeability and altered expression of occludin and zonula occludens (ZO)-1 have been observed in patients with allergic rhinitis to dust mites. This disruption of mucosal integrity may contribute to reduced response to therapy, making it an important area of research in the treatment of allergic rhinitis. Several studies have examined the role of oxidative stress in epithelial barrier dysfunction in allergic rhinitis [22].

Inflammation is characterized as a protective response of the immune system against endogenous pathogenic and non-infectious molecules. The recognition of foreign substances (especially pathogens and endogenous molecules) by cells of the immune system leads to the production of various pro-inflammatory cytokines and chemokines involved in inflammation. Consequently, the release of pro-inflammatory mediators attracts more circulating immune cells to the site of infection, resulting in the production of prostaglandins, reactive oxygen species (ROS) and cyclooxygenase-2 (COX-2), which increase inflammation. Inflammation can be reversed by removing foreign invaders and reprogramming the effector cells. Failure to eliminate foreign substances leads to long-term persistent inflammation, which is the cause and development of chronic and degenerative diseases such as diabetes, heart disease, digestive disorders, cancer, autoimmune diseases, etc. Chronic inflammation and related diseases will become serious health

problems around the world in the future. This discovery led to further efforts to explore new therapeutic strategies against inflammatory diseases. Various synthetic drugs have been used to treat inflammatory diseases with varying degrees of success. However, there are some health concerns associated with long-term use of these synthetic drugs. Therefore, it is necessary to develop safe and inexpensive treatment options to defeat this threat once and for all. For thousands of years, natural ingredients have been deliberately used to treat various human ailments. The therapeutic and anti-inflammatory potential of these natural compounds is well known. Many biologically active plant compounds, primarily flavonoids, can inhibit inflammation by reducing the levels of certain cytokines (IL-6, IL-1 β , and TNF- α) or by reducing their key mediators, such as prostaglandins, COX-2, and ROS. The diverse biological activities attributed to flavonoids in the human body, such as antioxidant, anti-inflammatory, antimutagenic, and antiviral activities, make them suitable for use in a variety of nutritional strategies [23].

There is fairly strong evidence that reactive oxygen species (ROS) are important deleterious mediators in asthma and allergic disease. Exposure of the respiratory epithelium to particles such as diesel exhaust particles, ultrafine particles and pollen leads to the formation of ROS. Pollen contains an intrinsic NADPH oxidase that induces ROS and mitochondrial dysfunction that contribute to the innate induction of allergic inflammation. ROS-induced DNA damage results in the release of 8-oxoguanine (8-OxoG) from the damaged DNA. The damaged base is cleaved by 8-oxoguanine DNA glycosylase-1 (OGG1), and 8-oxoG and OGG1 bind to form a signaling complex that activates NF- κ B and airway inflammation. Human studies have shown that asthma is associated with increased levels of ROS and lipid peroxides. Allergen exposure in asthmatics induces localized ROS in the airways. Observational and interventional studies have found conflicting evidence of a negative role for vitamin C in the development of asthma and allergic diseases. Most observational studies of vitamin E have demonstrated some effect of vitamin E supplementation in improving respiratory outcomes in patients with asthma/allergy, and limited intervention studies support these observational data. A major limitation of orally administered antioxidants such as vitamin C and tocopherol is that too little is released at the site of airway inflammation to increase local antioxidant capacity. Pharmaceutical companies should focus on developing oral or inhaled products that increase local levels of antioxidants in the respiratory system, thereby increasing their effectiveness in preventing asthma and allergic diseases [24].

The review intentionally aims to highlight the anti-inflammatory and anti-allergic potential of some antioxidants. In addition, it also provides insight into how antioxidants modulate allergy-related inflammatory biomarkers and other allergy-related parameters, as supported by recent data. All information will be useful for scientists and researchers to study and develop new allergy drugs with modifications.

Regulated physiological inflammation is a useful adaptive response that plays a role in defense against infection, tissue repair and adaptation to stress, or in establishing a "disturbance" of homeostasis. However, if left unchecked, it can become dangerous and manifest as tissue damage, septic shock, autoimmunity, fibrosis, metaplasia or homeostasis, and chronic autoinflammatory diseases. Whatever the cause, inflammation likely evolved as an adaptive response to maintain homeostasis. Many pathological and clinical manifestations of allergic diseases reflect the long-term consequences of chronic allergic inflammation in places of prolonged or repeated exposure to allergens.

Some immune responses can cause an overreaction or an overreaction. Diseases caused by an overactive immune response to allergens are called allergic reactions. Allergens are antigens



generally considered harmless and distinct from pathogenic organisms. Allergens can come from the environment, such as dust, smoke, sulfur dioxide, diesel fumes and ozone, bee venom or other pesticides, foods (eg, tree nuts, some components of propolis, pollen, royal jelly), or certain proteins or ingredients in medicines. Host factors that affect the risk of allergic reactions include heredity, sex, sex and age, diet, socioeconomic status and family lifestyle, stress, allergens, pedigree size, childhood infections, nutritional factors, and environment (urban versus rural). In addition to genetic factors, some environmental factors such as smoking can also contribute to allergic symptoms such as allergic rhinitis/asthma. In addition, evidence suggests that interactions with environmental and human microbiota play an important role in the regulation of the immune system. Changes in the host microbiome due to lifestyle, urbanization, dietary changes and overuse of antibiotics and their impact on the gut microbiota also contribute to an increased risk of allergic diseases and poor immune tolerance. In developed countries, the prevalence of allergies by sex, age and ethnicity has increased dramatically in recent years, with a corresponding increase in the burden on the health care system. According to the World Allergy Agency, allergies mainly affect children and young adults and are widespread [25].

An allergy is an allergic reaction caused by the human body's immune response following secondary exposure to an antigen, causing tissue damage that can lead to serious illness. An allergy (allergic or allergic reaction) is a side effect of the normal immune system, including allergies and autoimmunity. Allergic reactions cause itching, pain, and swelling and inflammation. Allergic diseases can have a serious impact on the vital activity of the body and lead to mental disorders in the patient, which affects the quality of life of the patient and society as a whole. Allergic reactions are divided into four types. In short, type I allergies are caused by the production of IgE antibodies. Reactions usually manifest as immediate allergic reactions to food and pollen, drugs, insect stings, or as severe anaphylactic reactions in patients previously exposed to the allergen. In addition to IgE antibodies, the response is characterized by hyperactivity of mast cells, activation of CD4 helper T cells (Th2), and recruitment of eosinophils. Type II allergic reactions are cytotoxic reactions involving specific IgM and IgG antibodies directed against certain body tissues that cause cell destruction in these tissues (for example, the end result of these reactions is phagocytosis, i.e., activation of killer cells by light). due to complement, activation of the complement system leads to opsonization, erythrocyte aggregation, lysis, and cell death. Activated neutrophils and myeloma play an important role in vascular damage in various tissues, especially in the kidneys, heart, arteries, and joints [26].

The unified model of asthma has now been replaced by a much more complex biological network of separate and interrelated inflammatory processes. The term "asthma" is now considered a collective diagnosis of several diseases with different mechanistic pathways (endotypes) and different clinical manifestations (phenotypes). Accurate identification of these endogens is essential for the treatment of asthma due to their inherent therapeutic and prognostic significance. This review describes the molecular mechanisms underlying the heterogeneity of airway inflammation in asthmatics. Asthma subtypes can be divided into type 2 (T2) high or low T2. Many biologics have been approved for the treatment of high T2 asthma, along with many other therapies that similarly activate and target specific molecular mechanisms. Together, these developments have changed the current asthma management paradigm to include new treatments [27].

The recent identification of key inflammatory markers has provided a more comprehensive approach to the study of asthma. The focus is on identifying precise pathogenic molecular

signaling pathways (endotypes). The theoretical basis of the final standardization corresponds to the current interest in personalized medicine. With the advent of an ever-expanding repertoire of biologics, an appropriate classification system with meaningful biomarkers is needed to leverage molecular data and make individualized treatment decisions. Thus, inflammatory endotype stratification is now considered a key component in the treatment of severe asthma [28].

Biologically active substances that increase immunity and have an antioxidant effect are, first of all, all vitamins, especially the class of antioxidants (vitamin C, carotene, vitamin E), vitamins from group B, as well as phenolic compounds with vitamin P and antioxidants. activity. (Catechins, flavanols, anthocyanins, hydroxycinnamic acids, etc.), polyphenols (tannins), minerals (especially selenium, zinc, iron, iodine, potassium, calcium, etc.), chlorophyll (a and b), terpenoids, essential oils, resins, glycosides with adaptive effects, polyunsaturated fatty acids, essential amino acids (especially sulfuric acids), whole proteins, fillers (fibre, pectin, inulin), fermented foods, etc. The vehicles of these substances are mainly plant products (fruits, berries, vegetables), berries, medical and technical botanical products, natural spices, algae, and flower pollen. In this chapter, we will discuss in sufficient detail almost all groups of these substances and their content in plant materials and foods, their therapeutic and preventive effects and their role in a healthy diet [29].

Biologically active food supplements ("Geomin", "Fitomin", "Geomin Forte") can be used in conjunction with traditional medicines for the treatment, rehabilitation and prevention of diseases caused by various factors. According to the pharmacological results, we note here that various clinoptilolites ("Geomin", "Fitomin", "Geomin Forte") are used in complex antioxidant therapy, and the beneficial effect is due to the powerful absorption properties of their preparations. It is known that zeolites are porous minerals with high absorption and ion exchange capacity. Its molecular structure is a dense network of AlO_4 and SiO_4 forming cavities into which water and other polar molecules or ions can enter/exchange. Although there are various types of synthetic or natural zeolites, the most commonly used and studied natural zeolite is clinoptilolite (ZC). ZC is an excellent detoxifying, antioxidant, and anti-inflammatory agent [30].

Selenium provides antioxidant protection and slows down aging. Selenium improves mobility and regulates thyroid function. Selenium-rich beef and pork liver and kidneys, fish and plant products - wheat bran, wheat seeds, legumes, sunflowers, nuts, corn, tomatoes, mushrooms, garlic and whole grain bread.

Lycopene is one of the most powerful carotenoids and has been shown to protect against breast, lung, endometrial and prostate cancer. Contains mainly tomatoes and tomato puree (1 tablespoon covers full daily dose).

Alpha Lipoic Acid is a general antioxidant that protects against oxidation and helps remove toxins from the body. Alpha lipoic acid may increase physical endurance. Alpha lipoic acid is also found in spinach, rice, and kale, as well as animal products containing animal acids: heart, liver, kidney, milk, eggs, and beef.

Green tea and cranberry extract contain a large number of polyphenols and flavonoids, very powerful natural antioxidants with a wide spectrum of action [31].

Lutein protects the retina by absorbing harmful UV rays. Lutein may reduce the risk of retinal degeneration, which is a cause of age-related blindness. Several large studies have shown that people who consume a lot of lutein have a lower risk of developing cataracts. Lutein is found in dark green leafy vegetables such as spinach, kale and broccoli, various fruits and breads. Carrots, zucchini and other vegetables containing orange and yellow pigments, as well as egg yolks, are



also sources of lutein. All of these foods are an important part of a healthy diet. However, it is difficult to get enough lutein daily from a regular diet, as most foods are very low in lutein. Therefore, an important source of lutein are specially prepared natural preparations - biologically active food supplements, standardized according to the content of this active food supplement [32].

In the fight against free radicals, many antioxidants are destroyed and become harmful to the body. Bioflavonoids, how to fix them, at least 4 bioflavonoid-rich foods per day: blueberries, onions, garlic and green tea. Proper and balanced nutrition, including fruits and vegetables in the daily diet, will help the body get the necessary number of antioxidants. Berries, fruits and vegetables are rich in antioxidants. Here is a list of the most useful: blueberries, raspberries, cherries, grapes, blackberries, plums, cherries, raisins, pomegranates, acai, black plums, oranges, raisins, beans, cabbage, beets, spinach, eggplant. Cocoa, green tea, olive oil and avocado also contain antioxidants [33].

Nature has hidden powerful antioxidants in bark and cockerel that can fight serious diseases that we often or always throw away without our knowledge. For example, apples, grapes, and other types of skins are best eaten mashed.

Fruits, vegetables and greens - natural antioxidants - an elixir of youth and health. An antioxidant is simply a molecule that prevents another molecule from being oxidized. Since many processes in the body lead to oxidation, an intake of antioxidants is necessary to counteract some of the negative effects of too many oxidized molecules in the body. Free radicals are unstable molecules that frantically search for lost electrons. Antioxidants satisfy the electronic needs of free radicals [34].

Vitamin C is the most abundant water-soluble antioxidant and vitamin E is one of the most abundant fat-soluble antioxidants. The main benefit of antioxidant-rich foods is that they prevent and prevent many types of cancer, as well as heart disease and other life-threatening diseases. If you want to know more, eating plenty of antioxidants can slow down aging.

Because antioxidants have been widely studied for their benefits, many pills have come on the market to meet consumer demand for these little cancer cures. However, the effectiveness and safety of these additives is questionable. There is no doubt that the best way to saturate your body with antioxidants is to eat raw fruits and vegetables and even some grains [35].

Antioxidants are substances that can prevent or delay cell damage caused by free radicals, unstable molecules produced by the body in response to environmental stress, exercise, breathing, and digestion. Antioxidants are molecules that fight free radicals in the human body. Free radicals are chemical compounds that can cause too much damage. They are associated with many diseases and can have a significant impact on health and quality of life. Antioxidants are found in foods, especially fruits, vegetables, and other plant foods. Some vitamins, such as vitamins E and C, are powerful antioxidants. Antioxidants also play an important role in food production by extending their shelf life. The human body constantly produces free radicals, and without antioxidants, free radicals can cause serious damage and even death very quickly. Free radicals also play important roles in health. For example, human immune cells use free radicals to fight infections, so the human body must maintain a certain balance between free radicals and antioxidants. When free radicals suppress antioxidants, they can cause a condition called oxidative stress. Long-term oxidative stress can damage DNA and other important molecules in the human body [36].

Antioxidants are essential for the survival of all organisms. The human body produces its own antioxidants. For example, glutathione is a cellular antioxidant. Plants and animals, like all other life forms, have their own defense mechanisms against free radicals and oxidative damage. Thus, antioxidants are found in all whole foods of plant and animal origin, and an adequate intake of antioxidants is important. In fact, human life depends on the intake of certain antioxidants, namely vitamins C and E.

Oxidation is a natural process. However, it can cause chain reactions that damage human cells. Vitamins, minerals, and enzymes called antioxidants can prevent these reactions. Antioxidants are considered an important part of a healthy diet that supports body systems, including connective tissue, respiratory, digestive, and cardiovascular systems. The best way to avoid deficiency is to get your daily dose of antioxidants from healthy plant foods like fruits and vegetables. However, you may need supplements to compensate for occasional oxidative stress (especially in elite athletes) or nutritional deficiencies [37].

Simply put, free radicals are highly reactive molecules that have a place for electrons and try to fill it by taking electrons from other molecules. Filling the free space makes it safe, but it has already done its "dirty" work. Having lost an electron, the molecule turns into a free radical and continues to fill the need for the missing electron. Free radical molecules are constantly formed in the human body due to a variety of redox processes that ensure the proper functioning of all organs and systems [38].

Under natural conditions, the number of free radicals is small and their pathological effect on the cells of the body is suppressed by antioxidants (when eating foods containing these substances). However, in case of metabolic disorders, under the influence of toxins, the protection of antioxidants weakens, the balance of the cell is disturbed, and the number of free radicals increases significantly [39].

High levels of free radicals are the starting point for many diseases, from the common cough to cancer. Violations appear in the body, inflammatory processes develop, atherosclerosis develops, the digestive system is disturbed, malignant tumors, heart disease, etc. appear. The human immune system plays an important role in the fight against free radicals. The appearance of signs of aging is associated with a decrease in immunity and the action of free radicals: weakness in the muscles and skeleton, loss of skin elasticity, decreased functioning of the senses - hearing and vision, as well as problems. various mental processes [40].

Free radicals constantly attack the cells of the body, and the cells actively resist this attack. But if the harmful molecule manages to penetrate the cell membrane and reach the DNA, it can cause irreversible changes leading to cancer. UV rays from the sun, polluted city streets, smoking, stress, and unhealthy diets (trans fats, processed foods, excess simple carbohydrates and proteins) activate free radicals that contribute to premature aging and reduced immunity. Antioxidants neutralize harmful free radicals and slow down aging. That is why it is so important to protect the body from free radicals [41].

All tocopherols and tocotrienols are powerful antioxidants that scavenge lipoperoxyl radicals. Until recently, most research on vitamin E has focused primarily on α T, as α T is the predominant tissue form of vitamin E, and low intake of this form causes immobility when deficient. in vitamin E. However, many human and animal studies of α T supplementation have shown disappointing results regarding its protective role in the prevention or treatment of chronic diseases, including cardiovascular disease and cancer. On the other hand, recent mechanistic studies, together with preclinical animal models, have shown that compared to α T, other forms of vitamin E appear to

have different and better biological properties that may be useful for prevention and treatment against chronic diseases. In addition, new evidence suggests that some long-chain vitamin E metabolites have even stronger anti-inflammatory effects than their parent vitamins. These metabolites may be novel anti-inflammatory agents and may contribute to the beneficial effects of vitamin E forms in vivo. Here, we review recent developments in non- α T forms of vitamin E with respect to their metabolism, antioxidant and anti-inflammatory properties [42].

All forms of vitamin E are powerful antioxidants that scavenge lipid peroxyl radicals by donating hydrogen from the phenolic group to the chromanol ring. Because they contain similar phenolic components, all forms of vitamin E are thought to have strong antioxidant effects. On the other hand, it has been suggested that tocotrienols are better than α T at scavenging oxygen radicals due to a more uniform distribution of tocotrienols in the phospholipid bilayer and are more efficient.

Propolis and its components are important for health protection, prevention and treatment of minor diseases. Propolis is an integral part of (bio)cosmetics and a natural antibiotic in the treatment of ear, nose and throat infections. The use of propolis is very wide and includes the food industry, medicine (as an immunomodulatory agent that heals wounds and burns), cosmetics and hygiene products. Despite the good properties of propolis, many studies have shown that it causes allergic reactions in people who are allergic to propolis components. Several experimental studies have shown varying degrees of response to propolis and its ingredients. Sensitivity to propolis has been demonstrated in European studies. Allergic reactions that have occurred: contact dermatitis, stomatitis, pharyngeal eczema, swelling of the lips, pain in the mouth, peeling of the lips and shortness of breath. Several allergens have been isolated from propolis, namely 3-methyl-2-butenyl caffeine, phenylethyl caffeine, benzyl caffeine, geranyl caffeine, benzyl alcohol, benzyl cinnamic acid, methyl cinnamic acid, ferulic acid, and tectoric acid. In addition, propolis appears to be one of the most common contact sensitizers and should be included in routine testing in children and adolescents prior to administration [43].

Chronic inflammation plays a key role in the onset and progression of chronic diseases such as diabetes, high blood pressure, cancer, allergies, and asthma. The diet can control various levels of inflammation because it is a rich source of antioxidants and bioactive compounds. Flavonoids are bioactive compounds found in various food groups such as vegetables, fruits, nuts, grains, and beverages. Recent work on flavonoids has revealed their ability to modulate or suppress inflammation. This is due to their anti-inflammatory, antioxidant, and immunomodulatory properties, making flavonoids an invaluable ingredient in foods, medicines, and medicines. However, the details of its anti-inflammatory action are still not well understood. This review is an attempt to clarify the chemical structure, dietary sources and anti-inflammatory properties of flavonoids in allergic diseases [44].

Propolis and its flavonoids are widely used in folk medicine as anti-inflammatory drugs and components of antifungal, antithrombotic, antiretroviral, antiallergic and anticancer drugs. Propolis has long been used in folk medicine. The anti-inflammatory effect of propolis is based on the inhibition of platelet aggregation, support for foot edema and arthritis in rats, the formation of eicosanoids, the production of cytokines and other important messengers to combat allergic diseases. Propolis is also known to have radiant properties. protects against damage to DNA by gamma and ultraviolet rays. For example, propolis protects the skin from many processes such as premature aging (wrinkles, flaking, dryness, capillary dilation and loss of collagen) and skin cancer. Particular attention should be paid to the therapeutic effect of propolis and its ability to induce the production of type I and III collagen and wound destruction. Propolis contains many

compounds that speed up the healing process of the skin, such as tensile strength and elasticity, and promote the growth, expansion, and migration of human keratinocytes. These biochemical properties and changes in propolis may promote re-epithelialization and thus promise wound healing. It is worth noting that the use of propolis as a wound healing dressing has led to its economical, safe and painless use to protect against infections. Helps improve the rate of wound healing and reduce the number of dressing changes during microhealing. sewing materials and more. In a recent return to nature, modern man is looking for natural products with healing properties, mainly from plants and bees, which tend to fight allergies and/or inflammation. Laboratory and clinical studies of propolis, its related phytochemicals, as well as flavonoids and other antioxidants, indicate their use in the prevention and treatment of many diseases, including allergies. This review summarizes current knowledge about the mechanisms involved in the formation of the sensitizing and/or inflammatory potential of the polyphenolic/flavonoid components present in propolis, their importance in the treatment of allergic diseases, and their allergenic properties [45].

Propolis is widely used in folk medicine as an antioxidant and anti-inflammatory agent. Propolis has attracted the interest of scientists in elucidating its biological properties and discovering new treatments for many diseases such as diabetes, cancer, bacterial infections, allergic rhinitis and wounds. Propolis inhibited platelet aggregation, the formation of eicosanoids and supported arthritis, and also had a strong anti-inflammatory effect. Beneficial effect of propolis treatment in a child with eosinophilic ulcers. Recently, some studies have shown that propolis has important antibacterial properties in the saliva of periodontitis patients, while diphenyl-4-hydroxycinnamic acid, 3-prenyl-4-dihydrocinnamic acid and 22-dimethyl-6-carboxylic acid have been confirmed. be the main antibiotic with the highest activity against bacteria. Propolis can reduce dentin hypersensitivity (acute, sudden pain caused by tactile, osmotic, thermal, or other stimuli to exposed dentin) by reducing fluid conductivity in dentin. In addition, there is sufficient evidence that propolis and plant flavonoids, depending on their structure, can inhibit secretory processes, mitogen synthesis and intercellular processes, including their possible effect on the expression and activity of the original molecules. In addition, flavonoids can influence gene expression, pro-inflammatory cytokines, and cell receptors. The antioxidant and radical action of propolis and flavonoids helps fight allergic reactions and inflammatory processes. Several studies have shown that flavonoids can inhibit mast cell degranulation and reduce the release of histamine, tryptase, IL-6 and IL-8 from cultured mast cells and macrophages. In addition, some flavonoids have the ability to release histamine, leukotrienes, prostaglandin D2, IL-4, IL-13 and GM-CSF from human mast cells and basophils in a concentration-dependent manner. All evidence to date suggests that flavonoids may have powerful anti-inflammatory and anti-allergic effects, especially in mast cell-mediated allergic inflammatory diseases such as allergic rhinitis, asthma, Alzheimer's, skin and gastrointestinal diseases [46].

Propolis and its compounds are effective against allergic diseases because many antioxidants inhibit the release of histamine from mast cells and basophils. Mast cells can be induced as long-lived cells by immunological or chemical methods. Mast cells and basophils expressing high-affinity IgE receptors play an important role in allergic inflammation by releasing chemical mediators such as histamine, heparin, serine proteases, cytokines, chemokines, prostaglandins, leukotrienes, and PAF. After IgE-mediated degranulation, mast cells can granulate, which is an important process in the development and duration of allergy [47].



Unlike the hypoallergenic properties of propolis described above, propolis does not interfere with the immune process of mast cell degranulation. Potential beneficial effects of propolis-based products as an adjuvant in patients with asthma. In particular, an ethanol solution of propolis showed better results than an aqueous solution in preventing mast cell degranulation. A possible explanation is that the ethanol solution contains a much higher content of flavonoids. These benefits may be related to the presence of caffeic acid (CA) derivatives such as caffeic acid phenethyl ester (CAPE) and other active ingredients in the extract. Propolis inhibited histamine release by a compound described as concanavalin A, suggesting an unknown flavonoid and anti-inflammatory compound. Propolis has shown an inhibitory effect on the activity of myeloperoxidase, ornithine decarboxylase, protein tyrosine kinase, NADPH oxidase, and hyaluronidase in guinea pig mast cells. This anti-inflammatory effect can be explained by the presence of active flavonoids and cinnamic acid derivatives such as acacetin, quercetin, naringenin and CA. An alcoholic extract of propolis (3, 10, 30, and 100 µg/mL) had no significant effect on the A23187 ionophore and ovalbumin-induced histamine release. Several authors have suggested that only high concentrations of propolis can directly activate mast cells, promoting the release of inflammatory mediators through cytotoxic mechanisms that may be associated with the allergic process in propolis-sensitive individuals [48].

Apparently, the anti-inflammatory properties of propolis may be due to the following mechanisms: (1) inhibition of the release of pro-inflammatory cytokines such as TNF- α and IL-1 β ; (2) increased production of pro-inflammatory cytokines such as IL-4 and IL-10; (3) prevent TLR4 activation; (4) suppression of LOX, COX-1 and COX-2 gene expression, (5) suppression of NF- κ B and AP-1 activity, and (6) reduction of monocyte and neutrophil infiltration [49].

CAPE, potent antioxidants, and NF- κ B inhibitors have been shown to alleviate asthma by modulating airway hyperresponsiveness through the ROS-responsive MAPK/Akt pathway. CAPE treatment reduced ROS levels in the airway microenvironment, reduced widespread inflammatory cell infiltration, and significantly inhibited foveal cell proliferation, collagen deposition, and fibrosis through secretion of jostaxin-1, TGF- β 1, TNF- α , IL-4, IL-13, monocytic chemotactic protein-1, IL-8, matrix metalloproteinase-9 and alpha-smooth muscle actin expression. As a marker of oxidative stress, malondialdehyde (MDA) and protein carbonyl (PC) production levels decreased significantly, while GSH levels increased after CAPE treatment in an animal model of allergic asthma. CAPE (free radical scavenger) prevents the release of oxidant-induced inflammatory mediators, airway smooth muscle contraction, and airway smooth muscle cell (ASMC) proliferation by reducing ROS levels. Caffeic acid phenethyl ester and other flavonoids, including quercetin and kaempferol, reduce airway inflammation and airway remodelling in chronic asthma by balancing the airway microenvironment. This effect was found to be related to a decrease in ROS levels since CAPE significantly reduces the phosphorylation of the Akt and MAPK pathways (caused by an increase in ROS) [50].

The activity of caffeic acid phenethyl ester was confirmed in a mouse model of systemic ovarian anaphylaxis (OVA). After challenge, all placebo-treated mice developed anaphylaxis, elevated plasma histamine and OVA-specific IgE, marked vascular leakage, NF- κ B activation, activating factor (PAF) production, and histological changes including pulmonary edema and hemorrhage. In contrast, CAPE-treated mice showed a decrease in plasma histamine and OVA-specific IgE, as well as inhibition of NF- κ B activation and PAF release. These results indicate that CAPE is effective in a model of systemic anaphylaxis, indicating that the hypoallergenic effect induced by CAPE may be due to its protective effect against IgE-mediated hypersensitivity. CAPE effectively

reduces monocyte and neutrophil infiltration and inhibits TLR activation by disrupting the interaction of the ligand (LPS) with the receptor complex (TLR4/MD2). CAPE affects several cellular oxidative processes: (1) inhibits myeloperoxidase (MPO) activity during PMN infiltration; (2) reduces respiratory rate in PMNL in humans; and (3) forms an oxide base in epidermal DNA isolated from treated mice in vivo. Inhibition of LOX and leukotriene production in peritoneal macrophages was also effectively inhibited by CAPE and CA. Its effect on LTC₄ was less pronounced in vivo. CAPE may have a protective effect against oxidative stress caused by experimental allergic encephalitis in rats. Therefore, as a selective inhibitor of NF- κ B activation and an inducer of apoptosis, CAPE may have multiple anti-inflammatory and immunosuppressive effects in various chronic diseases associated with oxidative stress and inflammation, such as allergic and autoimmune diseases [51].

Allergenic components isolated from Chinese and Brazilian propolis are kaempferol and chrysin. Chrysin and kaempferol act as antioxidants, stabilizing ROS and preventing allergic tissue damage. Chrysin and kaempferol inhibit IL-4, prevent eosinophil activation, and reduce the total number of eosinophils. In addition, kaempferol inhibits CD23 mRNA expression and prevents another marker of granulomatization in mast cells. Thus, the release of cytokines is reduced, which indirectly leads to a decrease in the number of eosinophils [52].

Other propolis compounds, including quercetin, an active bioflavonoid found in plants such as evening primrose petals, garlic, onion, and green tea, have shown strong anti-allergic effects. Quercetin is used clinically for a variety of conditions, including inhalant allergies, food allergies, Alzheimer's disease, chronic sinusitis, bronchitis, asthma, otitis media, and enteritis [53].

Quercetin inhibited basophilic antigen-induced ragweed histamine release at concentrations of 5-50 μ M (80-100% inhibition at 50 μ M) depending on the culture. Quercetin significantly inhibited antigen-induced and calcium-independent activation of basophils in the first phase of histamine release and inhibited the antigen-independent and calcium-dependent phases. Since quercetin does not affect the ability to release histamine after exposure to unstimulated cells, but inhibits it during or after antigen activation, it can be concluded that quercetin acts on the basophilic pathway, which is considered to be activated ("acting"), and leads to antigen activation. Quercetin then acts on the open calcium channels [54].

Quercetin is extremely safe in the treatment of allergic rhinitis. Quercetin has many other beneficial properties (antioxidant, anti-inflammatory, capillary-stabilizing, etc.). It is a strong inhibitor of degranulation of basophils and mast cells. In an immune response, basophils and mast cells sensitized by cell surface-bound IgE antibodies are largely degraded after repeated exposure to allergens. Degranulation requires the supply of energy and calcium (Ca²⁺) and leads to the simultaneous release of histamine, adenosine triphosphate and other mediators stored in the granules. During degranulation, mast cells use calcium-activated enzymes to assemble contractile microtubules that pull granules up to the cell membrane, where inflammatory contents leave the cell and trigger an allergic reaction. Quercetin prevents mast cell degranulation by preventing Ca²⁺ from entering the cell. Due to the activity of phospholipase A₂, additional inflammatory mediators, such as metabolites of arachidonic acid, are released outside the cell. Steroids are known to act as anti-inflammatory agents due to their ability to inhibit phospholipase A₂. Quercetin also inhibits several steps in the membrane eicosanoid pathway, including phospholipase A₂ and lipoxygenase. Several authors have confirmed that quercetin can: (1) inhibit mast cell degranulation; (2) reduces airway hyperreactivity; (3) reduces mucus and collagen production; (4) reduces the recruitment of eosinophils and neutrophils; (5) reduce



bronchial epithelial cell activation and expression of MMP-9 and MMP-12; (6) modulates the production of Th1/Th2 cytokines; (7) exhibits antifibrotic activity; (8) reduces collagen deposition by stimulating HO-1 activation; (9) reduces the production of IL-4, IL-5, CCL11 and LTB₄ and increases IL-4 and increases the concentration of IFN- γ ; (10) reduces the synthesis of type I and type III collagen; and (11) regulates P-selectin expression by inhibiting NF signaling. These effects may be associated with attenuation of PI3 kinase, Akt and NF- κ B signaling pathways. Quercetin, when combined with vitamin C, has been reported to reduce the symptoms of hay fever. Flavonoids have even been shown to inhibit enzymes that increase histamine release from mast cells and basophils: cAMP phosphodiesterase and calcium-dependent ATPase. Cyclic AMP phosphodiesterase cleaves cAMP; a large amount of cAMP blocks intracellular histamine stores. In addition, calcium-dependent ATPase breaks down ATP, releasing energy and promoting the release of Ca²⁺ from the cell membrane; High levels of intracellular Ca²⁺ also cause the release of histamine from storage granules. Quercetin has a high affinity for mast cells and basophils; stabilizes membranes, prevents the release of histamine, and may inhibit two enzymes that control the release of leukotrienes involved in the asthmatic response. By blocking the release of histamine and leukotrienes into the bloodstream, quercetin prevents allergy symptoms such as nasal swelling, nasal congestion, sneezing, watery eyes, and itchy eyes and nose [55].

The mechanism of the allergenic action of flavonoids, such as luteolin, quercetin and baicalein, which participate both in the IgE-mediated immune response and in the sensitization and action phase, is based on their structure and ability to inhibit: (1) hexosaminidase enzyme; as a key factor in reducing mast cell degranulation), phospholipase A₂ (PLA₂) and 5-lipoxygenase (5LO). (2) transport of ATPase for histamine secretion by rat mast cells. (3) human basophils stimulated by allergens; (4) Synthesis and secretion of cytokines IL-4, IL-13 and CD40 ligand (important for the differentiation of B-lymphocytes into IgE-producing cells), granulocyte-macrophage colony-stimulating factor, GM-CSF, interleukin (IL)-6 and tumors with necrosis factor (TNF)- α . At present, many of the mechanisms by which flavonoids inhibit histamine synthesis and release in response to high-affinity IgE receptor (Fc ϵ RI) cross-linking are unclear and require further investigation. According to many researchers, due to their antioxidant and anti-allergenic properties, flavonoids can inhibit the formation and release of many allergic mediators, including Th2-type cytokines (IL-4 and IL-13), as well as CD40 expression. an important ligand in many intercellular interactions. These cells (such as mast cells and basophils) express the immunoglobulin E (IgE) receptor with high affinity, leading to an increased inflammatory response. It turns out that to produce IgE, B cells need to receive two signals. the first signal comes from the cytokines IL-4 and IL-13, and the second comes when CD40L, which is induced on the surface of T cells after allergen exposure, binds to CD40 on the cell surface. is important for activation and induction of allele exchange in B cells. Reactive T cells, when encountering an allergen, express CD40L and can therefore target B cells, monocytes, DCs and epithelial cells using CD40. Polyphenol-flavonoid compounds control the Th1/Th2 balance and inhibit the formation of antigen-specific IgE antibodies by influencing the formation of allergic-IgE complexes and binding this complex to its receptor (Fc ϵ RI) on mast cells and basophils. In addition to Th2 cells, tannins isolated from apples can prevent food allergy by increasing the number of $\gamma\delta$ TCR T cells in intestinal epithelial lymphocytes [56].

It has been shown that the inhibitory effect of some flavonoids on mast cell degranulation results from the modulation of Ca²⁺ receptor channels in the cell membrane and β -exosaminidase as a marker of mast cell degranulation. For example, apigenin, luteolin, 3,6-dihydroxyflavones, fisetin,

kaempferol, quercetin and myricetin have been found to inhibit hexosaminidase release from mast cells with IC₅₀s less than 10 μ M, while quercetin, quercetin, scutellarin inhibit PLA₂ with IC₅₀s in the range 12.2 to 17.6 μ M. In addition, luteolin, apigenin and fisetin are the most potent inhibitors of IL-4 and IL-13 synthesis, while 3-hydroxyflavone, kaempferol, quercetin, eriodictyol, fustin and 7-hydroxyflavone also inhibit IL-4 production, but to a lesser degree. Classification. Classification. Sirsilol (3',4',5-trihydroxy-6,7-dimethoxyflavone) produced 97% inhibition of 5LO activity in rat basophils and 99% inhibition of cysteinyl leukotriene release from rat and guinea pig lungs. In particular, quercetin and kaempferol can inhibit IL-4 synthesis with an IC value of 15.7–18.8 μ M. Inhibitory effects of kaempferol on the biological activity of IL-5 and histamine release from basophils and mast cells. Hydroxylation of IL-4, 7 and 4' and the presence of OH at position 3 or 5 are required for maximal inhibition, whereas glycosylation at position 3 reduces activity [57].

By inhibiting IL-4 mediated signaling, flavonoids prevent differentiation of primary CD4⁺ T cells into effector T cells by inhibiting aryl hydrocarbon receptor (AhR) and NF- κ B activation. AhR is a ligand-activated transcription factor that mediates the toxic and biological effects of many aromatic environmental pollutants such as dioxin [58].

The antioxidant activity of flavonoids is mediated by nuclear factors/AhR in association with erythroid factor 2 (Nrf2) and results in increased activity of antioxidant enzymes such as peroxidase, glutathione peroxidase, catalase, peroxiredoxin, and heme oxygenase-1. By reducing oxidative stress, propolis and its flavonoids can inhibit the oligomeric nucleotide-binding domain, the leucine-rich repeat gene family, and the pyrine domain-containing inflammasome 3 (NLRP3) [59].

Propolis and its components such as CAPE, CA, quercetin and naringenin inhibit the formation of eicosanoids. Indeed, these compounds significantly inhibit the lipoxygenase pathway of arachidonic acid metabolism, with CARE being the most potent modulator. This CAPE activity may be associated with reduced N-terminal C-Jun kinase (JNK1/2) and NF- κ B activity, as well as reduced COX-2 expression [60].

Nobiletin, aminoflavon, quercetin, quercetin pentaacetate, flavone, resveratrol, apigenin, chrysin, kaempferol, galangin, and genistein have been shown to be non-selective inhibitors of COX-1 and COX-2. Hydroxylated but not methoxylated resveratrol analogues can be bound by enzymes. Thus, hydroxylated resveratrol analogs represent a new class of highly selective COX-2 inhibitors and promising candidates for in vivo testing. In addition, promising in vitro data have shown that treatment with specific COX-2 inhibitors such as curcumin, chlorogenic acid, CA, resveratrol, galangin, and the flavonoid silymarin may reduce the risk of Alzheimer's and Parkinson's disease and be of value in the treatment of asthma. and other allergic diseases [61].

The anti-inflammatory effects of flavonols (quercetin, rutin and morin) and flavanones (hesperetin and hesperidin) have been studied in animal models of acute and chronic inflammation. The anti-inflammatory potential of propolis and its flavonoids is attributed to several mechanisms, such as: (1) strong antioxidant activity and free radical scavenging, (2) regulation of inflammatory cell activity, (3) inhibition of arachidonic acid, a metabolic enzyme (phospholipase). A₂, COX, LOX) and nitric oxide synthase, (4) regulating the production of pro-inflammatory cytokines and mediators and (5) downregulating the expression of pro-inflammatory genes. It should be noted that the main flavonoid processes that determine anti-inflammatory activity consist of: (1) inhibition of pro-inflammatory enzymes (COX, LOX, and inducible NO synthase); 2) inhibition of NF- κ B transcription factors and activation of protein -1. (AP-1); (3) activation of phase II



detoxification enzymes by antioxidant factors including glutathione reductase, glutathione peroxidase, heme oxygenase, γ -glutamylcysteine synthetase, superoxide dismutase, and catalase; and (4) modulating signalling pathways such as protein kinase C, mitogen-activated protein kinase (MAPK), and erythrocyte nuclear factor-associated factor 2 (Nrf2), whose protein products are involved in detoxification and "elimination of reactive and electrophilic oxidants through functional conjugation reactions." and increase the oxidative capacity of cells, its action leads to inhibition of MCP-1 expression and adhesion of monocytes to endothelial cells, as well as migration and activation of p38 MAPK [62].

The document confirmed the anti-inflammatory effects of propolis and flavonoids such as quercetin, luteolin, anthocyanins, hyperin and alpinetin on the TLR4/NF- κ B/NLRP3 signalling pathway. it is based on interfering with several steps of NLRP3 inflammatory signaling in vitro and in vivo, reducing and/or inhibiting the expression of pro-inflammatory NLRP3 factors such as IL-1 β , IL-18, NLRP3 and caspase-1 β . Oligomerization with signalling molecules (eg, TLR4/NF- κ B/NLRP3, PPAR γ , TXNIP, and Syk/Pyk2. For example, EGCG reduces peritonitis by inhibiting NLRP3 expression and IL-1 β release in mice treated with NMSUL sodium urate crystals in NMSUL3 crystals) binds to a thioredoxin-interacting protein (TXNIP) in THP-1 cells, while quercetin inhibits NLRP3 expression and IL-1 β and caspase-1 activity in human colon epithelial cells [63].

The anti-inflammatory mechanism of resveratrol is based on its ability to remove ROS, inhibit COX, and activate several pro-inflammatory signaling pathways, including sirtuin-1 (Sirt1), which inhibits TLR4/NF signaling. κ B/STAT, which leads to a decrease in the production of cytotoxic and pro-inflammatory factors by passive immunity cells, macrophages and mast cells. Therefore, the addition of resveratrol to the human diet may be promising for the treatment of immune diseases, but only in the form of nanoparticles due to its rapid metabolism in the body [64].

Despite the low gut bioavailability of flavonoids and hence low effective plasma and target tissue concentrations, even low flavonoid concentrations appear to be sufficient to activate Keap1/Nrf2/ARE and Keap1/Nrf2/ARE NF- κ B signaling as main factor of health improvement system. The main mechanisms of anti-inflammatory action of flavonoids in the intestine are: (1) strong antioxidant properties and/or radical scavenging, (2) the effect of nitric oxide (NO) on metabolism, (3) inhibition of anti-inflammatory processes. effect, (4) inhibition of lipoxygenase and reduced production of leukotriene B4 (LTB4), (5) preservation of colonic absorption, and (6) influence of TLR and inflammation. Therefore, it is possible that propolis and its flavonoids are suitable compounds for limiting or even preventing the development of allergic/inflammatory reactions [65].

Cytokines, the main regulators of inflammation, are redundant and pleiotropic. different cytokines can act on the same receptor, and a cytokine can have multiple, even conflicting, effects. Cytokines have a specific effect on communication and communication between cells and regulate the strength and duration of inflammatory reactions [66].

Propolis and flavonoids have been shown to inhibit IL-10, IL-4 and IL-13. IL-4 and IL-10 inhibit IL-12 induced IFN- γ secretion. In addition, IL-10 counteracts many of the pro-inflammatory effects of TNF- α and IL-1 β , while IFN- γ can inhibit monocyte production of IL-4 and IL-10 [67]. Flavonoids can inhibit the expression of several pro-inflammatory cytokines/chemokines including TNF- α , IL-1 β , IL-6, IL-8 and monocyte chemotactic protein-1 in various cell types such as RAW macrophages, Jurkat in peripheral blood. T cells and mononuclear cells. Recently, CAPE

has been reported to have an inhibitory effect on the production of the pro-inflammatory cytokines IL-1 β , TNF- α , and monocyte chemotactic protein 1 (MCP-1) by lipopolysaccharide-stimulated RAW264.7 (LPS) macrophages. Macrophages are ubiquitous cells that secrete numerous potent biologically active inflammatory mediators, including growth factors, cytokines, proteolytic enzymes, proteoglycans, lipid mediators, and prostaglandins. They play a key role in all stages of the inflammatory process, including initiation, maintenance, and resolution. In addition, macrophages are important cells in the primary response to pathogens, maintaining tissue homeostasis, inflammation, and immunity. Macrophages, along with other types of inflammatory cells, provide a wide range of bioactive molecules that cause significant changes in inflammatory lesions through interaction with epithelial, mesenchymal and endothelial cells. For example, genistein, quercetin, luteolin, and luteolin-7-glycoside have been shown to inhibit the production of IL-6, IL-1 β , and TNF- α in human lipopolysaccharides such as macrophages, gastric epithelial cells, and osteoblasts, but only eriodictyol and hesperetin inhibited the release of TNF- α [68].

In addition to inhibiting cytokines, propolis and flavonoids can modulate chemokines including (1) CC or β -chemokines (MCP-1, MIP-1 α , RANTES and eotaxin) and (2) CXC or α -chemokines (IL-8, GRO). - α and neutrophil-activating peptide of epithelial origin (NEA-78). CC chemokines act primarily on lymphocytes, monocytes, basophils, and eosinophils, but not on neutrophils, while the cytokine IL-8 and other CXC chemokines act predominantly on neutrophils. IL-8 is produced by various tissues and blood cells, and its administration causes localized effusion and prolonged massive accumulation of neutrophils, which, when stimulated, release granular enzymes and large amounts of ROS. Since flavonoids have antioxidant and anti-inflammatory effects, they are important for the pharmacological control of ROS production. For example, flavonoids, which are Cycle B in the catechin group, have proven to be good inhibitors of the production of IL-1 β , IL-6, TNF- α , INF- γ , and IL-8 in whole blood assays. human, but less inhibited. measurement of IL-8 production. It is known that tumor necrosis factor-alpha (TNF-alpha) is present in the synovial fluid of patients with rheumatoid arthritis and induces the expression of pro-inflammatory cytokines in synovial cells. Since reactive oxygen species play an important role in mediating the effects of TNF- α , we investigated the effect of quercetin on TNF- α stimulated expression of IL-8 and chemokine protein-1 (MCP-1) in cultured human cells. body. synovial membranes. The authors demonstrated that quercetin inhibits TNF- α -dependent induction of IL-8 and MCP-1 expression by inhibiting NF- κ B activation. Quercetin is unique in its ability to inhibit TNF- α transcription by inhibiting JNK/SAPK phosphorylation and activation and thus AP-1 protein binding to DNA. However, quercetin and Ginkgo biloba extract (EGb 761) inhibited ERK 1/2 phosphorylation and the activity of p38 mitogen-activated protein kinases (MAPKs), which are important in the regulation of TNF- α mRNA transcription. Thus, dietary flavonoids play an important role in the regulation of the pro-inflammatory redox network from NF- κ B to MAPK by disrupting the redox network in immune cells[69].

NF- κ B is one of the most important transcription factors and regulates the transcription of over 400 genes, including the expression of inflammatory response genes. for example, cytokines such as IL-1 β , IL-6, TNF- α and IL-8, as well as COX-2. Inactivation of NF- κ B by flavonoids (daidzein, genistein, isorhamnetin, kaempferol, quercetin, naringenin, and pelargonidin) reduces pro-inflammatory cytokines, ROS production, and NF- κ B activation by LPS. Flavonoids inhibit the transcription of factors such as AP-1 or NF- κ B by modulating the PKC and MAPK signaling pathways. The main mechanism used by flavonoids (genistein, quercetin, galangin) to reduce the



inflammatory response is the inhibition of NF- κ B activation. In addition, daidzein, genistein, isorhamnetin, kaempferol, quercetin, naringenin, and pelargonidin have been reported to be inhibitors of LPS-NF- κ B activation. In addition, kaempferol inhibited ERK-1/2, p38 and JNK phosphorylation and NF- κ B IL-1 β activation in fibromyalgia. In the same study, kaempferol suppressed the production of COX-2, PGE₂, MMP-1 and MMP-3 [70].

In addition, flavonoids inhibit: (1) growth factors such as EGF, fibroblast growth factor, insulin-like growth factor 1, keratinocyte growth factor, hepatocytes, PDGF; and TGF- β , which generally promote cell proliferation and enhance inflammatory responses. (2) particulate filter; 3 - quinine; (4) trigger mask. (5) C-reactive protein. (6) serum amyloid A (7) vasoactive amines and (8) proteases [71].

It should be noted that some cytokines and growth factors use ROS as a second messenger, and ROS can be involved in many signaling pathways and processes, such as: B. cell growth or inhibition, mitogenesis, differentiation, apoptosis of certain cell types, impaired angiogenesis, immunosuppression, inhibition of cellular respiration, development of Treg and immature myeloid cells, etc.

Propolis and its flavonoid components have been shown to be effective in the treatment of atopic dermatitis, allergic rhinitis, asthma, atopic dermatitis and allergies in numerous in vitro clinical studies using various cell and animal models. disease. The anti-inflammatory and hypoallergenic effects are due to the inhibitory effect of propolis on cells and their mediators involved in the inflammatory process, including the activation of epithelial cells, mast cells, basophils and eosinophils and the release of various allergenic mediators and cytokines. . . The main benefits of propolis with anti-allergic properties are flavonoids such as quercetin, chrysin, kaempferol, galangin and pinocembrin, as well as cinnamic acid derivatives such as KARE and artemisin. Preclinical and clinical use of propolis as an adjuvant in the treatment of allergies. As a supplement or complementary treatment, propolis is safe and reduces various conditions such as asthma, atopic dermatitis, allergic rhinitis, and food allergies. The authors suggested that the hypoallergenic effect of propolis may not be observed in all samples of propolis due to different chemical composition. In addition, these data may stimulate further research on the possible protective effects of propolis and flavonoids in the prevention of allergic diseases and the isolation of propolis components that cause propolis allergy in a significant part of the population. Taking into account some epidemiological data and previous studies, propolis and its active ingredients may be one type of complementary and alternative medicine for the prevention and treatment of allergic diseases [72].

Using a new potent and selective arginase inhibitor (N ω -hydroxy-nor-L-arginine), we show that arginase inhibition reduces guinea pig airway reactivity in vitro by increasing NO production. In ex vivo studies using a guinea pig model of allergic asthma, we found that airway arginase activity increased after allergen exposure and induced AHR after the first asthmatic response, which induced neuronal cNOS rather than neuronal derivative NO due to decreased availability. L-Arginine. to the enzyme. In addition, we found evidence that post-delayed asthmatic response AHR is mediated by an arginase-induced decrease in L-arginine availability for iNOS, specifically a shift of the enzyme towards the NO isoform. All of these observations paved the way for the in vivo proof-of-concept study presented above. The role of arginase in airway remodeling suggests that arginase inhibition reduces airway smooth muscle hyperplasia, airway fibrosis, mucosal hyperplasia, and goblet cell hyperplasia after repeated allergen exposure [73].

There is growing evidence of an important role for arginase in patients with asthma. Arginase 1 expression and arginase and/or arginase activity are elevated in the airways and serum of asthmatic patients, and there is a correlation between arginase expression in bronchial brushes, serum arginase activity, plasma concentrations of L-arginine and its metabolites, and disease severity. lung function) and Fe (NO). In addition, ARG1 and ARG2 polymorphisms are associated with asthma, asthma severity (pulmonary function, AHR), and decreased response to β 2-agonists and glucocorticoids. In addition, recently there has been an increase in the expression of arginase 1 and 2 in the nasal mucosa and the activity of arginase in the blood serum [74].

Considered alternative medicine, herbal medicine is one of the complementary methods using natural extracts as medicines or treatments. In recent years, much attention has been paid to natural products in disease prevention due to their many health benefits and remarkable lack of toxicity and side effects. Many plant foods, such as grains, nuts, cereals, soybeans, spices, flaxseeds, fruits, vegetables, medicinal plants, and herbs, contain various phytochemicals such as phenols, carotenoids, alkaloids, nitrogen and organosulfur compounds, and vitamins.

Recent in vivo and in vitro studies have demonstrated the potential anti-inflammatory role of some known natural antioxidants. Combinations of natural antioxidants provide various mechanisms to reduce tissue oxygen metabolites, modulate signaling pathways, and regulate transcription factors, and may play a key role in reducing species-dependent reactive oxygen species (ROS) damage. Many bioactive plant compounds, including several polyphenols, have recently been tested for vascular disease [75].

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory airway diseases characterized by bronchial hyperreactivity and airflow limitation with acute bronchospasm, airway inflammation, chronic mucositis, and airway wall remodeling. Significant evidence suggests that oxidative stress, one of the causes of asthma, acts as a central event in the inflammatory response by activating transcription factors such as nuclear factor-kB (NF-kB) and protein-1 (AP-one). mediators of pro-inflammatory gene expression. Thus, bioavailable antioxidants can protect against the direct harmful effects of oxidants and fundamentally alter inflammation in the pathogenesis of various respiratory diseases [76].

The lungs have several natural antioxidant mechanisms to counteract the overproduction of oxidants (ROS, reactive nitrogen species, and lipid peroxides), including enzymatic and non-enzymatic antioxidants. These antioxidant defense systems form a tightly regulated network that resists any changes in the redox environment of the intracellular and extracellular spaces. Enzymatic antioxidants include catalase, glutathione peroxidase (GPX), and superoxide dismutase (SOD), while non-enzymatic antioxidants include vitamin C, vitamin E, albumin, uric acid, ceruloplasmin, and glutathione (GSH). Changes in these enzymatic and non-enzymatic antioxidants can alter ROS homeostasis in bronchial cells [77].

Deficits in intrinsic antioxidant defense have been reported in asthma. Devereux and colleagues hypothesized that people in Western societies gradually reduce their intake of fruits and vegetables, thereby reducing the antioxidant defenses of the lungs, making them more sensitive to inhaled irritants and allergens. Since many antioxidants are obtained from food, particular attention is being paid to the availability of antioxidants (vitamins A, C and E, polyphenols and carotenoids) and how they can help protect people suffering from dementia, oxidative stress and/or airway inflammation [78].

Plants have two main mechanisms for detoxifying harmful oxidants. One of them is the direct enzymatic cleavage of oxidative radicals using SOD, catalase, ascorbate peroxidase, peroxidase,



glutathione reductase, and monodehydroascorbate reductase. These enzyme systems convert various oxidative radicals into reduced products. The second method is to create antioxidant molecules such as vitamin C and vitamin E. These antioxidant compounds have a hydroxyl group (-OH) in an electron-deficient ring structure that is highly sensitive to ROS [79].

Of the more than 8,000 compounds described, flavonoids represent the largest group of polyphenolic secondary metabolites of low molecular weight plant polyphenols. They are found in fruits, vegetables, nuts, seeds, stems, flowers, roots, tea, wine and coffee and are common ingredients in the daily diet. The structure is a heterocyclic hydrocarbon, chroman, and replacement of the C ring in position 2 or 3 with a phenyl group (ring B) gives a flavan or isoflavan. The oxo group at position 4 leads to flavanones and isoflavones. The presence of a double bond between C2 and C3 gives flavones and isoflavones. An additional double bond between C1 and C2 gives these anthocyanidin compounds their color. According to their structure, flavonoids are divided into eight groups: flavans, flavanones, isoflavones, flavones, isoflavones, anthocyanidins, chalcones and flavonolignans [80].

Flavonoids prevent the oxidation of lipids and other molecules by rapidly donating hydrogen atoms to ROO• radicals. This ability of the flavonoid molecule to donate hydrogen (electrons), which serves to remove reactive radicals, is mainly due to the presence of a catechin group on the B ring (dihydroxy-B ring). An important structural feature that partially determines the antioxidant properties of flavonoids is the presence of a 2,3-unsaturated bond conjugated with the 4-oxo group in the C₆H₂O₂ cyclic catalyst. Intermediate phenoxy radicals are relatively stable, so they do not initiate other radical reactions and act as chain termination when interacting with other free radicals. Due to their favorable reducing potential compared to alkyl peroxy radicals, flavonoids are ideal scavengers of peroxy radicals and therefore effective inhibitors of lipid peroxidation. Therefore, this strong antioxidant property of flavonoids makes them protective against respiratory diseases caused by oxidative stress. Some epidemiological evidence even suggests a beneficial effect of flavonoids on asthma. In a population-based case-control study, consumption of apples or red wine was found to be negatively associated with asthma incidence and severity, respectively, probably due to the protective effects of flavonoids. In addition, a 30-year longitudinal epidemiological study found that the prevalence of asthma is lower in a population with a high intake of flavonoids [81].

In addition to their antioxidant activity, flavonoids inhibit the release of histamine and other mediators associated with preformed granules by inhibiting basophil and mast cell activation. Flavonoids also inhibit the formation of IL-4, IL-13 and CD40 ligands, but trigger the formation of new mediators of phospholipid origin. As one of the well-studied flavonoids, quercetin inhibits eosinophil secretion of crystalline Charcot-Leiden protein and eosinophil cationic protein in a concentration-dependent manner. In addition, the inhibitory effect of quercetin on other inflammatory cells appears to be greater than that of any other clinically available compound. Apigenin exhibits anti-inflammatory effects in mouse models of asthma and can shift the immune response to allergens towards T helper type 1 (Th1). These results suggest that flavonoids are effective antiallergic and anti-inflammatory agents in the treatment/prevention of asthma [82].

Vascular damage is one of the main factors in the pathogenesis of bronchial asthma. Changes include increased vascular permeability, vasodilation/edema, and angiogenesis/angiogenesis. Flavonoids and related compounds have been shown to modulate the expression of HIF-1, VEGF, matrix metalloproteinases (MMPs), and epidermal growth factor receptors, as well as inhibit NF-κB, PI3K/Akt and ERK1/2. These observations suggest that flavonoids and related compounds

inhibit several steps of angiogenesis, namely cell migration, microcapillary formation, and MMP expression [83].

The active ingredient in turmeric is curcumin, a polyphenolic plant substance with anti-inflammatory, anti-amyloid, antiseptic, anti-cancer, anti-allergic, and antioxidant properties. In addition to its use in cooking, curcumin has been used as a folk remedy for liver disorders (especially jaundice), indigestion, urinary tract disorders, blood cleansers, arthritis (rheumatism), insect bites, skin disorders, and atherosclerosis. Curcumin has been shown to be eight times more effective than vitamin E in preventing lipid peroxidation. Curcumin is also believed to play a role in reducing oxidative stress by inhibiting the formation of nitric oxide (NO), scavenging or neutralizing free radicals, especially superoxide anions, and inhibiting free radical-induced oxidative chain reactions [84].

Curcumin is considered an anti-inflammatory agent, but its exact mechanism of action is largely unknown. However, studies have shown that curcumin reduces the level of IFN- γ -induced NO synthase in lung tissue and the expression of cytokines such as IL-2, IL-5 and GM-CSF, acts as an HDAC activator, or inhibits histamine. publish. mast cells. This activation of curcumin reduces asthma phenotypes by reducing asthma symptoms, airway eosinophil recruitment, and airway hyperresponsiveness. These results suggest that curcumin may be useful as an adjunctive treatment for asthma [85].

Resveratrol is able to clear intracellular ROS by stimulating and stabilizing antioxidant enzymes such as catalase, SOD, glutathione peroxidase, and heme oxygenase. In addition to its anti-inflammatory properties, resveratrol has been shown to reduce inflammation through prostaglandin production and inhibition of ERK1/2 phosphorylation, cyclooxygenase-2 activity, and the activity of several transcription factors, including NF- κ B, STAT3, HIF-1 α and also reduces the level of β -catenin. Resveratrol is also known to inhibit protein kinases (eg src, PI3K, JNK and Akt) and the production of inflammatory mediators (eg IFN- γ , TNF, COX-2, iNOS, CRP and some interleukins). Resveratrol activates sirtuin-1 (SIRT1), which is associated with apoptosis and longevity. SIRT1 regulates the activity of poly (ADP-ribose) polymerase-1 (PARP-1) after DNA damage. Activation of SIRT1 by resveratrol leads to a decrease in PARP-1 activity and promotes cell survival, which may mitigate the inflammatory response [86].

Resveratrol is also able to modulate the innate immune response by inhibiting the expression of short molecules (CD80 and CD86) and major histocompatibility complex class I and II in bone marrow dendritic cells and by inhibiting the cell-mediated pathway of angiogenesis. VEGF, cathepsin D, ICAM-1 and E-selectin. These results suggest that resveratrol could be a very interesting compound for the prevention/treatment of asthma, as this compound has multiple therapeutic effects and has antioxidant, anti-inflammatory, immunosuppressive, and anti-angiogenic properties [87].

Total vitamin A is made up of preformed vitamin A (retinol) and provitamin A compounds called carotenoids, of which beta-carotene is the most important. Carotenoids are pigments found in plants and microorganisms. Several studies have shown that carotenoids can prevent or suppress certain types of cancer, atherosclerosis, immune system disorders, asthma, and other diseases. The antioxidant activity of carotenoids is mainly due to the ability of the conjugated double bond structure to remove unpaired electrons. Below this value, the singlet oxygen of β -carotene is inactive without degradation and reacts with free radicals such as peroxy, hydroxyl and peroxide radicals. This process prevents chain reactions that can lead to lipid peroxidation or DNA damage, which are considered precursors of pathological processes [88].



The role of carotenoids in asthma is limited. Judging by the results of a review of the literature, carotenoids, especially β -carotene, exhibit a dual behavior depending on many factors. They exhibit antioxidant behavior at low oxygen partial pressures, typically below 150 Torr, but at high oxygen pressures they can lose their antioxidant properties or even become pro-oxidants. The concentration of carotenoids similarly affects its antioxidant/pro-oxidant properties. At high concentrations of carotenoids, oxidative activity is manifested. In patients with bronchial asthma, compared with healthy individuals in whole blood, a decrease in the total content of carotenoids (lycopene, lutein, β -cryptoxanthin, α -carotene and β -carotene) was observed. In addition, vitamin A deficiency causes changes in the respiratory epithelium, such as metaplasia, and can cause respiratory infections that can exacerbate acute asthma attacks in children [89].

Lactic acid bacteria (LAB) are the main representatives of probiotics in the food and pharmaceutical market. INNs have been reported to have a beneficial effect on the treatment and maintenance of ulcerative colitis (UC). They have also been associated with improved metabolic disease. In addition, *Lactobacillus rhamnosus* and/or *Lactobacillus lactis* in fish played a positive role in improving the growth, immune system and oxidative status of sea bass. Probiotic bifidobacteria are also very commonly used as probiotic bacteria. It was able to boost immunity against cancer and relieve intestinal inflammation in women. *Bacillus* species are preferred in the feed industry due to their stability as spore-forming bacteria and their ability to produce various enzymes such as protease, amylase and lipase. Intestinal flora and mucosal immunity of fish can be developed with *Bacillus*, and mucosal immunity of chickens can also be enhanced by *Bacillus* treatment [90].

In addition to the positive results mentioned above, many discoveries made in recent decades have shed new light on the understanding of the antioxidant capacity of probiotics. Culture supernatants, intact cells, and intracellular extracts of cell-free bifidobacteria have been shown to remove hydroxyl radicals and superoxide anions in vitro, thereby increasing the antioxidant activity of mice in vivo. In addition, oxidative stress can be reduced in type 2 diabetic patients with various types of probiotics. LAB staining has been extensively studied in animals and humans. LABs have been shown to be resistant to ROS, including superoxide protons, superoxide anions, and hydroxyl radicals. Rats fed a high-fat diet with *Lactobacillus plantarum* P-8 showed increased antioxidant capacity, resulting in reduced liver fat accumulation and protection of healthy liver function. In humans, *Lactobacillus rhamnosus* exhibits a strong antioxidant effect under conditions of increased physical exertion. Athletes exposed to oxidative stress may benefit from the ability of *Lactobacillus rhamnosus* to increase antioxidant levels and scavenge reactive oxygen species [91].

Probiotics can produce several antioxidant metabolites such as glutathione (GSH), butyrate, and folic acid. Folic acid is a vitamin that accepts monocarbon units from donor molecules and is involved in many metabolic processes. The efficiency of DNA replication, repair, and methylation is affected by the availability of folic acid. Because of their potential antioxidant properties, the ability of various probiotic strains from various sources to produce folic acid has been extensively studied. Folate-producing bifidobacteria have been shown to improve folic acid status in mice and humans. In addition, the intracellular folic acid extract produced by the probiotic *Lactobacillus helveticus* CD6 has been shown to have antioxidant capacity as well as intact cells. GSH, the major non-enzymatic cellular antioxidant, scavenges radicals such as hydrogen peroxide, hydroxyl radicals, and peroxynitrite primarily through interaction with selenium-dependent glutathione peroxidase. Two antioxidant strains of *Lactobacillus fermentum*, E-3 and E-18,

contain significant amounts of GSH. In addition, his research team discovered for the first time that *Lactobacillus fermentum* ME-3 contains a complete GSH system. Butyrate is a short chain fatty acid (SCFA) produced by the microflora of the large and peripheral small intestine from resistant starch, dietary fiber and indigestible polysaccharides. The *Clostridium butyricum* MIYAIRI 588 strain is a butyrate-producing probiotic. It has recently been shown to exhibit antioxidant activity to suppress oxidative stress in the liver in rats with non-alcoholic fatty liver disease [92].

Host antioxidant metabolite levels can also be regulated by probiotic treatment. Folic acid and vitamin B12 deficiencies contribute to oxidative stress in adults with type 2 diabetes. Daily consumption of *Lactobacillus acidophilus* La1 yogurt significantly improved mean plasma folic acid and vitamin B12 levels in children of study age compared to their B12 levels. improve the degree of oxidation. Vitamin B1 can protect cells and animals from oxidative stress. In healthy young women, daily consumption of 200 g of probiotic yogurt and plain yogurt for two weeks resulted in an increase in total vitamin B1 intake, resulting in an increase in plasma thiamine levels. In addition, GSH concentration and GSH synthesis were also increased in rats treated with probiotics to reduce oxidative stress during experimental acute pancreatitis [93].

Carotenoids can regulate the activation of various transcription factors. Treatment of oxidative stressed cells with β -carotene suppresses NF- κ B activation and production of IL-6, TNF- α , and pro-inflammatory cytokines induced by oxidative stress. Carotenoids can influence the process of cell death in healthy cells. While the pro-apoptotic protein Bax is downregulated upon stimulation with external stimuli, β -carotene can upregulate the expression of the anti-apoptotic protein Bcl-2 in normal cells. In addition, β -carotene has a pro-apoptotic effect on colon cancer and leukemia cells, and these effects are achieved through a repair mechanism associated with NF- κ B activity. Lycopene has also been shown to regulate transcription factors. Lycopene-treated breast cancer cells have been shown to inhibit AP-1 binding and reduce insulin-like growth factor I. This dual role of vitamin A, including carotenoids, in apoptosis allows carotenoids to be used as powerful anti-inflammatory agents. inflammatory factors in various diseases [94].

α -lipoic acid (LA), an organosulfur compound derived from octanoic acid, is a naturally occurring compound also known as thioacid. LA is readily absorbed from food and rapidly converted to the reduced form of dithiol, dihydrolipoic acid (DHLA). LA and DHLA are powerful antioxidants. Most of the LA in food is processed by lipoamide-containing enzymes and is associated with the amino acid lysine (lipopolisin). Plant sources rich in lipolysin include spinach, broccoli, and tomatoes. LA is a non-vitamin nutrient essential for life. It is not classified as a vitamin because it is produced in the body. It is often involved in the oxidative decarboxylation of keto acids and has been shown to be a growth factor in some organisms. While LA is involved in cellular energy production, its primary role as a dietary supplement may be as a powerful antioxidant. Unlike other antioxidants, LA is soluble in fats and water, easily absorbed and transported through cell membranes. LA directly quenches reactive oxygen species, regenerates/recycles endogenous and exogenous antioxidants such as vitamins C and E and GSH, removes redox metals including Cu (II) and Fe(II), restores oxidized proteins and regulates the activity of transcription factors, those. like NF- κ B and LA have the ability to regenerate other antioxidants such as vitamin C, vitamin E and GSH for later use after free radical scavenging [95].

Asthma is characterized by persistent inflammation and is associated with increased oxidative stress and subsequent lung damage. Endogenous or exogenous ROS production is required for the asthmatic inflammatory response. Although there are endogenous antioxidant mechanisms that

counteract the ROS-induced inflammatory response, in inflammation, there is an imbalance of two opposing mechanisms. Modifying these phenomena by increasing antioxidant levels opens up unique possibilities for therapeutic strategies for disease prevention, inflammation suppression, or inhibition of airway remodelling. However, the cellular and molecular mechanisms of these compounds are still undergoing significant improvements. In addition to their antioxidant activity, plant antioxidants have anti-inflammatory effects by regulating various inflammatory cells and mediators, protecting vessels, and acting as a gatekeeper in various signaling pathways. Natural biological compounds can be used alone or in combination with other available anti-inflammatory drugs, which can reduce costs and/or reduce side effects. It remains an open question whether these data are sufficient for the consequences of human diseases since the action of naturally occurring biological compounds is chronic and depends on bioavailability and metabolism at relatively low concentrations [96-97].

Conclusions

Reactive oxygen species (ROS) are produced by living organisms as a result of normal cellular metabolism. At low to moderate concentrations, they are involved in normal cellular processes, but at high concentrations, they cause harmful changes in cellular components such as lipids, proteins, and DNA. The shift in the balance of oxidants/antioxidants in favour of oxidants is called oxidative stress. Oxidative stress contributes to the development of many pathological conditions, including cancer, neurodegenerative diseases, atherosclerosis, hypertension, ischemia/reperfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, COPD, and asthma. Aerobic organisms have built-in antioxidant systems, including enzymatic and non-enzymatic antioxidants, which are generally effective in preventing the harmful effects of ROS. However, under pathological conditions, antioxidant systems can be overloaded. In this review, we summarize the cellular mechanisms of oxidants and antioxidants, as well as redox and redox regulation in health and disease.

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THE KEY ISSUES PROSPECTS, PROGNOSIS, ACHIEVEMENTS, PERCEPTION, CHALLENGES AND ASPIRATIONS OF ARTIFICIAL INTELLECT SERVICES IN MEDICINE, PHARMACEUTICS AND PUBLIC HEALTH

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ABSTRACT

The aim of the study was to examine and analyze the prospects for the use of artificial intelligence in pharmacy, medicine and health services. Digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in recent years has led to exciting new areas of digital health, including mobile health applications. and wearable technologies. Telehealth and telemedicine, artificial intelligence, advanced robotics and genomics. Digital health also includes other digital health uses such as the Internet of Things, advanced computing, and big data analytics. While they can provide significant benefits, there are also risks, especially in terms of health disparities, data privacy, and the limitations of artificial intelligence. Digital health is a broad term and its definition will change as new medical technologies emerge.

While digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in recent years has led to exciting new areas of digital health, including mobile health applications. and wearable technologies. Telehealth and telemedicine, artificial intelligence, advanced robotics and genomics. Digital health also includes other digital health uses such as the internet of things, advanced computing, and big data analytics. While they can provide significant benefits, there are also risks, especially in terms of health disparities, data privacy, and the limitations of artificial intelligence. Digital health is a broad term and its definition will change as new medical technologies emerge.

Digital health is largely shaped by experts outside the health sector and offers the opportunity for cross-disciplinary collaboration to lay the foundation for digital health education. Pharmacy and pharma-scientist education must be needs-based in order to meet the current and ever-changing demands of digital health. These requirements should reflect the needs of all members of all industries and career levels in pharmacy and pharmaceutical sciences, from clinical pharmacists to drug discovery. digital medicine. Currently, the digital medical system contains four main components: an inert sensor embedded in an inert tablet, a patient-worn non-drug (patch) sensor, a mobile application, and a web-based control panel. Upon interaction with gastric juice, the recorded sensor is activated and connected to a wearable sensor which sends a signal to a mobile device where it can be viewed by patients or later by healthcare professionals and caregivers via secure mobile and cloud applications. The vast amount of medical data enables more use of artificial intelligence and machine learning in pharmaceutical practices to solve important questions related to drug management and administration. Analyzing trends in large data sets can reveal individual risks of adverse events, behavioural issues, compliance patterns, and more. A

pharmacist is a professional expert who can complement the expertise of a data scientist to create services. Understanding the terminology and concepts used in artificial intelligence will help pharmacists interact with data scientists and collaborate constructively to develop models that improve patient care. Digital health systems can also empower and engage patients, making them co-creators of care. Shared decision-making between healthcare professionals and patients requires trust, partnership and transparency in mutual relationships. Healthcare professionals become companions in the patient's journey to health, while demonstrating empathy and humanity to support the patient well-being.

Software based on BR. It can also record other behavioural and physiological parameters such as physical activity, heart rate, skin temperature, sleep, and digital therapy. Aspiring pharmacists, pharmaceutical scientists and healthcare professionals. Students are getting more and more involved in the era of digital transformation. Their participation in digital health education processes is an important opportunity as they support the adoption and promotion of these digital health technologies. Several studies have been conducted to understand the digital health skills, knowledge, and competencies of pharmacy students. With much of the research being conducted in countries like the US, UK, and Australia, the global state of digital health in pharmacy schools is not fully understood.

Keywords: Perspectives, artificial intellect, service, pharmacy, medicine, public health.

Introduction

The term "telemedicine" was introduced in the 1960s and has extended to all forms of communications technology to provide public health care and education in rural and remote areas, as well as to train students in telepharmacy. The International Federation of Pharmacists defines telemedicine as "the use of information and. Communications Technology (ICT) Delivery Telepharmacy is a relatively recent development in the healthcare sector, enabling the delivery of quality pharmaceutical services in rural and remote areas. It drew a lot of attention during the COVID-19 pandemic. Digital health technologies save lives, improve health and well-being, expand access to health care and help build effective health systems and healthy populations. As healthcare challenges increase and the population ages, digital health may be key to addressing many unmet healthcare and service needs [1-3].

Digital health is a key priority for public policies and health organizations involved in implementing digital health and improving digital literacy standards. The World Economic Forum pointed out that "few sectors have the potential for such profound digital transformation as healthcare [4-5].

Recent technological advances have revolutionized clinical practice from disease prevention to diagnosis, monitoring and treatment, generating unprecedented public interest and commitment to self-care and health [6-7].

The COVID-19 pandemic has accelerated digital health. Industries like healthcare have the potential to be profoundly transformed by digital technologies. Recent technological advances have revolutionized clinical practice from disease prevention to diagnosis, monitoring and treatment, generating unprecedented public interest and commitment to self-care and health. The COVID-19 pandemic has accelerated the transformation of digital healthcare, which will impact healthcare services in the long term. Important lessons can be learned from this digital transformation of healthcare [8-10].

Many digital health technologies are highly dependent on healthcare professionals understanding and using them appropriately. There is a clear need for increased attention, concerted action and investment in education, training and skills development to ensure healthcare professionals understand and use digital health to achieve the intended benefits. Universities and educational institutions offer digital medical education, with most programs focusing on certification models. There is a lack of digital medical education and training, and a nationally or professionally oriented initiative could be an impetus for inclusion in education [11-12].

The profession of pharmacist is historically linked to information technologies. Therefore, he has the ideal skills and abilities to offer patients more digital health services. Realizing the full potential of digital health requires a pharmaceutical workforce that is confident, capable, agile and digitally savvy. Pharmaceutical staff can only keep pace with the digital transformation of the healthcare system with better training and further education [13-14].

Digital health is largely shaped by experts outside the health sector, providing opportunities for interdisciplinary collaboration to develop the foundations of digital medical education. Education in pharmacy and pharmaceutical sciences must be needs-based to meet the current and changing demands of digital health. These requirements should reflect the needs of all members in all sectors and career levels of pharmacy and pharmaceutical science, from clinical pharmacist to drug discovery [15-16].

Aspiring pharmacists, pharmaceutical researchers and healthcare professionals. Students are most involved in the era of digital transformation. Their participation in digital health education processes is an important opportunity as they support the adoption and promotion of these digital health technologies. Several studies have been conducted to understand the knowledge, skills, and competencies of pharmacy students in digital health. Since most research is conducted in countries such as the US, UK and Australia, the global state of digital health in pharmacy schools is not fully understood [17-18].

Aim of the research was to study and analyze the perspectives of artificial intellect in service of pharmacy, medicine and public health.

Methodology

The main question of this article was to research and analyses the perspectives of artificial intellect in service of pharmacy, medicine and public health. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Reuters and Google Scholar mostly, using search terms bases, including the words to research and analyses the perspectives of artificial intellect in service of pharmacy, medicine and public health. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming at easy understanding of the public. To establish these outcomes, over two hundred articles were investigated. We brought together all published data to comprehensively examine the effects in a systematic review, to define the roll out of the study of the research and analyses of the perspectives of artificial intellect in service of pharmacy, medicine, and public health.

Results and discussion

Many pharmacy schools and faculties do not offer digital medical education. Similarly, only a small proportion of the students and professionals surveyed received digital health education or training as part of their continuing education. Interviewed students and teachers mistakenly believe that digital medical education and e-learning are considered interchangeable terms.

Digital medical education has a long way to go to create a ready and flexible pharmacy education that can cope with the rapid changes in digital healthcare. Integrating digital health into a higher pharmaceutical education program is an important strategy for improving digital health. "Much remains to be done to make pharmaceutical education ready and flexible to keep up with the rapid changes in digital healthcare. About half of the teachers agreed that their students have the skills to deliver digital health services and that their individual schools can easily identify and add new digital health literacy skills to the curriculum as they become available in practice. Although this discovery shows the potential for overall progress Because it can promote health awareness and lifelong learning, pharmacists are more likely to receive digital health education through continuing professional development if they have already taken a digital health course in school. The most common digital health education reported by schools and colleges was a lack of previous experience, followed by a lack of resources n[19-20].

The answers of the specialists showed that they are not familiar with new digital health technologies such as blockchain technology, bots, digital medicine and artificial intelligence. One of the biggest gaps in digital medical education is the skills and knowledge to use technology to solve existing clinical problems and improve care. Practitioner expectations for the clinical benefits of digital health in practice have remained low. This may be due to the fact that, from the point of view of the scientist, the introduction of digital health tools into clinical care was one of the concepts that were least often included in pharmaceutical education. Existing digital health courses seem to be more focused on teaching administrative and functional skills to facilitate business processes and improve operational efficiency [21-22].

Pharmacists, pharmaceutical schools, educators, students and professionals have indicated that they should support national organizations, schools, workplaces and student associations in providing advice, training, infrastructure and educational resources for digital health.

Training in the implementation of digital health tools was a key need cited by students and professionals alike. The lack of supportive policies, the availability of digital health tools and data, and technical limitations have been identified as the biggest challenges in implementing digital health in practice.

This report is the first of its kind global study of digital health in pharmaceutical education that examines the readiness and responsiveness of pharmaceutical education and identifies gaps in knowledge and skills among pharmacist professionals. We believe this report will encourage further research and development in this area to expand digital health among the pharmaceutical workforce [23-24].

Digital health is a top priority for political and health organizations involved in implementing digital health and raising digital literacy standards. Recent advances in technology have revolutionized clinical practice, from prevention to diagnosis, monitoring and treatment of disease, and have led to unprecedented public interest and participation in self-care and health [25-26].

The COVID-19 pandemic has accelerated the digital transformation of healthcare, with a lasting impact on healthcare. There are important lessons to be learned from this digital healthcare transformation. New digital health technologies must be people-centred, of high quality, evidence-based and effective, work for both providers and consumers, be sustainable, inclusive, fair and reliable so that they can be integrated into practice [27].

Many digital health technologies rely heavily on their use and proper use by healthcare professionals. It has become necessary for healthcare professionals to equip themselves with digital health literacy in order to deliver new and evolving models of healthcare services.

Pharmacy traditionally uses information technology. As such, he has the ideal skills and competencies to deliver more digital healthcare services to patients.

According to the World Health Organization (WHO), digital health is “a field of knowledge and practice related to the development and use of digital technologies to improve health.” Technology and digital transformation are rapidly changing information ecosystems and the design of healthcare systems. The use of various digital technologies, such as artificial intelligence and machine learning, offers enormous opportunities to improve healthcare services, access to healthcare, healthcare workforce and health outcomes.

While digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in recent years has led to exciting new areas of digital health, including mobile health applications (mHealth). and wearable technologies. Telehealth and telemedicine, artificial intelligence, advanced robotics and genomics. Digital health also includes other digital health uses such as the Internet of Things, advanced computing, and big data analytics. While they can provide significant benefits, there are also risks, especially in terms of health disparities, data privacy, and the limitations of artificial intelligence. Digital health is a broad term and its definition will change as new medical technologies emerge [28-29].

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An electronic medical record (EMR) is a digital version of a paper patient record. Electronic health records are real-time patient records that make information easily and securely accessible to authorized users. While the EHR contains patient and patient records, the EHR system is designed to go beyond standard clinical data collected in a healthcare provider's office and can include a broader view of patient care. patients. Electronic health records can: contain a patient's medical history, diagnoses, medications, treatment plans, vaccination dates, allergies, x-ray images, and lab and test results; provide access to evidence-based tools that healthcare providers can use to make decisions about patient care; as well as supplier workflow automation and optimization [32-33].

An electronic medical record (EMR) is a digital version of a paper patient record. Electronic health records are real-time, patient-accessible records that make information easily and securely accessible to authorized users. While EHRs contain patient and patient records, the EHR system is designed to go beyond standard clinical data collected in a healthcare provider's office and can provide a broader view of patient care. patients.

An EHR can: contain a patient's medical history, diagnoses, medications, treatment plans, vaccination dates, allergies, x-ray images, and lab and test results; Provide access to evidence-

based tools that healthcare providers can use to make decisions about patient care. as well as automating and optimizing supplier workflow [34-35].

One of the key features of the EHR is that health information can be created and managed by authorized healthcare providers in a digital format that can be shared with other healthcare providers across multiple healthcare organizations. health. EHRs are designed to share information with other health care providers and organizations such as laboratories, specialists, medical imaging centers, pharmacies, emergency rooms, and school and occupational clinics, in order to that they contain information from all clinicians involved in patient care [36-37] .].

One of the key features of HR is that health information can be created and managed by authorized healthcare providers in a digital format that can be shared with other healthcare providers across multiple healthcare organizations. health. EHRs are designed to share information with other healthcare providers and organizations such as laboratories, specialists, medical imaging facilities, pharmacies, urgent care facilities, and schools and clinics in workplace, so that they include information from all physicians involved in patient care [38-38]. 39].

Pharmacists provide patient care across the continuum of care and must actively participate in the electronic health record, researching and documenting information. The use and implementation of the EHR is driven by funding and policy changes, and pharmacists should be part of development and implementation teams. As medical information technology develops rapidly and EHRs are developed and deployed in healthcare environments, meeting the workflows and information needs of pharmacists in EHRs is essential to optimize quality of drug therapy and patient outcomes. Although pharmacists use many different advanced functions in the EHR, three main applications are described in the literature: documentation, medication matching, patient assessment and follow-up [40-41].

Pharmacists provide ongoing medical care to patients and must actively participate in electronic health records, information retrieval, and documentation. The use and implementation of the EHR is driven by changes in funding and policy, and pharmacists need to be part of development and implementation teams. As health information technologies proliferate and online medical records are developed and implemented in the healthcare environment, it is essential that pharmacists' workflows and information needs are met in online medical records to optimize the quality of care. medication and patient outcomes. Although pharmacists use many different advanced features of electronic health records, three main areas of application are described in the literature: documentation, medication matching, and patient assessment and follow-up [42-43].

Electronic Prescribing and Electronic Delivery Electronic prescribing is the ability for a prescriber to electronically send an accurate, error-free, and understandable prescription directly to a pharmacy from the point of care. It is an important element in improving the quality of patient care. Electronic dispensing is defined as the electronic retrieval of a prescription and delivery of the drug to the patient as specified in the associated electronic prescription. Once the medication is delivered, the dispenser reports information about the dispensed medication(s) via software. The benefits of both technologies include increased patient safety, reduced medication costs, better access to patient prescription records, and improved pharmacy workflow [44-45].

Electronic Prescribing and Electronic Delivery is the ability for a prescriber to electronically submit an accurate, error-free, and understandable prescription directly from the local pharmacy. This is an important element in improving the quality of patient care. Electronic dispensing means receiving a prescription electronically and dispensing a drug to a patient as specified in the

associated electronic prescription. Once a drug is dispensed, the dispenser provides the program with information about the dispensed drugs. The benefits of both technologies include increased patient safety, reduced drug costs, better access to patient prescription records, and increased pharmacy efficiency.

A blockchain is a growing list of records, called blocks, linked together and protected by cryptography. A blockchain can serve as a "public and distributed ledger" or "common ledger" that can record transactions between multiple parties in an efficient, verifiable, and permanent manner. Once blockchain enters the pharmaceutical environment, various activities of pharmacists can be further automated, such as managing patient records, distributing patient information, and managing reimbursements [46-47].

A blockchain is an ever-expanding list of records, called blocks, linked to each other and protected by cryptography. A blockchain can be an "open and distributed ledger" or a "shared ledger" that can record transactions between multiple parties in an efficient, verifiable, and permanent manner. As blockchain enters the pharmaceutical realm, various activities of pharmacists can be further automated, such as patient record management, patient information dissemination, and reimbursement management.

An online pharmacy is an online store that sells medicines and can function as independent internet sites, "AGUs", which are associations between pharmacies. From a consumer perspective, online pharmacies seem to offer a lot of potential value, but not necessarily in price. For patients at home, the possibility of ordering and delivering drugs at home is obvious. For those who live in remote areas and for consumers who have little time and energy to go to the pharmacy, ordering online has clear advantages. There are also people who seek personal products and prefer anonymity [48-49].

Wearable medical device refers to technology that the user can properly place on the body and control important aspects of health according to today's standards. These devices can collect data through non-invasive monitoring of physiological parameters or detection of the substrate of body parts in a minimally invasive manner. These technologies may pave the way for pharmacists to monitor drugs to improve clinical outcomes and patient safety [50-51].

A bot (also known as a web bot or internet bot) is a software application that uses steps or scripts to automate a task. Chatbots use natural language recognition (NLU) services through the many toolsets available. At NLU, chatbots focus on using a conversational interface, allowing the user to interact in a natural way. After adding clinical discovery and medical content to the bot structure, the resulting virtual personal health assistants can interact with the user on topics related to well-being, perceived health, questions about diseases, and information about medical interventions. Bots can help optimize adherence by answering medication-related questions, informing the patient about what to expect during the first few weeks of medication, or reducing the likelihood that a medication will not be taken as prescribed [52-53].

A bot (also known as a web bot or internet bot) is software that uses steps or scripts to automate a task. With the various tools available, chatbots use natural language recognition (NLU) services. NLU-enabled chatbots focus on using a conversational interface that allows the user to interact using a natural form of conversation. . . , intended health, disease problems and care measures. Bots can help optimize adherence by answering medication-related questions, telling patients what to expect during the first few weeks of medication, or reducing the chance of taking another medication than prescribed [54-55].

Digital medicine. Currently, the digital drug system contains four main components: an inert sensor embedded in an inert tablet, a non-drug sensor (patch) worn by the patient, a mobile application (app); and web control panel. When interacting with gastric fluid, the swallowed sensor is activated and connected to a wearable sensor, which sends a signal to a mobile device where it can be viewed by patients or later by healthcare professionals and caregivers via mobile apps and in the secure cloud. . software-based.²⁰ It also has the ability to record other physiological and behavioral parameters such as physical activity, heart rate, skin temperature, sleep and digital therapy [56-57].

Digital therapy (DTx) is a new treatment modality that uses digital systems such as smartphone applications, digital sensors, wearable devices, certain virtual reality or artificial intelligence devices as prescribed therapeutic interventions approved by authorities for prevention, treatment management or medical therapy. requirements. DTx products have a number of different potential roles, including modifying drug use, changing patient behavior independent of drug use, and treating a disease or influencing a patient's underlying physiological response. Many also have the option [58].

Remote Patient Monitoring (RPM) uses digital technology to collect health data from people in one location, such as a patient's home, and electronically relay the information to healthcare providers in other locations for evaluation and recommendations. Local pharmacy services have traditionally been product-related, but pharmacists have skills in medication management, disease assessment, and patient counseling that can contribute to an RPM improvement program [59].

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Online/remote (patient) counseling and telemedicine/telehealth/virtual care: Telepharmacy has many recognizable benefits, such as easy access to health services in disadvantaged, remote and rural areas, economic benefits, patient satisfaction due to effective patient education. and minimal shortage of local pharmacists and pharmacy services.

Online/Remote (Patient) Consultation and Telemedicine/Telemedicine/Virtual Care: Telepharmacy has many distinctive advantages, such as easy access to healthcare services in disadvantaged, remote and rural areas, economic benefits, patient satisfaction through effective patient guidance and minimal shortage of local pharmacists. and pharmaceutical services [60].

Artificial intelligence (AI) is an area of computer science that aims to emulate human intelligence through computer systems. This mimicry is achieved through iterative tuning of complex patterns, usually at a speed and scale beyond human capabilities. AI has the potential to have a profound impact and shift our focus from providing medicines to providing a wider range of patient care services. Improved budgeting, lower transaction costs and greater overall organizational efficiency will be seen as positive outcomes of AI data analytics. AI aims to revolutionize pharmaceutical care by connecting different pharmaceutical datasets, data platforms, medical and analyze pharmaceutical records, develop holistic treatment plans o Report adverse events or non-compliance with treatment regimen. In addition, AI can help automate repetitive pharmacy tasks, such as checking prescriptions or reviewing profiles of polypharmaceuticals (e.g. signaling overconsumption or interactions) [61].

Artificial intelligence (AI) is a branch of computer science that aims to mimic human intelligence using computer systems. This mimicry is accomplished by combining complex, repetitive patterns, often at a speed and scale beyond human capabilities. AI can have a powerful impact, shifting our focus from delivering medicines to providing a broader range of patient care services. Improved budget, reduced operating costs and improved organizational efficiency are seen as positive outcomes of AI data analysis. or report adverse events or non-compliance. In addition, AI can help automate repetitive tasks in the pharmacy, such as B. checking prescriptions or displaying polypharmacy drug profiles (alert eg overdose) [62].

Big data can be defined as digital data generated in large amounts and with great variety, accumulating at high speed and resulting in very large data sets for traditional data processing systems.³¹ Scientific data can be defined as a set of principles fundamentals, driving the fundamental extraction of information and insights from data.³² The pharmaceutical side of healthcare is saturated with data. Healthcare providers and pharmacy workers regularly collect and share vast amounts of information from patients to ensure they receive the care they need. While this data has traditionally only been used to ensure the right prescription is given to the right patient at the right dose, key stakeholders recognize that the information can also be used to improve several other important areas of pharmaceutical practice. The use of data is particularly impacting pharmaceutical practice in managing health plan expenditures, monitoring consumer prescription drug use, and directing research and development efforts [63].

Mobile apps can help people manage their own health and well-being, promote healthy living and provide access to useful information when and where they need it. These tools are adopted almost as quickly as they can be developed. Mobile apps allow pharmacists to stay abreast of disease status patterns, maintain adequate pharmaceutical stocks, access drug information systems, view patient health information, and use tools to calculate individual drug doses and accurately convert between units of measure. Mobile devices can also help pharmacists, turning smartphones into point-of-care diagnostic devices like otoscopes or blood pressure monitors. Mobile apps can also help patients manage disease states, improve therapy adherence, and capture important medical histories [64].

The coronavirus (COVID-19) pandemic has been a powerful impetus to accelerate technology deployment. In the age of digital health technologies, the focus of new models has shifted to virtual visits, virtual care, remote monitoring of patients and websites, and chatbots (for risk assessment, screening, screening).³⁶ This pandemic has demonstrated the usefulness of digital health. solutions and represents an opportunity to integrate these solutions into our healthcare systems. More than ever, digital technologies and remote assistance have been integrated into our daily lives and, above all, into health. As a result, the digitization of healthcare practices is increasing exponentially [65]. As part of its National Health Plan for COVID-19, the Australian Government has accelerated the delivery of electronic prescriptions. Australian pharmacists can offer a range of paid services (medical tests, diabetes check-ups, home medication reviews and home medication management reviews) via telemedicine. The impact of digitization on health has been significant and is expected to be even greater in the future. To appreciate this, a broader perspective must be taken. Achieving broader health system goals, including quality, access, efficiency and equity, is the goal against which new digital health services must be measured.

Decisions to introduce new digital health services at different levels of the health system are best based on evidence of their effectiveness in relation to health system goals. These goals in a

broader sense remain unaffected by the digitization process. Management must be designed and adapted to adequately capture all relevant changes [66-67].

Many digital health technologies are highly dependent on their acceptance and proper use by healthcare professionals. This can lead to new medical professions as well as existing healthcare professionals acquiring new skills and competencies to work with new digital healthcare services. Co-creation in the development of new digital health services may make sense to increase acceptance and ease of use in practice. The experience of professionals using the technology is also critical to monitor and incorporate into any assessment.⁴³ When digital health technologies are well understood, designed and deployed, healthcare professionals can coexist with them, which can provide some relief for spend more time with patients or perform salvage tests [68].

Digital health systems can also empower and engage patients and make them co-creators of care. This joint decision-making by physicians and patients requires trust, partnership and transparency in their interactions. Healthcare professionals become collaborators in the patient's journey to health, providing empathy and a human touch to support patient well-being.

Digital health systems can also empower and engage patients and make them co-creators of care. Joint decision-making by health professionals and patients requires trust, partnership and transparency in their interactions. Healthcare professionals become collaborators in the patient's journey to health, providing empathy and a human touch to support patient well-being.

Client Interventions: Clients are community members who are potential or current users of health services, including health promotion activities. This group also includes caregivers of clients using health care. **Interventions for health professionals:** Health professionals are members of the medical team who provide health services. **Health system interventions or resource managers:** Health system and resource managers are involved in the management and oversight of public health systems. Interventions in this category reflect management functions related to supply chain management, health care financing, and human resource management. **Data Services Interventions:** Data services consist of cross-functional capabilities to support a variety of data collection, management, use, and sharing activities.

In many countries, pharmacists were among the first healthcare professionals to adopt all four pillars of information systems listed above to optimize pharmaceutical care services. Managing thousands of medications in stock, checking drug interactions, and facilitating sequencing by analyzing substitution rates are just a few of the reasons pharmacists are often used to working with computers as physicians adopt electronic prescribing systems. Pharmacists have a structured mindset that comes from a rigorous educational track. They like to analyze data and support decision tools derived from reliable data systems

The profession of pharmacist is undoubtedly a profession that has a certain technical aura. Therefore, it has the perfect predispositions and skills to offer patients more digital health services.

Some of the key areas where digital technologies will impact the pharmaceutical industry can be summarized as follows: Integrating wearable data into decision-making: As more and more wearable devices are able to monitor an increasing amount of health data and well-being, the well-being of patients. , the patient, these data can be used as digital biomarkers in pharmaceutical decision making. Digital biomarker data can be described as objective and quantitative data collected by wearables, wearables, and even devices or implanted devices to track digestive health. Consider smartwatches with proven ECG apps that can help the pharmacist determine the effectiveness and safety of cardiac procedures. Or a meditation device that provides data about a

patient's state of mental relaxation, which may help improve the effectiveness of potential migraine treatments. There are many examples where pharmacists can ask how they can use this data to improve their services by predicting outcomes, adverse events and patient satisfaction. Once pharmacists have access to this data, they can interpret patients' vital signs in real time and communicate them to their primary care physician or specialist to optimize pharmaceutical care as needed. Nowadays, such access should be possible, but not universal.

Use of health apps: As healthcare moves to phone-based access models, patients will have access to an increasing amount of digital biomarker data 24/7. The global interoperability of these data is increasing due to the increasing standardization of health data. This, along with computers becoming faster and mobile phones becoming more powerful, will make the patient's mobile environment a hub of care information. As with wearable devices, pharmacy information and communication technology systems should ideally connect to these patient environments, exchange patient informed consent data, and turn it into valuable tools for care delivery . **BR** Finally, this becomes important as digital therapy (DTx) becomes more and more integrated into the standard of care. DTx provides patients with evidence-based, high-quality software-guided therapeutic interventions to prevent, manage, or treat a wide range of physical, mental, and behavioral conditions [69–70].

Automated robots to support robotic dosing processes, packaging systems to create individualized doses, and chatbot information technology to answer frequently asked questions are examples of robotics that can improve the efficiency of the pharmaceutical process. Robotics can also reduce dispensing errors, leading to avoided hospitalizations, deaths and costs for health systems.

Conclusion

A large amount of health data provides the opportunity to use more artificial intelligence and machine learning in pharmacy practice to solve important problems related to the management and use of medicines. Trend analysis on large data sets can reveal the risk of adverse events in individual patients, behavioral aspects, compliance profiles, etc. A pharmacist is a professional expert who can extend the knowledge of a data scientist to create services. Understanding the terminology and concepts used in AI will help pharmacists to work constructively with data scientists to develop models that improve patient care. Digital health systems can also empower and engage patients as co-creators of care. Joint decision-making by healthcare professionals and patients requires trust, a sense of partnership, and transparency in their interactions. Healthcare professionals become partners in the patient's journey to health, but still provide empathy and a human touch to support patients' well-being.

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THE SCIENTIFIC DISPUTES OF THE KEY ISSUE RELATED TO FEATURES, ASPIRATIONS, PROSPECTS, PROGNOSIS, ACHIEVEMENTS, PERCEPTION, AND CHALLENGES OF THE PHARMACIST'S OCCUPATION IN MEDICINE AND HEALTHCARE

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ABSTRACT

The main goal of the study was to analyze the key issue related to features, aspiration, perspectives, prognosis, achievement and challenges of the pharmacist profession in medicine and health care. The study was a quantitative investigation and analysis of the features of inclination, achievements, tenacities, innovations, aspirations and perspectives of pharmacists' profession in Georgia and globally by using questionnaires. Were conducted a survey study. The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients participated in the study. Questionnaire for the employed pharmacy faculty-student: 222

employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study. Were used methods of systematic, sociological (surveying, questioning), comparative, mathematical-statistical, graphical analysis. The data were processed and analyzed with the SPSS program. Were conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p < 0.05$ as significant for all analyses. Were sub studied the scientific disputes of the key issue related to features, aspirations, perspectives, prognosis, achievements and challenges of the pharmacist's profession in medicine and healthcare. According to the study results, the respondents' vast majority considered that the issues to for pharmacists were in need of the further regular studies or trainings in the following fields: new medications, issues of pharmacotherapy of certain diseases, pharmacology and pharmacotherapy, drugs toxicity. From the study results it is obvious that in the higher pharmaceutical institutions' pharmaceutical educational programs and curriculum need upgrade, renewal, modernization and adaptation to the new modern medical challenges. Therefore, continuous pharmaceutical educational programs should be created. These programs should be more focused on new medications, pharmacotherapy, drugs toxicity and dosage, routes of drug administration, selection of OTC drugs, cost-effectiveness and cost-benefits of drugs. A clinical pharmacist is in no way a competitor of a doctor, on the contrary, he must refer patients who need qualified medical care to a doctor. It is difficult to imagine that a pharmacist does not know the alphabet of medicine and does not have relevant knowledge of the main clinical syndromes. Must have a particularly good knowledge of the nomenclature of medicines (mainly over-the-counter medicines). In essence, a clinical pharmacist must provide a defined pharmaceutical supply and make a decision about the dispensing of the drug. The respondents' vast majority considered that pharmacist should provide assistance in teaching patients to understand the prescribed drugs intake rules. According to that higher quality pharmaceutical service could be only provided by the pharmacists of higher pharmaceutical education, graduated from the authorized, accredited and licensed by the state higher education institutes and universities.

Keywords: Issue, features, aspiration, perspectives, prognosis, achievement, challenges, pharmacist, profession, medicine, health care.

Introduction

The pharmacists' role is expanding in health-care services. That mentioned as a new report from the International Pharmaceutical Federation (FIP). Pharmacy is a gate toward healthcare. Pharmacist supporting population to hold better health. Consideration the present situation of patient interest in health care. Present pharmaceutical services connected to self-health care and the significance that pharmacist professionals drive the health care frame systems in the new modern direction. It sets out the modern supervisors of the self- healthcare system and deeply changes on the new direction of health care schemes [1-2].

Responsible administering of drugs involves that healthcare network mediator capabilities and activities are balanced to assure that patients get the right drug, on the proper time, using properly and patient have profited from them. Delivering the right drugs into patients' demands commitment of all representatives, inclusive Government and a desire on how to consolidate private and public interests and mobilize sources. That is significant for the public to be

guaranteed that expenses on pharmaceuticals productions are an equivalent cost of cash. On the viewpoint of the pharmacists' comprehensive academically field and their traditionary function in composing, qualifying, delivering and ensuring drugs. A pharmacist is informing customers, consumers and patients on the drug using; they are greatly positioned to suppose professional liability for the monitoring of pharmacotherapy. They are members of the healthcare team immediately engaged in patients' health care services. Their responsibility is to assistance patients in using their drugs, which is impossible to do alone. Thus, in terms pharmacists' profession have been progressed. New type pharmacists have done the work a in more efficient way. Pharmacists holding the higher, university-level education. They understand the biochemical mechanisms of metabolism, mechanisms actions of drugs, medicines pharmacotherapeutic characteristic, side effects of drugs, potential interactions of drug and the argumentations monitoring. It is conjugated of specialized knowledge of biochemistry, anatomy, therapy, physiology, pathology, pharmacology and other pharmacy subjects. The pharmacists explain this particularized knowing when communicating with physicians, patients and another health care providers [3-6].

Being healthcare occupational means of to be a member of a group, which is centered on one purpose: serving with a patient to obtain better health. Pharmacist plays the centric role on the delivering of communication to patients and society about using of medicines. They effectively cooperate with doctor prescribers to assure a general treatment to patients by the delivery information and advice. The pharmacists are involved in a multidisciplinary treatment to the contribution the rational pharmacotherapy. They sufficiently informing patients and common society about the adverse influences of the drugs. They are monitoring these side effects via partnership together with different health care vocational. Pharmacists provide education on medications, disease states and the lifestyle issues as a part of clinical prevention, as well as educational programs to groups on issues such as drug abuse or others that are an example of population health activities. Pharmacists do counsel on a wide range of health promotion products found in the typical retail pharmacy such as sunscreens, dental hygiene products or vitamin and mineral products. Moreover, pharmacists provide immunization services and participate in screening activities [7-8].

Though the quantity of pharmaceutical productions on the world market is growing, the approach of vital medicines is till now lacking in a lot of parts of the worldwide. Health care expenses rise and the technological, social, political and economic conditions change have made the health care transformation crucial across the worldwide. The renewed treatments are required reforms at the personal and public levels to ensure effectively, quality and safe pharmacotherapy to the patients in more ever complicated surroundings condition [9-10].

The pharmacists hold the great condition to satisfy the necessity for health care vocational to ensure effective and safe using of medicines. To do this, pharmacists should suppose higher liability than they at the present time do for the monitoring of pharmacotherapy for the customers, consumers and patients they are serving. That liability goes completely behind the traditional distributing and dispensing practices that have long been the maintenance of pharmacy activities [29]. Pharmacists' liability should be enlarged conclude controlling of the pharmacotherapeutic progression and thereby improve therapeutic outcomes and patients' life quality, advising with doctor prescribers and consolidating with different health care workers and practitioners on behalf of patients [30]. Pharmacists' involvement into pharmaceuticals may consist in drug storage, drug supply, dispensing, manufacturing, formulation, distribution, marketing, quality warranty, licensing, information management, monitoring, development, education, and research. Drug

supply and medicine information management system is the main part of pharmaceutical services and proceeds forming the basement of pharmacy activities. The higher pharmaceutical schooling and education hold an appropriate duty and responsibility to generate post-graduate professionals who are qualified and authorized to provide the pharmaceutical care services. Sufficiency results promote to quality warranty by provided that easily approachable working standards [11-12].

Community pharmacists' activity is at the forefront of medical care, working at their own pharmacies or in the private ones. Pharmacist's job is all about helping the public, as they participate in the medicines distribution and offering advice to patients and maintaining their health. Pharmacist work is a very demanding occupation in the world. Pharmacists usually are greatly honorable members of the society. Changes in the role of pharmacist and pharmacy community as a medical supplier accelerate along with the fast-moving environment. Today to offer advanced medical services pharmacies deliver educational information at multiple points of contacts and also to raise awareness of the disease are of great importance. These include over the counter (OTC) and the personal care aisle, a pharmacy counter, specialties publications and pickup areas prescription. These innovations are useful not only for customers' pharmacies but also create opportunities for pharmaceutical marketers, measurable return on investment. The educative center of occupational programs and schemes growingly identifies the necessity for the possibility to use the knowledge obtained via simulation laboratories or experiential studying, which needs corresponding faculties and personnel conditions to satisfy these educational necessities. Innovations in faculties and personnel positions with greater consideration to learning, or practice also include accentuation on the research within the framework of PharmD programs. There is a need to encourage the pharmacy's graduates to encounter that, as well as to conducting PharmD degree programs in postgraduate level masters or doctoral scale in philosophy or promoted scientific basement grants for the pharmaceutical, biomedical, clinical, administrative and other fields of researches in the pharmacy direction [13-14]. In the higher pharmaceutical institutions and academy, the health occupations schooling-education programs should contribute career possibilities for pharmacy faculty post-graduates. Pharmacy schoolmaster must make more energetically engaged at the growth for particular training /educational possibilities to arrange and overlook the newest generation for pharmacy faculty or program personnel positions in higher education institutions. In order to engage pharmacy faculty post-graduates to take part in the scientific research. Pharmaceutical faculty program post-graduate professionals should be supported to research the capacity function and role of various pharmaceutical, medical/health care, academic and educational, research and scientific program schemes for to growth consideration in inter-professional scientific groups upon the health professions formation, teaching and education; which is very significant for the high-quality patient care services [15-16].

The health systems of many other countries have developed similar claims of competence for pharmacists. As a critical care pharmacy specialist, it is difficult to describe a typical day, but usually busy with the elements of a pharmacist's support process during the day. It is believed that the clinical pharmacist will be responsible for all aspects of the administration of the drug. Every day, the clinical pharmacist assesses and evaluates new patients and updates the progress of previous patients, identifies drug-related issues and potential problems, develops a problem list and treatment plan for optimal dosage based on the renal and hepatic function, potential drug interactions and serum concentration. The clinical pharmacist joins the multidisciplinary rounds with the intensive care team and applies the treatment plan by teaching the medical residents the

correct order of entry or by entering the orders themselves according to a collaborative practice agreement and by them. documenting in an electronic health record. A major contribution to medication management is identifying therapies that are no longer needed, reducing the cost and risk of adverse events, and supporting antimicrobial stewardship programs with infectious disease physicians and pharmacists. The clinical pharmacist also supervises the performance of quality measures such as the appropriate prevention of venous thromboembolism, the appropriate use of drugs to prevent stress gastritis, the addition of aspirin to increase the levels of troponin associated with I coronary ischemia, and discussing the need for central tubing and urinary catheters. The clinical pharmacist educates the team on drug-related topics and related literature through tours and didactic discussions. A clinical pharmacist is always available for emergencies and resuscitation, and to answer questions related to medication [17-19].

For each new patient, a member of the pharmacy team compiles a medication history from electronic records, family, patient, local doctors or pharmacies and documents in the electronic medical records. The clinical pharmacist will then cross-check this list to determine medication-related reasons for hospitalization, such as non-adherence or overdose, and advise on which medications to choose to avoid withdrawal reactions or other adverse events. While the clinical pharmacist has a more limited role in verifying drug orders in the electronic medical records and has little role in the actual distribution of drugs, the clinical pharmacist serves as a liaison with technicians and pharmacists specializing in parenteral products and drugs. Distribution systems to ensure medications are present when needed. Nurses have a formidable task of prescribing drugs, and the clinical pharmacist facilitates this process by providing information on intravenous injection compatibility and teaching unknown treatments [20-22].

Goal

The main aim of the study was to analyze the scientific disputes of the key issue related to features, aspirations, perspectives, prognosis, achievements, and challenges of the pharmacist's profession in medicine and healthcare.

Material and methods

Research objectives are materials of sociological research: the study was a quantitative investigation by using a survey (Questionnaire). The study was quantitative investigation by using survey (Questionnaire). The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients (customers of drug-stores) participated in the study. Questionnaire for the employed pharmacy faculty-student: 222 employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study.; Totally 3888 respondents were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. Results and discussion: The survey was conducted through the questionnaires. 1506 patients were interviewed in Georgia. Questions and answers are given in the tables. On each question are attached diagrams or table. Questionnaire and diagrams are numbered. Study of the data was processed and analyzed with the SPSS program. We conducted descriptive statistics and



regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p < 0.05$ as significant for all analyses. The study's ethical items. In order to provide the study's ethical character each participant of it was informed about the study's goal and suggested of willingness of the work to be done. So, the respondents' written or oral compliance was got on that issue. All the studies were carried out by the selected organizations administrations' previous compliance. Were used Informed consent form for each respondent to participate in an anonymous survey. During the whole period of research, the participants incognita was also provided. For the international rules and criteria' conformity this human subject comprising given study was discussed and confirmed on the Bioethics Committee sessions of the YSMU. In order to meet the objectives, set in the research we also used the results obtained through analysis of available official information, studies and opinions about pharmacists, as well as the methods of quantitative studies. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. The research implementation required the following sub studies: the scientific disputes of the key issue related to features, aspirations, perspectives, prognosis, achievements and challenges of the pharmacist's profession in medicine and healthcare

Results and discussion

On the basis of performed study results the following have been found.

Clinical pharmacists today have the in-depth therapeutic knowledge and scientific skills to serve as pharmacotherapy experts in the medical setting. Establishing an Institute of Clinical Pharmacists has been talked about in Georgia for a long time, but it seems that it has not yet been officially established due to the inertia of the administrative infrastructure. At the same time, the medical, including pharmaceutical, infrastructure in Georgia is rapidly developing, and we can safely say that practice has forced some pharmacists to take on this role - in fact (functionally) the Institute of Clinical Pharmacists was created by life. For example: "receptionist pharmacists" of large pharmaceutical companies often have to consult patients, "consulting pharmacists" of insurance companies actually fulfill the function of clinical pharmacists [23-24].

As already mentioned, clinical pharmacy is a complex science. One of its characteristics and a distinguishing feature of neighboring medical fields is the integration of information technology with natural sciences (mathematics, engineering). In 2007, about 5,400 drugs were registered in Georgia, and their number is growing rapidly. The number of drugs is much higher in economically developed countries. Of course, manipulating this set of information is making a comparison analysis is not possible without specialized information systems, which requires not only the use of these sciences, but also integration with them. Therefore, in Georgia, as part of the project "Georgian Electronic Medical Encyclopedia" by Lali Dateshidze, work has been going on for several years to create an "automated workplace" for a clinical pharmacist [25-26].

The main difference between clinical pharmacists and conventional registered pharmacists is the ability of clinical pharmacists to interact with patients and that they can recommend specific drugs and drug dosages for a specific patient in order to monetize a drug. The term "pharmaceutical care" comes from clinical pharmacy. The two concepts are compatible and appear to have similar goals. One way to differentiate between the two would be to use the description clinical pharmacy as a pharmacy practice within a larger pharmaceutical supply system to which the pharmacist

would contribute. The aim is to achieve pharmacotherapeutic results and improve the quality of life of patients. Pharmaceutical care can be defined as “the direct and rapid delivery of medical care to achieve specific outcomes that improve the patient's quality of life”. Thus, pharmaceutical care can be seen as part of clinical pharmacy [27-28].

The purpose of this statement is to help pharmacists understand pharmaceutical care. Such understanding must precede efforts to implement pharmaceutical care, which is a top priority in all practices. Many pharmacists have embraced the concept of pharmaceutical supply with enthusiasm, but there has also been significant inconsistency in the way it has been described. Some characterize it as a new name for clinical pharmacy; Others describe it as any action by pharmacists that can lead to favorable outcomes for patients [16-18]. Directly in the clinical environment, there are many goals and tasks that clinical pharmacists can fulfill. For example, in the United States, clinical pharmacists work in almost 80% of medical institutions, which contributes to the rational use of drugs and saves drugs by about 10-20%. The involvement of a clinical pharmacist is important at all stages of creating a treatment algorithm. A clinical pharmacist is required to participate in the development of a drug use policy, collaborate with specialists in the development of methodological recommendations and guides for the treatment of specific diseases, participation in the sale of drugs and the manufacture of drug formulations in processes [29-30].

The profession of pharmacist has yet to develop into a clinical profession in Georgia and is now more focused than ever on moving from a product-oriented profession (including procurement, preparation and evaluation of medicines) to a patient-oriented profession. The pharmacist has an important role to play in ensuring the health of the patient. In 2006, the American College of Clinical Pharmacy (ACCP) identified the largest differences between clinical pharmacists and the regularly registered pharmacists as clinical pharmacists [23-25], which improves the quality of life of patients. Therefore, pharmaceutical care can be considered as a form of clinical pharmacy. The establishment of clinical pharmacy in Georgia can be considered when the registration of clinical pharmacy appeared in the National Register of Qualifications, however, there is still no framework, a document that would define the role of clinical pharmacy and career opportunities, although many Clinics participate in international clinical trials, in which, according to the international protocol, a clinical pharmacist should participate, although at this stage such a profession and staff in clinics are not established, it turns out that general pharmacists formally perform the functions of a clinical pharmacist, what confirmed in our survey. The role of the pharmacist in Georgia needs to be developed, which remains a problem: some clinical guidelines have been developed in Georgia [31-32].

Unfortunately, we have not yet seen a pharmacist in the writing group for any of the guidelines. We already consider the participation of the clinical pharmacist in the recommendation development process to be necessary. The involvement of a clinical pharmacist is important at all stages of creating a treatment algorithm.

A clinical pharmacist is required to participate in the design of a drug use policy, collaborate with specialists in the development of recommendations and methodological guidelines for the treatment of specific diseases, and participate in the purchase and sale of drugs, the creation of medicinal formulations, etc. The pharmacist profession is not yet a clinical profession, but is more focused than ever on its transformation from a product-oriented profession (including the procurement, preparation and evaluation of medicines) to a patient profession - job-oriented. The clinical pharmacist plays an important role in ensuring patient health [33-34].

In 2006, the American College of Clinical Pharmacy identified a key difference between clinical pharmacists and regular registered pharmacists. Clinical pharmacists improve the quality of life of patients. Therefore, pharmaceutical care can be considered a form of clinical pharmacy. The establishment of clinical pharmacy in Georgia in 2019 can be considered as the moment when an entry for clinical pharmacy appeared in the national rating system, however, there is still no regulatory document defining the role of clinical pharmacy [35-36].

Clinical pharmacy and career opportunities, although many clinics across the country participate in international clinical trials, which according to international protocol should have a clinical pharmacist participate, although at this stage such a profession and staff clinics turns out to be general practitioners formally fulfill the functions of a clinical pharmacist, which is confirmed in our survey that a pharmacist is needed to expand the role at Georgia. Clinical pharmacy as the field of pharmacy concerned with the science and practice of rational drug use. With this definition, the possibilities for clinical pharmacists are endless. Many career options are available to pharmacists seeking clinical opportunities in their practice. As a clinical pharmacist, you can provide general clinical services. However, there are several highly specialized areas that cover different patient groups [37-38].

Pharmaceutical supply will be an important new concept, representing the growth of the profession beyond clinical pharmacy as commonly practiced and beyond the other activities of pharmacists, including the preparation and dispensing of medicines. In Europe, however, all these professional activities are important and strongly support the need for pharmacists to be involved. In practice, these activities should be integrated and result in the pharmaceutical care of individual pharmacists for individual patients [36-39]. The philosophy of pharmaceutical care (PA) is the sum of the pharmacist's responsibilities to meet all of the patient's medication-related needs through direct patient care and collaboration with other facets of the healthcare system. Clinical pharmacists have in-depth therapeutic knowledge and scientific skills that enable them to act as experts in drug therapy in healthcare settings. The American College of Clinical Pharmacy (ACCP) defined clinical pharmacy as a discipline in which specialized pharmacists are involved that deal with the science and practice of rational drug therapy. Clinical pharmacists apply scientific knowledge to ensure and advise on the best use of medicines for optimal drug therapy. In addition, they participate in various [39-40]

Research activities to generate new knowledge and practical skills that can further improve health and quality of life. Over the years, the role of pharmacists has evolved to be part of a multidisciplinary healthcare team, participating in patient advisory groups and reviewing the patient profile with the aim of identifying and resolving drug-related problems. Pharmacist interventions such as B. Patient counselling to improve adherence and compliance, have contributed to the steady development of clinical pharmacy services around the world, the lack of specific legislation and recognition by other healthcare providers [41-42].

Possible reasons may include a lack of acceptance of the pharmacist's professional position by other healthcare professionals, poor leadership skills, patient perceptions, and the existence of communication gaps between pharmacists and physicians. These challenges are particularly noticeable in developing countries. Physician expectations and perceptions about the roles and responsibilities of pharmacists are the main factor influencing the advancement of clinical pharmaceutical services in hospitals [43-44].

Recent reforms to hospital implementation guidelines state that pharmacists should be assigned to hospitals for the benefit of patients. Prioritizing national guidelines, the undergraduate pharmacy

curriculum shifted toward patient-centered practice by including a mandatory one-year internship program as part of academic training. Hospital clinical pharmacists began to work as an integral part of healthcare teams. Clinical pharmacists sporadically provided various care services to patients.

This includes managing drug therapy, dose adjustments, interventions to optimize drug therapy, and providing information about drugs to healthcare professionals and patients. Hospital. A better understanding of the perspectives of healthcare professionals regarding clinical pharmaceutical services may provide a better opportunity to identify future challenges and opportunities for clinical pharmacists in the hospital. Therefore, the present qualitative study aimed to examine the challenges and opportunities of clinical pharmaceutical services provided in the hospital from the perspective of healthcare professionals [45-46].

A clinical pharmacist is in no way a competitor of a doctor, on the contrary, he must refer patients who need qualified medical care to a doctor. It is difficult to imagine that a pharmacist does not know the alphabet of medicine and does not have relevant knowledge of the main clinical syndromes. Must have a particularly good knowledge of the nomenclature of medicines (mainly over-the-counter medicines). In essence, a clinical pharmacist must provide a defined pharmaceutical supply and make a decision about the dispensing of the drug [47-48].

While curricula have been adjusted to prepare pharmacists for this new role, changes in practice have focused on other issues, such as: B. the emerging Covid epidemic which has brought about significant changes in the medical care industry in terms of practice and law. Clinical pharmacy should be viewed as a different professional approach than hospital pharmacy. It is important for pharmacists to have a complete picture of a patient's condition so they can assess drug therapy and communicate effectively with other members of the healthcare team. Pharmacists need to establish a good relationship and connection with the multidisciplinary medical team by asking them to move from the pharmacy to the wards where they dispense medication and see doctors.

Staffing issues and a lack of trained clinical pharmacists have resulted in pharmacists being unable to work in clinical settings. In particular, the following pharmaceutical support functions were missing [49-50].

The concept of pharmaceutical care has evolved into integrated medication management as part of clinical pharmacy. Drug treatment has expanded as treatment regimens have become more complex and specialized, particularly in more complex patients who may have five comorbidities and are taking an average of eight drugs at a time. To achieve the best results of drug therapy in these patients, systematic and complex drug therapy is required [51-52].

More than one third of respondent pharmacists were not satisfied with professional career, about one third of them were partially satisfied with professional career (See fig.1). It is significant, that pharmaceutical companies make study of their own pharmacists' satisfaction with professional career. The pharmaceutical companies should study a combination of all factors that affect the satisfaction with professional career.



Q-13. Satisfaction professional career (In percent %)

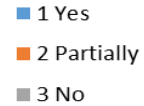
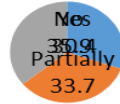


Figure 1. Satisfaction professional career of the respondents (pharmacists).

About a quarter of respondent pharmacists were not satisfied with work; more than one third of them were partially satisfied with work (See fig.2).

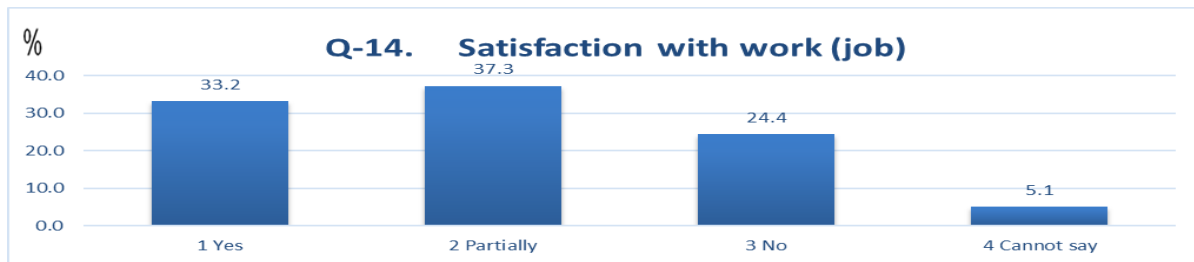


Figure 2. Satisfaction with work of the respondents (pharmacists).

Base on study results it is considerable, that pharmaceutical companies make study of pharmacist's work satisfaction. The pharmaceutical companies should determine the combination of factors that effect on the pharmacists' work satisfaction. Therefore, we recommend to the pharmaceutical companies to study and analysis features of main factors that influences on the pharmacists' job gratification, See Table -1. [53-54].

Table 1.

Report of impacting factors, which influenced on the respondents (pharmacists) work satisfaction, estimated under the 5- point scale system

Q-15. Estimation of the impacting factors influenced on the work satisfaction (estimation for each factor)	Mean	Median	Std. Deviation
q15_1 The content of work	4.03	4.00	1.061
q15_2 Position held	3.92	4.00	1.025
q15_3 Correspondence of qualification to work	4.09	4.00	1.009
q15_4 Correspondence of nature of work to my capabilities, aspirations, and inclinations	4.10	4.00	0.990
q15_5 Existence of perspective for professional promotion	3.85	4.00	1.171
q15_6 Existence of perspective for career promotion	3.81	4.00	1.204
q15_7 The possibility to enhance improve qualifications	4.03	4.00	1.085

q15_8 - Existence of a high degree responsibility for the work results	4.02	4.00	1.124
q15_9 Regimen of work	3.66	4.00	1.145
q15_10 Labor salary	2.43	3.00	1.253
q15_11 Existence of the system of benefits scheme for employees	3.52	4.00	1.243
q15_12 Support and assistance of a manager (chief)	4.17	5.00	1.090
q15_13 Direct relationships with manager	4.24	5.00	1.062
q15_14 Relationships to colleagues	4.57	5.00	0.815

During the research we found and evaluated some impacting factors which have influenced on the work satisfaction of pharmacists. These factors were: the content of work, position, correspondence of qualification to work; correspondence of the work nature to capabilities, aspirations, and inclinations of pharmacist; existence of perspectives for the professional promotion (enhancement) and the career promotion; the possibility to improve qualifications; existence of a high degree of responsibility for the work results, regimen of work, labor salary; existence of the system of benefits scheme for employees; support and assistance of a manager (chief); direct relationships with manager and colleagues.

About a quarter of respondent pharmacists (pharmacists) have realized professional capabilities, skills and habits partially; less than 50% of them - of own potential; about half of them have realized professional capabilities, skills and habits partially; more than 50% of them - of own potential (See fig.3). Pharmaceutical companies should create constructive working conditions for pharmacists to maximally realize their professional capabilities, skills and habits. This will increase the quality of pharmaceutical care in pharmacies [55-56].

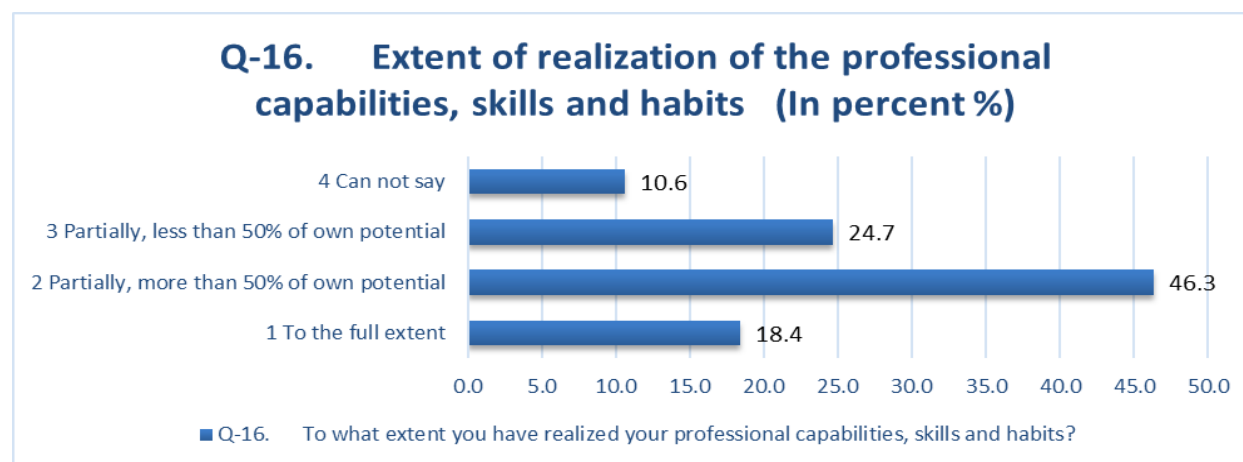


Figure 3. Extent of the respondents' (pharmacists) realization of the professional capabilities, skills and habits

During the research there were found and evaluated the factors, influencing on the pharmacists' professional development: interesting and valuable (informative) work; the favorable (prosperous) psychological climate within the colleague's team; possibility of the career growth; possibility of



the professional education or training; the social importance of the profession; independence in work (See tabl.2) [57-58].

Table 2. Report of factors, influencing of the respondents' (pharmacists) professional development evaluated under 5-point scale system

Q-17.Evaluation of the factors, influencing on the professional development of the respondents (evaluation for each factor)	Mean	Median	Std. Deviation
q17_1 Interesting and valuable work	4.03	4.00	0.967
q17_2 The favorable psychological climate within the colleagues team	4.04	4.00	1.008
q17_3 The possibility of career growth	3.90	4.00	1.075
q17_4 The possibility of professional education or training	4.15	4.00	0.969
q17_5 The social importance of the profession	4.11	4.00	1.010
q17_6 Independence in work	4.08	4.00	1.036

The respondents (pharmacists) ' majority considered that education should not be ceased; the minority of them - that it is possible to cease education after getting specialist diploma (degree) or the specialist certificate (See fig.4). On our view it is of the crucial necessity that all the pharmacists should realize, reconsider and understand the importance of continuous pharmaceutical and medical education in constantly. Further diploma pharmaceutical education is a very important factor for the upper qualification of pharmacists and essential index for the high-grade of pharmaceutical care [59-60].

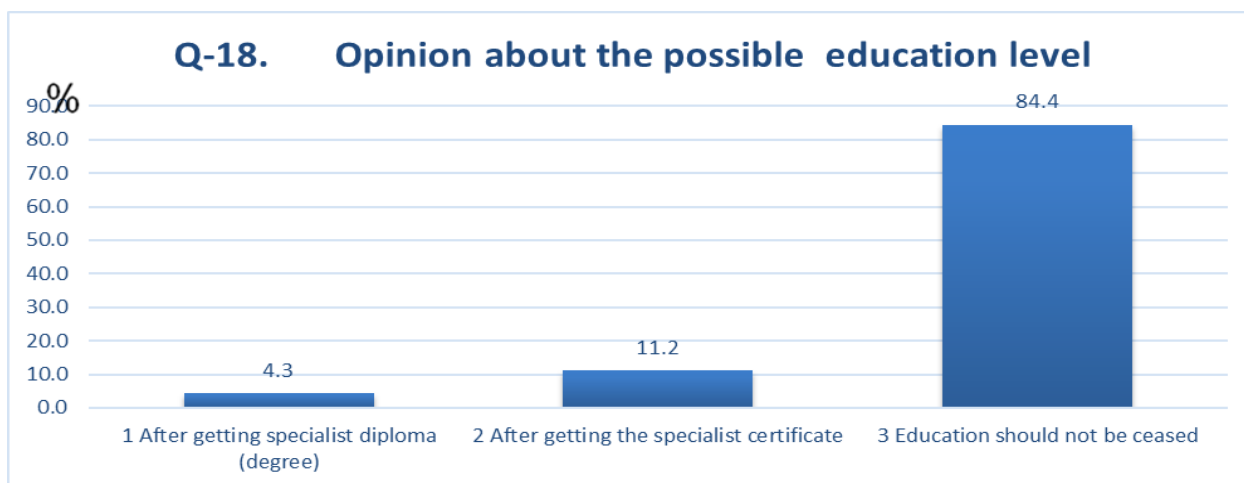


Figure 4. The respondents' (pharmacists) opinion about the possible education level.

The minority of respondent pharmacists had not used knowledge in their practice, obtained from professional publications; less than half of them had partially used that knowledge (See fig.5). It is very important that pharmacists have to use knowledge obtained from the professional publications, journals and the modern pharmaceutical literature in their practice [61-62].

**Q-19. Opinion of respondents about their knowledge, obtained from professional publications used in the practice
 (In Percent %)**

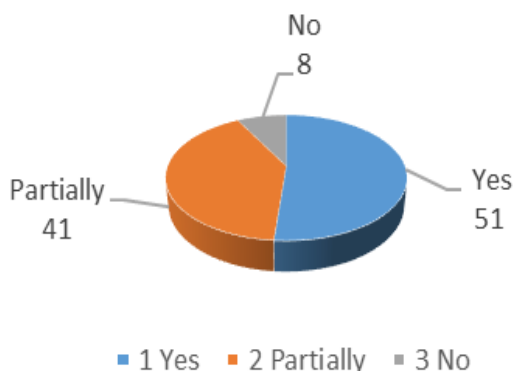


Figure 5. Opinion of the respondents about their knowledge, obtained from professional publications used in the practice.

Mostly essential pharmaceutical activity issues for the respondents' (pharmacists) majority were: new drugs, generic drugs, chemical and brand names of them; psychology of communication (relationships) with customers; issues of pharmacotherapy of certain diseases, pharmacology, pharmacodynamics, pharmacokinetics and pharmaceutical care (See tabl.3). It is apparent, that in the higher pharmaceutical education universities programs should be emphasized on the following subjects: pharmacotherapy, pharmacology, pharmaceutical care, clinical pharmacy and drugs toxicity.

The minority of respondents (pharmacists) had neutral attitude toward learning and qualification upgrading (improvement) study courses (See fig.6). The professional trainings, complementary educational programs, skill enhancement learning instruction, professional workshops are appear to be very necessary for the further professional advancement , vocational development and for occupational improvement strategies [63-64].

Table 3. Mostly essential pharmaceutical activity issues for the respondents (pharmacists).

Q-20. The most essential (relevant) for respondents issues of pharmaceutical activity (several answers were possible)	Count	Percent (%)
1. New drugs, generic drugs, chemical and brand names of drugs	518	64.0
2. Psychology of communication (relationships) with customers	478	59.0
3. Issues of pharmacotherapy of certain diseases	541	66.8
4. The safety, effectiveness and quality of the drugs	558	68.9
5. Pharmacology, pharmacodynamics and pharmacokinetics issues	572	70.6
6. The normative legal regulation of pharmaceutical activity	364	44.9
7. Drug technology issues	241	29.8



8. Pharmacognosy	110	13.6
9. Pharmaceutical organization and economics and pharmaceutical business	154	19.0
10. Pharmaceutical management and marketing	281	34.7
11. Pharmacchemistry	90	11.1
12. Toxicology	96	11.9
13. Clinical pharmacy	267	33.0
14. Pharmaceutical care	487	60.1
15. Pharmaceutical analysis	77	9.5
16. Toxicological chemistry	50	6.2
17. Pharmaceutical technologies	86	10.6
18. Nutrition	95	11.7
19. Pharmaceutical cosmetics and perfume	178	22.0
20. Social pharmacy and Public Health	146	18.0
21. Computer technology and pharmaceutical information	140	17.3
22. Phytotherapy	132	16.3
23. Routes of drug administration	183	22.6
24. Drug forms and drug design	158	19.5
25. Drugs' toxic effects	196	24.2
26. Rules of drug administration	237	29.3
27. Cost-effectiveness and cost-benefits of drugs	124	15.3
28. Terms and conditions of storage of drug (conditions and shelf-life)	259	32.0

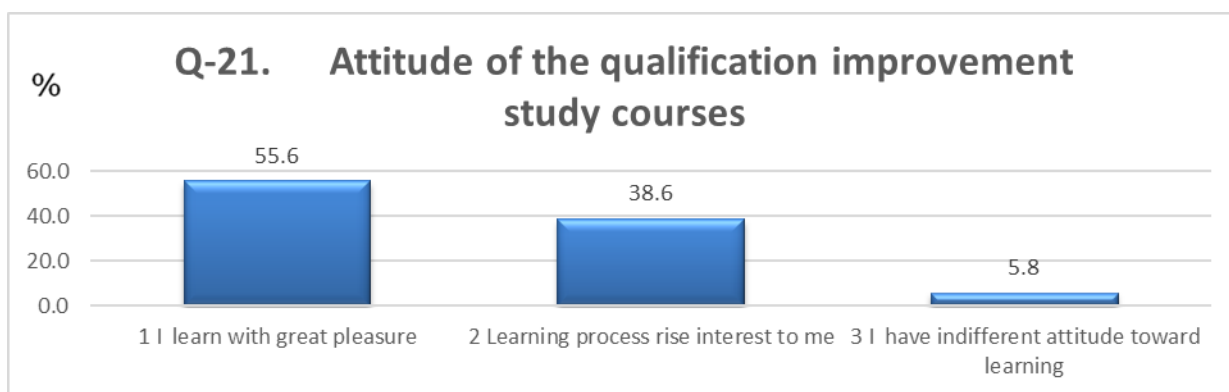


Figure 6. Attitude of the respondents to qualification upgrading (improvement) study courses

A large majority of respondents' (pharmacists) consider that the Government should make the certification of pharmacists (See fig.7). As revealed, it is very important that the occupation of pharmacist should become regulated health profession. To raise pharmacists' specialists' professionalism, Government should make the certification of higher pharmaceutical education pharmacists. That is very essential for pharmacist's professional perfection, for successful higher pharmaceutical education, for pharmacist self-realization, for pharmacist's career advancement, for to exist pharmaceutical continuous professional education, for pharmacist professional growth,

for pharmacist job gratification, for pharmacist career satisfaction, for pharmacists much higher status between health care specialists. Pharmacist certification is essential for pharmacists economic (material) welfare, for allows pharmacists to realize fully the received knowledge from higher education institution in work by the full extent, for to have private pharmaceutical activity, for pharmacists vocational development, for correspondence of pharmacist qualification to work, for further improvement perspective for pharmacists' professional promotion, for possibility to career enhancement strategy, for to realize by the full extent pharmacist professional capabilities, skills and habits, for occupational growth, for pharmacists professional satisfaction, for career enhancement perspective, for satisfaction of income (salary). Therefore, pharmacists' certification should start immediately and pharmacist vocation should become regulated health profession like family doctors [65-66].

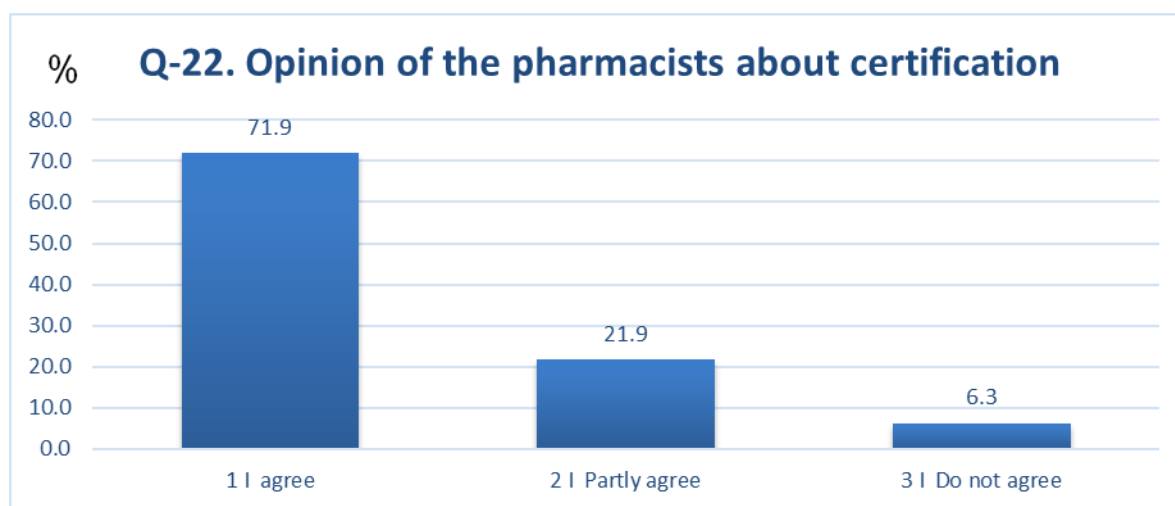


Figure 7. Opinion of the respondents (pharmacists), on the question- if the pharmacists' certification should done by the Government.

Less than half of respondent pharmacists are engaged in planning of professional career, more than a third of respondent pharmacists are engaged partially in planning of professional career (See fig.8).



Figure 8. The respondents (pharmacists) engagement in planning of professional career

During research were found and evaluated goals that achieve as a result through professional career for pharmacists. These goals for pharmacist were obtain more power and authority, much higher status, independence, self-realization, power, economic (material) welfare, professional growth and career advancement (See tabl.4).

Table 4. Report of the respondents (pharmacists) on the question – “What goals do you want to achieve as a result through professional career?”

Q-24. What goals do you want to achieve as a result through professional career? (Please evaluate each of the chosen option by 5 point scale system)	Mean	Median	Std. Deviation
q24_1 Obtain more power and authority	3.71	4.00	1.245
q24_2 Much higher status	3.84	4.00	1.203
q24_3 Independence	3.88	4.00	1.253
q24_4 Self-realization	4.08	5.00	1.203
q24_5 Power	3.16	3.00	1.449
q24_6 Economic (material) welfare	4.51	5.00	0.877
q24_7 Professional growth	4.54	5.00	0.858
q24_8 Career advancement (growth)	4.50	5.00	0.937

More than one third of respondent pharmacists are not satisfied with the balance between the workload and personal life, less than one third respondent pharmacists are partially satisfied with the balance between the workload and personal life (See fig.9). The balance between the workload and pharmacist's personal life should be more harmonized, comfortable, convenient,

resourceful and more poised. That flexibility will further improve pharmacists' work ability and motivation toward the job [67-68].

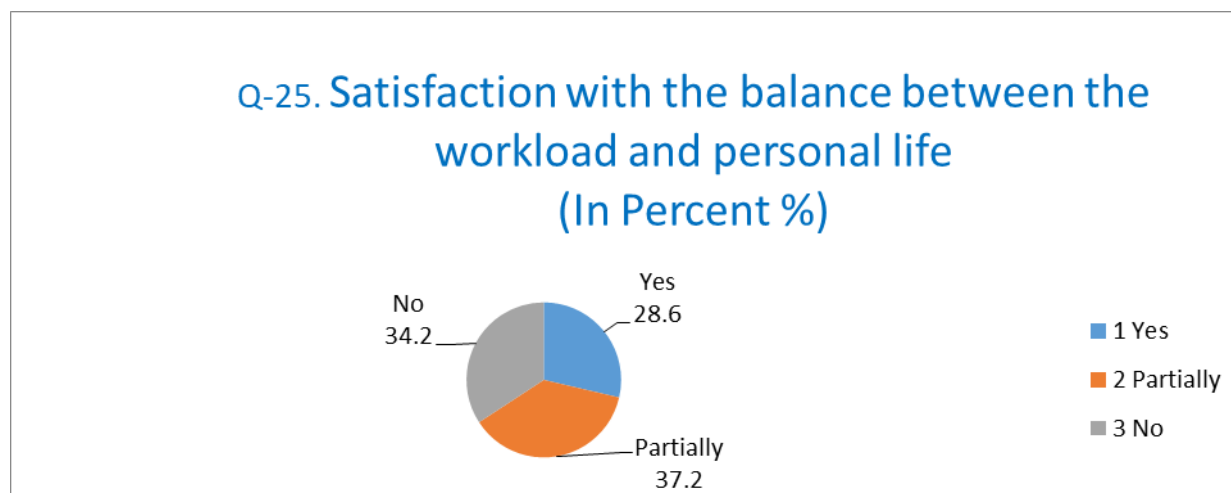


Figure 9. The respondents' (pharmacists) satisfaction with the balance between the workload and personal life.

Less than half of respondent pharmacists are not satisfied with the time duration of job, more than one third of respondent pharmacists are partially satisfied with the time duration of job (See fig.10). It is very important that pharmaceutical companies have created such working schedule and working conditions for pharmacists, which will contribute to improve pharmacists' satisfaction according the time duration of job. That flexibility working schedule and working conditions will further enhance pharmacists' work ability and motivation toward the job. These factors will improve the quality of pharmaceutical care in pharmacies.

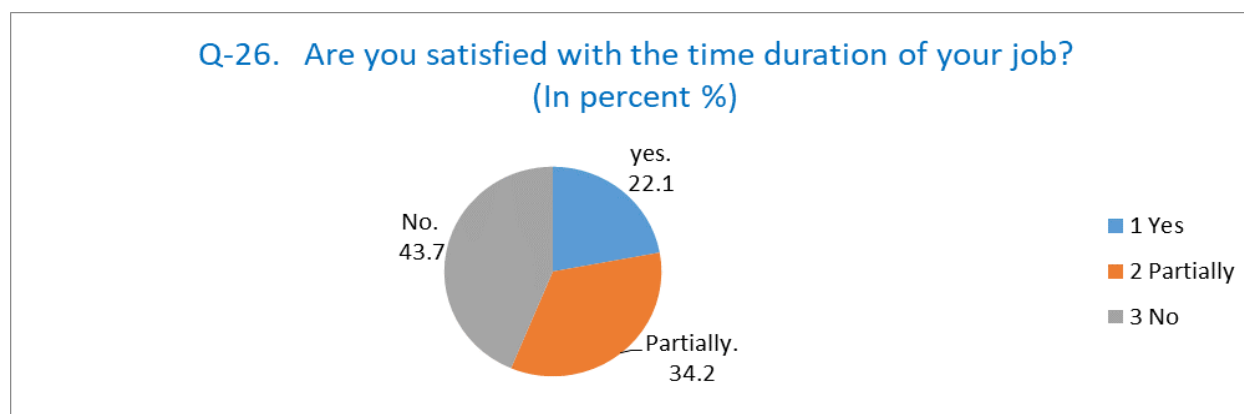


Figure 10. The respondents' (pharmacists) satisfaction with the time duration of job.

The Majority of the respondents are not satisfied with income, a quarter of them are partially satisfied with income (See tabl.5). It should be noted, that pharmacist's satisfaction with income is a very sensitive factor that has a significant impact on the quality of pharmaceutical services



performed in pharmacy. Therefore, pharmacist salary should be increased [69-70] according pharmacist' professional competences, occupational motivation, theoretical and practical knowledge, in our opinion pharmacist satisfaction with income could be enhance and regulate via creation pharmacists' periodic certification, licensing and accreditation systems in Georgia.

Table 5. Satisfaction of the respondents (pharmacists) with income.

Q-27. Are you satisfied with your income?	Frequency	Percent (%)
1. Yes	83	10.2
2. Partially	206	25.4
3. No	521	64.3
Total	810	100.0

The majority of the respondent chief pharmacists searching for the specialists applied Internet and advertisements in mass media or in printed and electronic media (See fig.11).

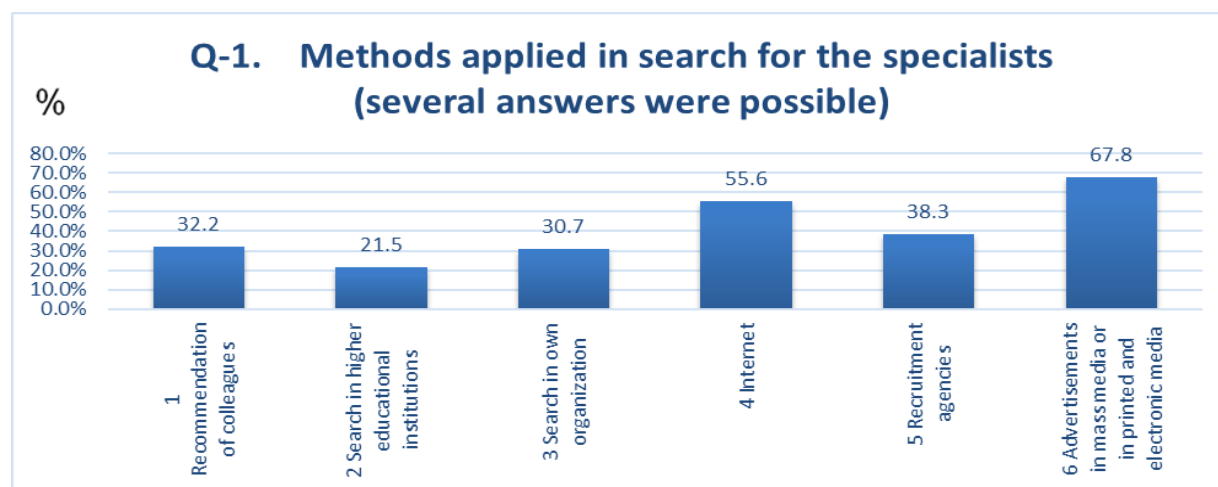


Figure 11. The methods respondents applied in search for the specialists.

The main time length required for searching of pharmacists on vacant position by respondent chief pharmacists was up to 3 months (See fig.12).

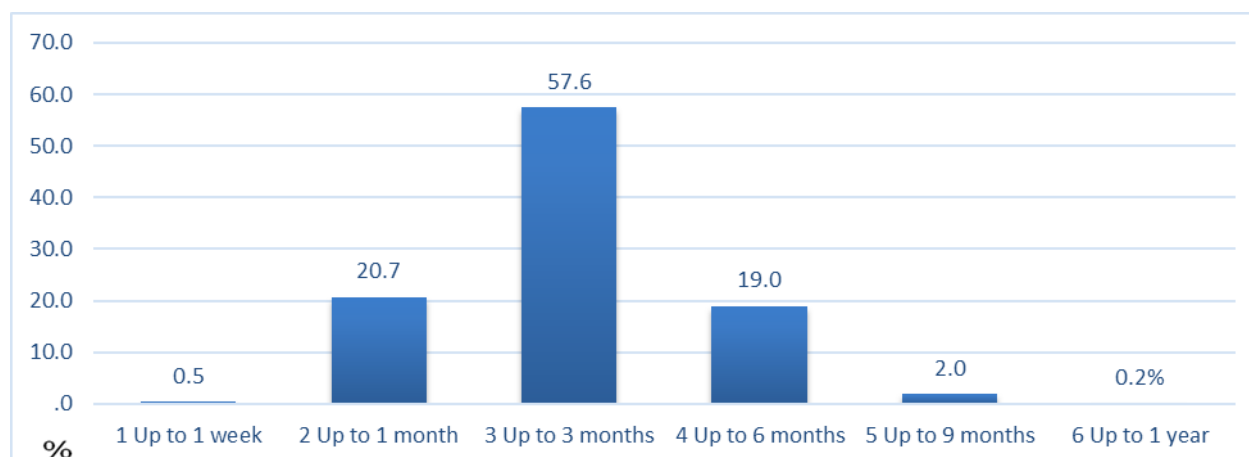


Figure 12. Time required for searching of specialists on vacant position for the respondents (chief pharmacists).

The majority of the respondents (chief pharmacists) considered that main qualities, capabilities and skills required for pharmacists were ability to make decision fast and love towards their profession.

Less than half part of chief pharmacists considered that main qualities, capabilities and skills required for pharmacists were flexibility while changing the labor functions, ability to build up relations with people and high level of culture (See tabl.6) [71-72].

Table 6. The respondents' opinion about qualities, capabilities and skills required for specialists.

Q-3. The qualities, capabilities and skills required for specialists (several answers were acceptable)	Count	Percent (%)
1. High intelligence level	46	11.2
2. Professional competency	120	29.3
3. Flexibility while changing the labor functions	166	40.5
4. Ability to make decision fast	254	62.0
5. Love towards the profession	210	51.2
6. Sense to get innovation	89	21.7
7. Ability to build up relations with people	179	43.7
8. High level of culture	186	45.4
9. Culture of speech	89	21.7
10. Orientation towards the creative work (focus on creativity)	108	26.3
11. High motivation to work	67	16.3

The majority of respondent chief pharmacists considered that main personal features required for a young specialist was attentiveness. Less than half of respondent chief pharmacists considered that personal features required for a young specialist was ability to work in a team, purposefulness, ability to learn, kindness, politeness and higher motivation to work (See tabl.7) [73-74].

**Table 7.** The respondents' opinion about personal features required for a young specialist.

Q-4. The personal features required for a young specialist (several answers were acceptable)	Count	Percent (%)
1. Goodwill or amiability	83	20.2
2. Initiative ability	153	37.3
3. Ability to work in a team	195	47.6
4. Purposefulness	176	42.9
5. Ability to learn	203	49.5
6. Kindness and politeness	175	42.7
7. Attentiveness	215	52.4
8. High motivation to work	162	39.5

The majority of respondent chief pharmacists' requirements for a young specialist were: working experience, higher education and recommendations. About one third part of respondent's requirements and demands for a young specialist were proximity of place of residence to working place, marital status, plan for career development and high motivation to work (See tabl.8). We concluded that higher pharmaceutical education was necessary precondition to start work on the pharmacist position. As it found pharmacist should have attentiveness, ability to learn, ability to work in a team, purposefulness, kindness and politeness, high motivation to work [75-76].

Table 8. The respondents' requirements for a young specialist.

Q-5. The requirements demanded from a young specialist (several answers were acceptable)	Count	Percent %
1. Working experience	218	53.2
2. Proximity of place of residence to working place	131	32.0
3. Marital status	131	32.0
4. Children	76	18.5
5. Higher pharmaceutical education	240	58.5
6. Recommendations	209	51.0
7. Plan for career development	141	34.4
8. High motivation to work	131	32.0

The majority of respondent chief pharmacists considered that necessary time period for adaptation of a young specialist ranged from 9 months till up to 1 year (See fig.13).

The majority of chief pharmacists considered that the mostly essential difficulties in professional adaptation of young employees were lack of professional knowledge and also of special skills (computer skills and etc) [77-78].

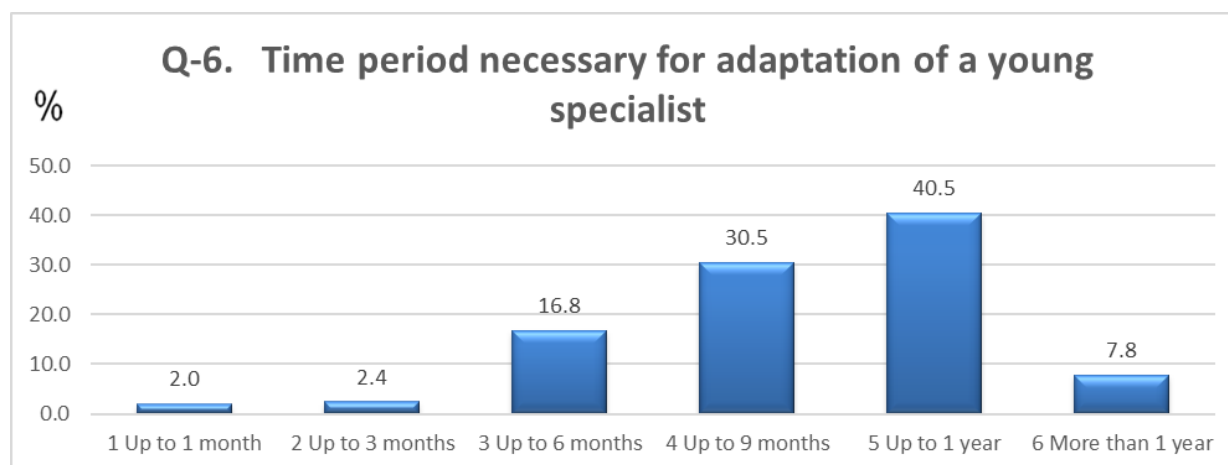


Figure 13. The respondents' opinion about the time period necessary for adaptation of a young specialist

Less than half part of respondents considered that the mostly essential difficulties in professional adaptation of young employees were difficulties with adaptation within the colleagues' team, difficulties in relationship with administration (leadership), non-compliance of a job with own ideas (See tabl.9). According to that university pharmacy program should be more orientated to special skills, which gives possibility and capability to pharmacists to use gained professional knowledge in practical situation.

Table 9. The respondents' opinion about the mostly essential difficulties in professional adaptation of young employees.

Q-7. The most essential difficulties in professional adaptation of young employees (several answers were acceptable)	Count	Percent %
1. Lack of professional knowledge	250	61.0
2. Lack of computer skills or other special skills/ certain peculiar specific skills	271	66.1
3. Difficulty with adaptation in to collective (within the colleagues team)	139	33.9
4. Difficulties in relationship with administration (leadership)	196	47.8
5. Non-compliance of a job with own ideas	164	40.0
6. Having excessive ambitions	90	22.0

The chief pharmacists' majority considered that most effective forms of professional assistance while adapting of the specialist to work were independent practical activity and personal conversation. Less than half part of respondents considered that most effective forms of professional assistance while adapting of the specialist were discussion on work of young employees within the colleagues' team and on special training programs. About one third each of them considered necessary to work with a mentor, internship and qualification upgrading courses (See tabl.10).



Table 10. The respondents' opinion about the most effective forms of professional assistance while adaptation of the specialist.

Q-8. The most effective forms of professional assistance while adaptation of the specialist (several answers were possible)	Count	Percent %
1. Independent practical activity	262	63.9
2. Working with a mentor	142	34.6
3. Internship	137	33.4
4. Discussion of work of young employees within the colleagues team	196	47.8
5. Personal conversation	293	71.5
6. Qualification improvement upgrading courses	120	29.3
7. Special training programs	169	41.2

During research there were found and evaluated the chief pharmacists' factors having an influence on the professional development of young specialists. These factors were: interesting and valuable work, the favorable psychological climate within the team of colleagues, possibility of career development, social importance of profession, and independence in work, professional education, professional trainings (See tabl.11).

Table 11. Report about the respondents' opinion regarding the professional development of young specialists.

Q-9.The directions of acting by chief pharmacists for professional development of young specialists (each factor was evaluated by 5-point system)	Mean	Median	Std. Deviation
q9_1 Interesting and valuable work	4.64	5.00	0.813
q9_2 The favorable psychological climate within the team of colleagues	4.38	4.50	0.732
q9_3 Possibility of career development	4.13	4.00	1.024
q9_4 Social importance of profession	4.10	4.00	1.028
q9_5 Independence in work	3.76	4.00	1.186
q9_6 Professional education or professional trainings	4.25	5.00	0.956

Less than half part of the respondents considered that the level of basic training of pharmacists was not corresponding to the contemporary requirements (See fig.14). According to the sociological study results of the public care specialists it is obviously, that all pharmacists should have higher pharmaceutical education from the state recognized and accredited higher education institutions and universities. Pharmacists' specialty should become a regulated health care profession. According to that Government should make certification, licensing and accreditation of pharmacist professionals.

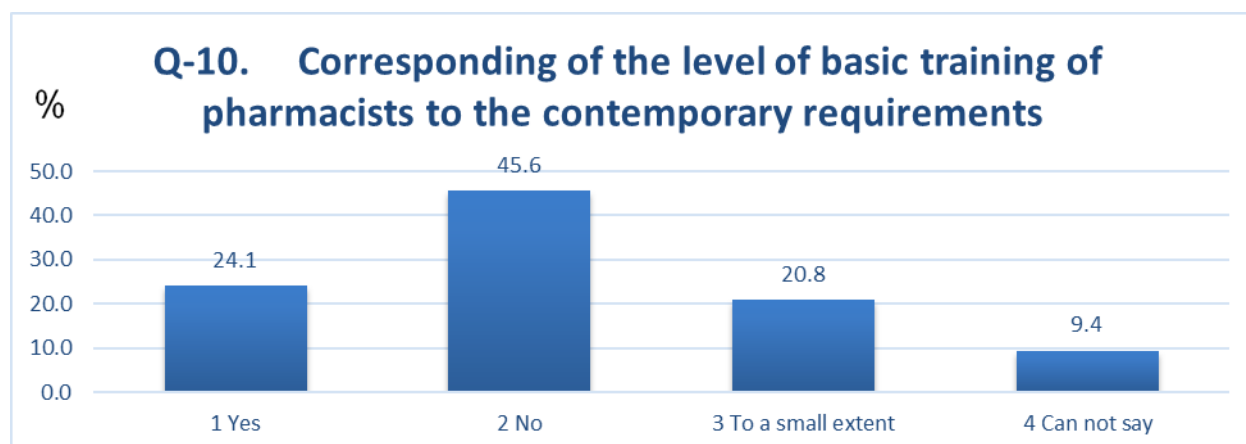


Figure 14. The respondents' opinion about pharmacists' basic training level correspondence to the contemporary requirements.

The respondents' vast majority considered that the issues to for pharmacists were in need of the further regular studies or trainings in the following fields: new medications, issues of pharmacotherapy of certain diseases, pharmacology and pharmacotherapy, drugs toxicity (See tabl.12). From the study results it is obvious that in the higher pharmaceutical institutions' pharmaceutical educational programs and curriculum need upgrade, renewal, modernization and adaptation to the new modern medical challenges. Therefore, continuous pharmaceutical educational programs should be created. These programs should be more focused on new medications, pharmacotherapy, drugs toxicity and dosage, routes of drug administration, selection of OTC drugs, cost-effectiveness and cost-benefits of drugs.

Table 12. The respondents' (public health specialists) opinions about the issues for pharmacists necessary for further regular studies or trainings.

Q-11. The issues for pharmacists necessary for the further regular studies or trainings (several answers were possible)	Count	Percent %
1. New drugs	187	60.9
2. Psychology of communication with customers	103	33.6
3. Issues of pharmacotherapy of certain diseases	197	64.2
4. Safety and effectiveness of drugs	154	50.2
5. Pharmacology and pharmacotherapy	224	73.0
6. Normative legal regulation of pharmaceutical activity	94	30.6
7. Drugs toxicity	164	53.4
8. Drugs dosage	112	36.5
9. Routes of drug administration	110	35.8
10. Drug forms	61	19.9
11. Drug design	43	14.0
12. Rules of drug administration	123	40.1
13. Drugs generic, chemical and brand names	57	18.6



14. Selection of OTC drugs	108	35.2
15. Cost-effectiveness and cost-benefits of drugs	96	31.3

Approximately half part of the respondents was not familiar to the concept of pharmaceutical care; while more than a quarter of the public health specialists were well familiar to the concept of pharmaceutical care (See fig.15).

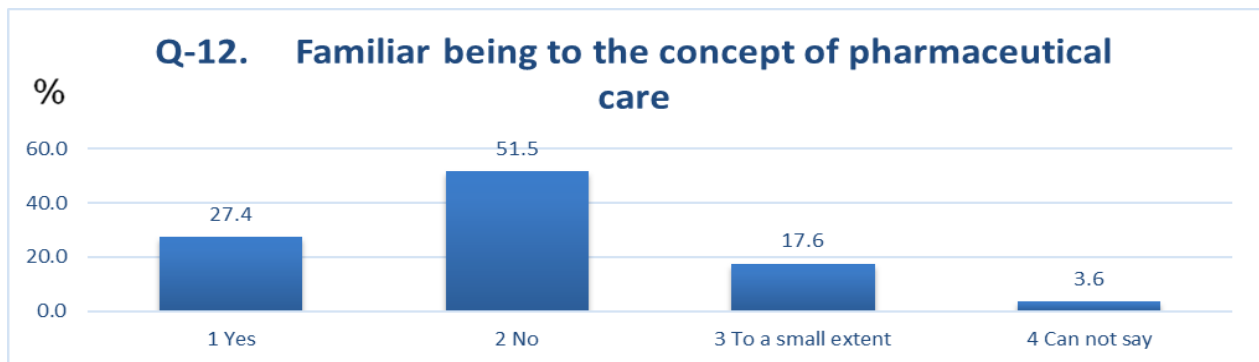


Figure 15. The respondents' (public health specialists) cognition of the concept of pharmaceutical care.

The respondents' large majority considered necessity of provision of cooperation between pharmacists and physicians on the issues of pharmacotherapy (See fig.16). The pharmacist must provide information to doctor about new drugs pharmacotherapy, the generic replacement drugs, the cost-effectiveness and cost-benefits of drugs, drugs' generic, chemical and brand names. In our opinion and vision cooperation between pharmacists and physicians on the issues of pharmacotherapy is positively reflected on patients' health and has great importance for provision higher quality health care service for patients' safety.

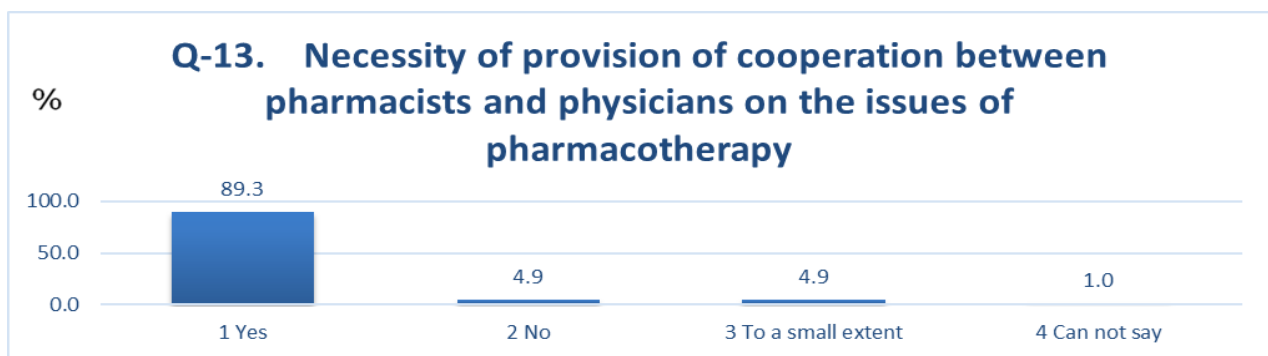


Figure 16. The respondents' opinion about the necessity to provide cooperation between pharmacists and physicians on the issues of pharmacotherapy.

More than half part of the respondents considered that pharmacist is not in charge of treatment as a physician, meanwhile about a quarter of the public health specialists considered a pharmacist to

be in charge of that (See fig.17). Properly educated pharmacist can minimize and reduce the mistakes made by a doctor in the recipe. That has a great importance and value for provision higher quality health care service for patients' safety.

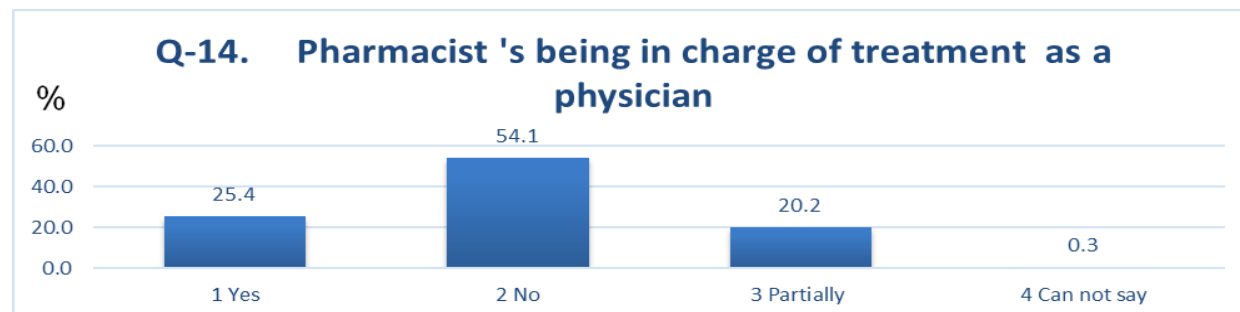


Figure 17. The respondents' (public health specialists) opinion about pharmacist's being in charge of treatment as a physician.

Conclusion

A clinical pharmacist is in no way a competitor of a doctor, on the contrary, he must refer patients who need qualified medical care to a doctor. It is difficult to imagine that a pharmacist does not know the alphabet of medicine and does not have relevant knowledge of the main clinical syndromes. Must have a particularly good knowledge of the nomenclature of medicines (mainly over-the-counter medicines). In essence, a clinical pharmacist must provide a defined pharmaceutical supply and make a decision about the dispensing of the drug. The respondents' vast majority considered that pharmacist should provide assistance in teaching patients to understand the prescribed drugs intake rules. According to that higher quality pharmaceutical service could be only provided by the pharmacists of higher pharmaceutical education, graduated from the authorized, accredited and licensed by the state higher education institutes and universities.

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CHARACTERISTICS OF IMMUNE SYSTEM OF THE SKIN (REVIEW)

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Being the largest organ of the body, skin protects the internal organs from various external insults, such as invading pathogens (bacteria, fungi, viruses, parasites, and mites), exogenous physical stresses, chemicals, and others. Besides, it has an essential role in regulating temperature, electrolytes, water, and others, and providing essential vitamins to the whole body, ie, Vitamin D. Unlike other mucosal epithelia, skin possesses a dry (due to lipids) and a formidable layer of epithelia, which prevent the ease of access of microorganism entry.^{1,2} Despite other routes of pathogen entry, the skin plays an important role in protecting from pathogens. Besides, skin cells also produce many chemicals, such as fatty acids and defensins (antibacterial peptides), to destroy the pathogens. As such, skin is composed of three different major layers, which harbor several types of cells, including immune cells, that perform various functions.³ Considering this high amount of immune niches in the skin, it is regarded as “skin immune system” or “tertiary lymphoid structures” or “tertiary lymphoid organs” .^{4,5} In addition, damaged or tender skin is the best route of entry for many microorganisms. Therefore, regulation of immune responses in the skin is at most important. The skin-associated lymphoid system is composed of tightly coordinated innate and adaptive arms of the immune system. Despite the innate immune system, humoral immunity (also called antibody-mediated immunity) in the adaptive immune system is also critical for regulating immune homeostasis in the skin. B-cells and their subtypes in the skin have been implicated in antibody-mediated protective immunity. However, the type of antibody production (either self-reactive or non-self-reactive) depends on the type of antigen (self or foreign) exposed, and may drive or suppress the inflammatory response. Therefore, B-cells are implicated in both homeostatic and pathogenic mechanisms in the skin. Although information about localized skin-resident B-cells is inadequate, their migration, via expressing cutaneous lymphocyte-associated antigen and chemokine receptors, to the skin during the inflammatory diseases is well established. Many autoimmune skin diseases are positively correlated with the infiltrating B-cell subsets. Moreover, the skin-homing B-cells respond to local antigens and produce antibodies, which is devoid of primary and secondary lymphoid organs. These antibodies play a crucial role in autoimmune diseases. Some B-cell-mediated autoimmune diseases are mostly by autoreactive B-cells that are possibly devoid of T-cell involvement. The precise source of the autoreactive B-cells in the skin is unknown and is debatable. It is assumed that autoreactive B-cells are generated from either bone marrow or secondary lymphoid organs. However, how these cells are produced by escaping the central or peripheral tolerance checkpoints is still an unanswered question. Once autoreactive B-cells differentiate into memory B-cells and plasma cells in the germinal centers, they become culprits for systemic secretion of autoantibodies.^{6,7} Once the plasma cells are generated, it's their innate nature to reach bone marrow and become a reservoir for a long time (even lifelong) of autoantibody secretion, upon antigen encounter. In skin-associated or cutaneous autoimmune diseases, the presence of autoantibodies is considered a unique diagnostic method. The skin resident autoreactive B-cells amplify or aggravate the

autoimmune disease via antibody secretion (IgM, IgG, and IgA), antigen-presentation, T-cell stimulation, pro- and anti-inflammatory cytokine secretion (IL-6, IL-10, and TGF- β), and growth factors secretion (platelet-derived growth factor, basic fibroblast growth factor) in the microenvironment. Skin-associated lymphoid tissue contains both innate and adaptive immune systems, which confer protection locally and systemically. 7. Disturbance in the above system leads to episodes of opportunistic infections and the development of tumors or other immunological diseases. The skin protects the host from most infectious agents by two mechanisms; antigen-nonspecific and antigen-specific. 8. If a physical barrier (stratum corneum or sebaceous gland secretions) is breached, the innate immune system comes into action. Like other parts of the body, the innate immune system is the first-line defence in the skin, and keratinocytes, monocytes, macrophages, Langerhans cells, dendritic cells, mast cells, and complement components are the innate components of the skin.9,10.

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CURCUMIN AND RESVERATROL TREATMENT OUTCOMES IN DERMATOLOGY

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Curcumin originates from turmeric or *Curcuma longa* and belongs to the family of Zingiberaceae or ginger that is usually used as spice for food flavouring. Turmeric is commonly-used in South Asia, India, and Indonesia and is often used as a dye or food color since it exists in bright orange-yellow crystals.1. According to Panahi et al⁴⁹ turmeric contains curcuminoids which include curcumin or specifically, deferuloylmethane (75%), demethoxycurcumin (20%), and bisdemethoxycurcumin (5%). Curcumin is chemically known as [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]. It is a keto-enol tautomer and is a natural polyphenol that have many important uses.2. Additionally, curcumin is used in the treatment of several diseases since the molecule rapidly penetrates the cell membranes and acts on multiple targets in different-cellular pathways. Some studies reported that curcumin is 1) a useful antimicrobial agent, 2) a preservative, and 3) possesses different therapeutic actions against cancer, dyslipidemia, skin diseases, osteoarthritis, diabetes, metabolic syndrome, endothelial dysfunction, autoimmune disease, non-alcoholic fatty liver disease, respiratory disease, depression, premenstrual syndrome, and hyperuricemia. Resveratrol, a stilbenoid in a phytoalexin group was first discovered in 1939 and is chemically introduced as 3,5,4'-trihydroxy-trans-stilbene. Resveratrol, which was first discovered from the white hellebore, also known as the roots of *Veratrum grandiflorum* and also available from the root of *Polygonum cuspidatum*, is usually utilized in Japanese and Chinese medicines. Interestingly, resveratrol is produced by plants in response to stressors like insects, animals, mechanical injury, UV radiation, and also microorganisms including fungal infection. Resveratrol exists in more than 70 plant species, although it is most abundant in grape skin besides being present in other foods and beverages including wine.3. Ruivo et al⁷⁷ reported that resveratrol is also found in cranberries, peanuts, cocoa, chocolate, and tomatoes. Skin aging is classified into either extrinsic or intrinsic. The former is primarily caused by environmental factors like pollutants, lifestyle, and solar radiation, while the latter are changes that progress over time, depending on the anatomy, genetics, hormones, and ethnicity. An important factor contributing to skin aging is activated MMPs that cause damage to the skin structural integrity, leading to wrinkle formation. TNF- α -induced expression of inflammatory cytokines and MMPs is inhibited by resveratrol through a sirtuin 1-dependent mechanism. Evidence and Understanding Their Mechanism of Action

Resveratrol appears in cis- and trans-isomeric forms with the trans-form being the biologically active version.4. The cis-form is isomerized from trans-resveratrol via UV irradiation and in the presence of high pH during grape skin fermentation. Currently, resveratrol is an important significant nutritional supplement as it has various benefits such as cellular defense against oxidative stress.5. The pharmacological effects include anti-inflammatory, antimicrobial, anti-cancer, anti-aging, and neuroprotective effects, making resveratrol a potential natural product for human health. In some reports, resveratrol is useful for amelioration of cardiovascular disease,

diabetes, skin disorders, and obesity. It is also high in antioxidants and combats free radical damage by acting as a potent radical scavenger.⁶ Skin aging is classified into either extrinsic or intrinsic. The former is primarily caused by environmental factors like pollutants, lifestyle, and solar radiation, while the latter are changes that progress over time, depending on the anatomy, genetics, hormones, and ethnicity.⁷ An important factor contributing to skin aging is activated MMPs that cause damage to the skin structural integrity, leading to wrinkle formation. TNF- α -induced expression of inflammatory cytokines and MMPs is inhibited by resveratrol through a sirtuin 1-dependent mechanism.⁸ According to the same article, 0.8% of resveratrol analogs, resveratryl triacetate (RTA) confer some anti-aging activity by enhancing sagging, wrinkles, elasticity, and moisture. Furthermore, in a study by Liang et al, short-term resveratrol injection retards the process of oocytes aging in mice, occurring via 1) enhancement of the expression of the anti-aging molecule sirtuin 1, 2) promotion of the mitochondria function, and 3) reduction in ROS production. Resveratrol protects normal human fibroblasts from the damaging effects of hydrogen peroxide by attaching to specific epidermal receptors. Deloche et al⁸⁴ demonstrated that skincare products containing resveratrol (0.25%) and oligoside (4%) can reduce wrinkles and improve skin firmness. Buonocore et al⁸⁵ investigated a supplement which consisted of dried grape extract containing trans-resveratrol, procyanidin, punicalagin-ellagic acid, and punica granatum, which are strong antioxidants found to enhance skin conditions like a reduction in skin roughness, increased skin moisturization, as well as elasticity. Additionally, resveratrol ameliorates skin inflammation by decreasing the expression of AP-1 and NF- κ B transcription factors, collagen breakdown, and inflammation. Skin disorders like wounds occur due to tissue injury caused by trauma and other factors.⁹ Therefore, factors influencing the healing process like nutrition, drugs, and age are also important in reduction of scarring and shortening of the healing period. In a previous study, the grape seed extract (GSE) which is a source of resveratrol can heal wounds when topically applied as a 2% cream.¹⁰ Its antimicrobial, antioxidant, and anti-inflammatory activities cause wound contraction and closure as by 1) forming a protective area in the epithelium and 2) raising the cell density and elevating the displacement of connective tissue at the wound area which enhances the wound cellular construction.

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EMBELIN AND NARINGENIN TREATMENT EFFECTS ON SKIN DISEASES

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Embelin; Embelin, from the *Embelia ribes* Burm that belongs to the Myrsinaceae family and *Lysimachia punctata*, from Primulaceae family with the chemical formula of 2,5-dihydroxy-3-undecyl-p-benzoquinone. The chemical structure of embelin contains a polar dihydroxy-1, 4-benzoquinone ring which is a two carbonyl oxygen atom adjacent to the two vinyl hydroxyl groups. 1. Embelin, which is frequently referred to as “False Black Pepper”, is an Indo-Malaysian species that originates from Malaysia, Singapore, India, Sri Lanka, and South China. *Embelia ribes* Burm is also widely used in Tibetan, Folk Indian, Homeopathy, Unani, and Siddha traditional medicinal systems in the treatment of several illnesses including the heart and urinary condition, severe inflammatory disease, tumor, insect, and snake bites. Embelin has various medicinal and pharmacological activities such as analgesic, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, antidiabetic, anxiolytic, hepatoprotective, and antifertility effects. Park et al stated that embelin is a potent inhibitor of NF- κ B and X-linked inhibitor of apoptosis protein (XIAP) that halted the binding of XIAP to procaspase-9.2. Kundap et al also reported that the fruit of *Embelia ribes* Burm can be used in the treatment of mental disorders, central nervous system (CNS) disease, and as brain tonic in the traditional medicinal system. Psoriasis is a hyperproliferative skin disorder occurring due to inflammation, as signified by the unusual differentiation and proliferation of keratinocyte, stimulation of T-cells, and polymorphonuclear leukocytes aggregation. In their investigation on the effect of embelin on skin inflammation in mice, the researchers also confirmed that the pathogenesis of psoriasis is mainly caused by TNF- α . There was a dose-dependent decrease in LPS-induced TNF- α level when several concentrations of embelin were used with an effective dose 50% (ED50) at 9.8 mg/kg.3. The researchers also investigated chronic dermatitis inflammation by 12-O-tetradecanoyl-phorbol-13-acetate-induced mice ear. Embelin can reduce edema, decrease the thickness of skin and weight, reduce stimulation of inflammatory cytokines, reduce neutrophil initiation, improve histopathological indicators, and lead to the departure of polymorphonuclear leukocyte.4. It was concluded that the anti-inflammatory effect of embelin is attributed to the suppression of TNF- α and IL-1 β as well as the inhibition of leukocyte aggregation, overall indicating that embelin is useful against psoriasis and dermatitis. Oral embelin yielded a higher weight of granulation tissue and tensile strength as seen in a dead space wound model indicating 1) that there is improved collagen development through formation of cross-linking between collagen fibres and 2) the existence of high protein content. In histology of wound tissue in the embelin-treated group, it can be observed that there was a complete healing process, with many fibroblasts having a higher number of blood vessels and collagen tissue, similar to the control group. All of these findings indicate that embelin confers a good wound healing activity as an alternative for wound healing.5.

Naringenin is a flavone from naringin or the hydrolysis of narirutin (its glycone precursor). Naringin, which is a bitter principle of grapefruit obtained from the juice, flower, and fruit rind, represents up to 10% of the fruit's dry weight. Nevertheless, flavonoids including naringenin have some limitations, especially in terms of bioavailability and limited source. Therefore, several



efforts aimed at producing naringenin from metabolic engineering of specific pathways in the microbial system like *E. coli* and *Saccharomyces cerevisiae* have been made.⁶ It confers some pharmacological activities such as anti-inflammatory, anti-microbial, hepatoprotective, anticancer, anti-atherogenic, and anti-mutagenic effects. Furthermore, naringenin also exhibits gastrointestinal, rheumatological, cardiovascular effects, and is useful in controlling malignant and infectious diseases.⁷ Naringenin is useful against atopic dermatitis; an inflammatory skin disease. As was reported by researchers that naringenin decreases the atopic dermatitis skin lesion growth in NC/Nga mice as initiated by 2,4-dinitrofluorobenzene (DNFB) via 1) inhibition of the formation of interferon-gamma (IFN- γ) by activated CD4⁺ T-cells and 2) reduction of the infiltration of skin lesions through CD8⁺ T-cells, CD4⁺ T-cells, mast-cells, and eosinophils. There was also improvement in the ear swelling in the naringenin-treated group of mice following a histological analysis on the epidermis thickness.⁸ Besides, an *in vivo* study of naringenin microsphere gel formulation indicated a reduction in inflammation as confirmed by the decrease in the total white blood count and thickness of the ear flap in the dermatitis rat model, overall highlighting the significance of the microsphere gel carrier system that can enhance its therapeutic effect. Due to its anti-inflammatory effect, naringenin is also useful against psoriasis. Trombino et al demonstrated that the solid lipid nanoparticle (SLN) containing naringenin, linolenic acid, and cyclosporine synergistically decrease psoriasis-mediated inflammation. In another study, (R)-naringenin 1) suppresses T-cell proliferation, 2) decreases pro-inflammatory cytokines like TNF- α and IL-6, and 3) caused proliferation of human peripheral blood mononuclear cells (hPBMC).⁸ Since a TNF- α blocker is useful in psoriasis, naringenin, which has anti-inflammatory effects, is a good treatment choice.⁹ Therefore, naringenin is a good candidate as an anti-psoriatic agent since it inhibits the over-expression of IL-6 and ameliorated psoriasis along with reducing the transepidermal water loss. Skin damage such as thermal burns can cause multiple complications if not appropriately treated. Naringenin can treat thermal burn-induced injury in a rat model by suppressing the pro-inflammatory markers like TNF- α , interleukin, NF- κ B, caspase-3, nitric oxide (NO) level, leukotriene-B₄ (LTB₄), PGE₂, and also through the antioxidant effect.¹⁰ As for the oxidative parameter, naringenin caused an increase in glutathione (GSH), glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD), while reducing thiobarbituric acid reactive substances (TBARS) after a 7-day treatment.

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STATE REGULATORY POLICY TO ENSURE INCLUSIVE VALUES IN THE FIELD OF NON-STATE PENSION INSURANCE IN UKRAINE

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ABSTRACT

One of the key tasks of the State and public administration is to prevent social tensions associated with poverty, property differentiation of the population, unemployment, etc. by increasing the level of social protection of the population, ensuring the inclusion of non-state pension insurance, including through an effective policy in the field of pensions. To achieve these objectives, it is necessary to create a pension system that would stimulate retirement savings, ensure a significant increase in the level of income of pensioners, maximize the dependence of pension payments on personalized contributions of insured persons, motivate work and legalize wages, etc. The problem of introducing such a pension system is particularly relevant given the current demographic situation - low birth rates, the outflow of Ukraine's economically active population abroad, and the aggressor's military actions aimed at destroying Ukrainians. This emphasizes the relevance of the chosen research topic.

Keywords: pension provision, pension system, inclusion, inclusive values, financial control, non-state pension funds.

Analysis of recent publications

In the national economic science, the problem of non-state pension insurance has been covered by such scholars as V. Vygovska [1], M. Kravchenko, N. Kovaleva, M. Lazebnoi [2], D. Leonov, A. Fedorenko [6], N. Mrachkovska, L. Pavlovska [3], L. Pozdnyakova, L. Ptashchenko [4], M. Marich, A. Shuper [5] and others. Scientists analyze the regulatory framework for the establishment of non-state pension funds (hereinafter - NPF), the mechanism of their functioning, and study the foreign experience of non-state pension funds. However, a number of issues remain unresolved today to ensure the efficiency of NPFs in particular and the development of the financial market in general, as well as the transparency of funds' activities. It is also still relevant to develop a set of measures for the development of the NPF network, the involvement of active financial services market players, the State, and corporations in private pension insurance to stimulate growth in the number of NPF participants, i.e. inclusiveness.

The purpose of the article is to study the problems of the State policy in the regulation of non-state pension funds in Ukraine and, based on the study of international experience, to formulate proposals for ensuring inclusive values in the field of non-state pension insurance.

Main body

Inclusion or inclusiveness is the process of including all citizens in a society in a certain system (for example, pension insurance), regardless of their physical, physiological or other characteristics. Inclusive values are, above all, the recognition of diversity, equality, justice, cooperation, and participation [7].

Inclusive development aims to ensure that all citizens of society benefit from sustainable economic and social development. Many organizations implement this approach in the fight against poverty by supporting education and providing livelihoods for those in need. It is the inclusive approach that will help Ukrainians become more active in making decisions about the need to invest in a decent life after they leave the workforce.

At the same time, inclusive values are not working in the field of private pensions. The goals declared when the third pillar of the pension system was introduced have not been achieved.

1. Pension savings have not become an effective tool for ensuring a decent old age. As of June 30, 2021, pension payments (one-time and fixed-term) amounted to UAH 1,196.2 million, which is 16.2% more than in the same period in 2020, with one-time payments increasing by 9.4% and fixed-term pension payments by 26.4%. The analysis of the dynamics of the number of NPF participants leads to the conclusion that the system is developing not in an extensive way, but through simple replacement due to the natural attrition of the labor force, although it should be noted that the trend is positive as defined benefit pensions are increasing much faster.

2. Pension savings have not become a significant source of investment resources for the needs of the national economy. The total value of assets formed by non-state pension funds as of June 30, 2021 amounted to only UAH 3,712.9 million,

3. Non-state pension funds have not become an effective institution for attracting funds from individuals. As of the beginning of 2019, the amount of funds accumulated by NPFs amounted to UAH 2,745.2 million, which is an average of UAH 3,210 per system participant [8].

In our opinion, the main reason for the unsatisfactory pace of development of private pension provision is the conceptual error of the implemented model. The error is caused by two factors:

First, the formation of voluntary funded pension systems has historically occurred in developed societies. Since an individual decides whether to join a voluntary pension savings system, contributions to a future pension begin to compete with other expenditure items (food, clothing, durable goods, education, medical treatment, etc.) that may become more urgent at certain stages of the life cycle, which is what is happening in Ukraine. In general, it can be argued that voluntary pension savings are characteristic of developed countries, which, unfortunately, do not include Ukraine. In countries with weak economies, external motivational factors play a crucial role, but in Ukraine they are virtually absent.

Secondly, the development of voluntary funded pension systems in developed countries mostly occurred during the period of smooth economic growth, i.e., in the absence of significant financial and economic shocks.

The insufficient level of motivation of the population to participate in NPFs should be considered a consequence of the following factors.

1. Insufficient public awareness of the principles of functioning of the NPF institution.
2. Low level of public confidence in NPFs.
3. Insufficient awareness and low level of public trust in the financial system.
4. High level of paternalism in the public consciousness. In answering the question "Who should take care of decent provision for your old age?" the vast majority of respondents give the main role to the state, namely: "the state" - 41%, "both the state and myself" - 49%. Moreover, younger



respondents are most likely to believe that ensuring a decent old age is their personal responsibility, while more than half of those aged 60 and older believe that providing a pension is the responsibility of the state.

5. Significant transaction costs associated with making contributions to NPFs: insufficient benefits for NPF participants, complicated mechanism for refunding overpaid personal income tax.

6. Economic instability in the country due to COVID and the war. This, in turn, leads to such negative consequences as the outflow of economically active people abroad or their involvement in the defense of the country, loss-making enterprises and certain industries (due to destruction or inability to operate in emergency conditions).

In many countries, NPFs are one of the main instruments for improving the level of pension provision of the population. Among the types of NPFs, open funds prevail because of their versatility. After all, any citizen can become both a contributor to an open NPF and a participant without restrictions on professional or employment status. The functioning of these funds is not subject to restrictions established by law, for example, for corporate NPFs. An open NPF makes it possible to attract a wide range of interested businesses and individuals as depositors. Some experts believe that the advantage of this fund is a simpler procedure for concluding pension contracts by both individuals and legal entities with different numbers of employees. In addition, with the participation of depositors in an open fund, an enterprise can develop a more flexible corporate program than, for example, with a corporate NPF. A legal restriction for an open NPF is the prohibition to invest in securities of its own founders (corporate funds have the right to buy them).

Statistics show that although companies have already started pension insurance for their employees, people are in no hurry to save money for retirement on their own. As of today, just over 2% of the economically active population are members of non-state pension funds.

Participation in NPFs is voluntary for both individuals and employers. Over time, after the adoption of the relevant law, employers will be required to make mandatory pension contributions to NPFs for the benefit of employees working in hazardous and difficult working conditions. Such mandatory pension contributions will be paid to professional and corporate funds.

There is a problem of insufficient control over the activities of NPFs. There are negative trends in the financial performance of funds, which is caused by non-transparent relations between NPFs and their counterparties, in particular the high cost of services of AMCs, auditors and other NPF participants. This situation is typical for economic relations in the financial services market. At the same time, international experience shows that the role of the state in regulating the activities of non-state pension funds in countries with weak economies is significantly different from its role in countries with established market relations, stable legislative and legal framework, developed stock and insurance markets [2, p.50].

Non-state pension funds in developed countries play an extremely important role - they have taken over some of the functions of the state, in particular in relation to citizens who have reached retirement age. In order to ensure that non-state pension funds fulfill their obligations properly, a system of regulation and supervision is being created.

The International Social Security Association (ISSA), established in 1937, provides advice and a platform to its members (350 member organizations in 150 countries) to shape dynamic social security and its policies worldwide [9].

In 2004, the International Organization of Pension Supervisors (IOPS) was established to improve the quality and efficiency of supervisory activities for private pension funds around the world, thereby contributing to their development, increasing the efficiency of their operations and increasing the level of security of this source of income for pensioners [10].

The share of non-state pensions depends on the type of pension system that operates in a country. There are three types of pension insurance systems (Table 1).

Only Bolivia has a purely funded pension insurance system, meaning that 100% of Bolivian pensioners' income comes from their own lifetime savings. In the United Kingdom, which has a two-pillar system, this figure is 25%, in the United States - 70% [2].

Table 1. Types of pension systems [Source: 4].

Type of pension system	Composition	Countries in which the system operates
One-pillar system	Solidarity	Germany, Sweden, Switzerland, Czechoslovakia, Romania Bolivia
	Accumulative	
Two-tier system	State (solidarity) and non-state (funded) systems operate in parallel	France, UK, Denmark, Netherlands, USA, Chile, Australia
Three-pillar system	The first pillar is a mandatory PAYG pension system; the second pillar is a mandatory funded pension system; the third pillar is a voluntary funded pension system	Latvia, Hungary, Kazakhstan, Poland, Croatia, Ukraine

The study of the organization of financial control in the system of non-state pension funds of the countries of the world made it possible to conclude that the greater the share of pensioners' income accounted for by non-state pension insurance, the better and more efficient the system of state regulation and supervision of such institutions should work.

In many countries, specially authorized bodies are created to regulate the activities of non-state pension funds (Table 2). The main purpose of the Pensions Regulator in the UK is to protect the interests and assets of members of non-state pension funds [12]. The Pension Regulator's powers can be grouped as follows:

- preventive - used for chronic risks;
- detective - used to study the causes of a particular problem;
- educational - used to increase the level of knowledge of trustees;
- corrective - used to return to the planned level of economic benefits;
- penalties - used to prevent the repetition of past offenses.

In most countries independent auditors play an auxiliary role in the control of non-state pension funds by state supervisory bodies, who are obliged to notify such bodies about any revealed violations (Belgium, Germany, Turkey and others). However, there are countries, Luxembourg in particular, where auditors are not obliged to communicate the information if: such information is a commercial secret; there are contractual restrictions on disclosure of information on the audited subject; disclosure of information would violate the principles of professional ethics [13].

**Table 2.** Supervisory bodies of NPFs in some countries of the world [11].

Country	Name of the supervisory authority
Australia	Australian Prudential Regulation Authority
Austria	Financial Market Authority
Belgium	Banking, Finance and Insurance Commission (CBFA)
Botswana	Non-Bank Financial Institutions Regulatory Authority
Brazil	Ministério da Previdência e Assistência Social
Bulgaria	Financial Supervision Commission
China	Chinese Insurance Regulatory Commission
Croatia	Croatian Financial Services Supervisory Agency (HANFA)
France	ACAM
Germany	Federal Financial Supervisory Authority (BaFin)
Spain	Ministry of Economy and Finance
Ireland	Pensions Board
Turkey	Pension Monitoring Center, Undersecretariat of the Treasury
Israel	Ministry of Finance
United Kingdom	The Pensions Regulator
Italy	Pension Funds Supervision Commission (COVIP)
Jamaica	Financial Services Commission
Kazakhstan	Agency of the Republic of Kazakhstan on Regulation and Supervision of Financial Markets and Financial Institutions
Netherlands	De Nederlandsche Bank
Norway	Financial Supervisory Authority
South Africa	Financial Services Board

Despite the differences in legislation, the practice of setting normative requirements to the establishment of internal audit services in non-state pension funds is widely accepted in most countries of the world.

The Netherlands, Poland, Jamaica, Turkey, Germany, and Australia - this is not the whole list of countries where requirements to information disclosure by non-state pension funds are enshrined at the state level. An important feature of such disclosure is the publication of information on the financial condition of the fund in certain periodicals [11].

In studying the issues of pension insurance, attention should be paid to the problem of distribution of pension insurance premiums between the employer and employees. According to some foreign experts, in order to maintain and increase the competitiveness of enterprises in the world market, it would be advisable to redistribute pension insurance funding equally to all pension insurance payers. In particular, countries with a developed market economy, by introducing a cumulative pension system due to compulsory and voluntary pension insurance, relieved enterprises of part of the burden of financing pension payments to the population. The specified financing was transferred to the able-bodied population [6].

Ukraine at present is not yet able to make a radical transition to a compulsory funded system. For this purpose it is necessary: general development of national economy, growth of incomes of the population, formation of effective system of non-state pension funds, developed legislative base and preparation of society as a whole for practical introduction of such reforms.

Directions for solving problems of intensifying the implementation of the cumulative pension system in Ukraine are summarized in Figure 1. Insufficient awareness of the principles of functioning and the low level of confidence in the institute of NPF can be overcome mainly through appropriate explanatory and educational work.

DIRECTIONS FOR ENHANCING THE INCLUSIVENESS OF THE FUNDED PENSION SYSTEM IN UKRAINE	
	Expanding the base of insurance contributions by legalizing and increasing the level of wages (for formalizing labor relations, strengthening the role of social dialogue in setting the level of income from which contributions to mandatory state pension insurance are collected, reducing underemployment and unemployment)
	Introduction of a single social contribution and creation of a state register of social insurance
	Gradual introduction of parity payment of insurance premiums by insurers and insured persons
	Strengthening control and responsibility for compliance with labor remuneration and insurance premiums
	Revision of the right to early retirement based on the results of job evaluation and retirement age in line with the increase in life expectancy.
	Eliminating the possibility of making decisions on revising pension amounts without taking into account the real capacities of the Pension Fund budget and relevant reasonable calculations

Figure 1. Priority directions of state policy for regulating the inclusiveness of the non-state funded pension system in Ukraine

Consequently, the government should consider creating appropriate public awareness programs to provide broader coverage of all aspects of the pension reform, in particular private pensions. The main emphasis should be focused on the following points:

- The potential possibility of obtaining an additional pension in old age through the NPF institution;
- The individual (personified nature) of pension accruals;
- Minimization of possible losses of own pension assets as a result of their diversification;
- regulation and supervision of the activity of NPF, administrators, AMC, custodians by the state regulators (National Securities Commission, National Commission on Financial Services) [14].

It is expedient to involve private financial institutions having experience of presence at the domestic financial market, enjoying faultless reputation and providing all complex or separate services on non-state pension provision to implementation of this program.

An effective factor in motivating individuals could be the co-financing of pension contributions by the employee and the employer at the initiative of the employee in the ratio, which should be calculated actuarially, taking into account the following initial conditions:

- the state loses part of its income tax due to the allocation of the amounts contributed to the NPF to gross expenses.

- the employer loses a part of profits, therefore the corresponding compensating mechanisms should be provided for;
 - the employee voluntarily gives up part of his consumption in favor of saving for his old age.
- A possible option could be the legally established right of a citizen (spouse) to educate their children at the expense of budgetary funds (if there is an amount of pension savings in the amount of payment on a commercial basis).

Conclusions

Given that inclusion aims to benefit all members of society from sustainable economic and social development, solving the problem of inclusion of pension insurance in Ukraine will overcome poverty among socially vulnerable and economically inactive members of society, inequality, social exclusion, etc. The inclusion of non-state pension insurance will help Ukrainians to become more active with decisions about the need to invest in a decent life after retirement.

However, inclusive values in the field of private pensions do not work in Ukraine. After all, the goals declared in the introduction of the third level of the pension system have not been achieved. In conclusion, the presence of significant savings in the system of non-state pension provision may serve as a basis for an earlier retirement from the mandatory cumulative system (in case of its introduction) and even from the solidarity system. In our opinion, the definition of retirement age in all three components of the pension system should be connected in a certain way, i.e. represent a comprehensive motivational system.

The study of the world experience of non-state pension funds and regulatory support of non-state pension funds in Ukraine led us to the conclusion that they are quite reliable and promising actors in the financial services market, and their effective development will accelerate the pension reform in Ukraine and thereby enhance investment processes and improve the welfare of pensioners. In order to solve the problems it is necessary to refer to the positive world experience, to create an effective system of regulation and supervision of the activities of private pension funds.

As a compensating mechanism for employers may be offered access to loans at preferential rates in state banks in case of exceeding the amount of pension contributions of certain amounts. Such volumes could be differentiated according to established characteristics (e.g., by industry, taking into account the profitability of production).

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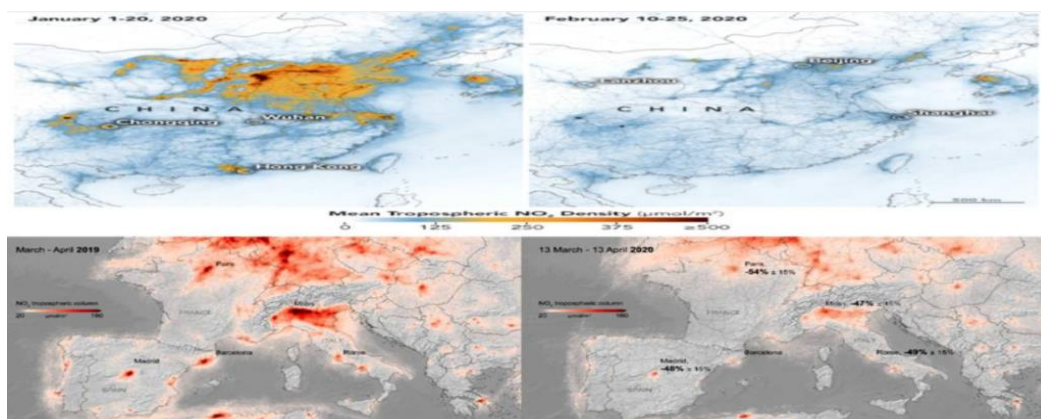


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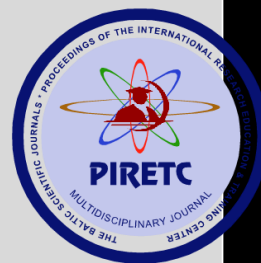
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