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PATHOLOGICAL FORECAST OF SOME ESSENTIAL DISORDERS

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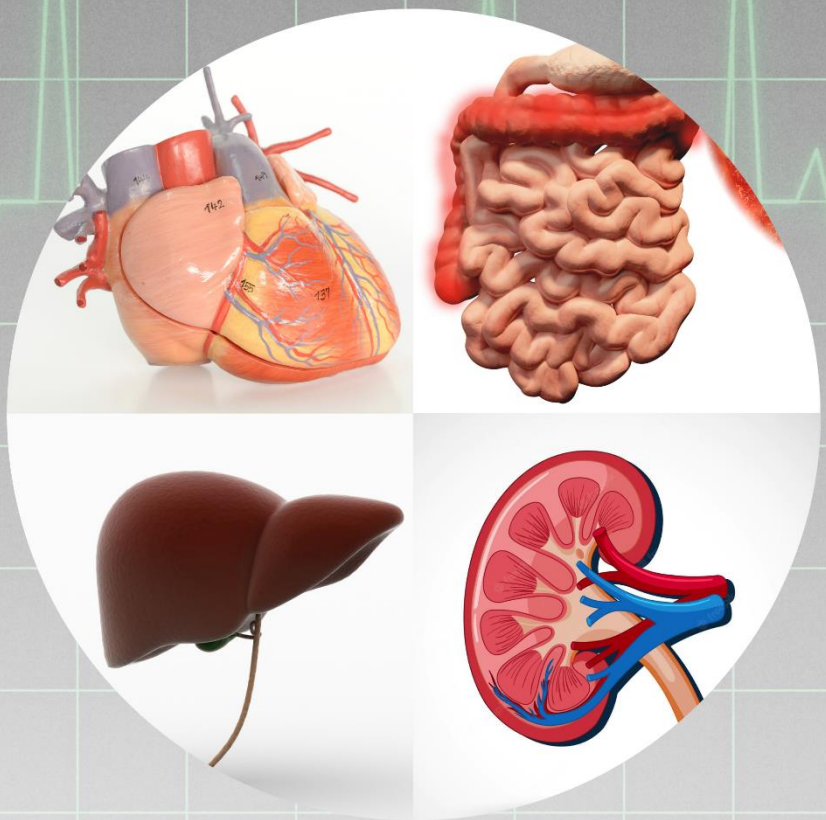
Prof. (Dr.) S. M. Firdous



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PREFACE

This book offers a thorough, current study of the pathology of several pathological conditions that affect humans, including heart disease, peptic ulcer disease, diabetes, diabetic complications, and renal complications. The natural products that are potentially having healing effects and working against certain disorders were also emphasized. The pathologic and pertinent clinical aspects are examined, and the most important laboratory test indicators are provided together with thorough information on the origin and pathophysiology of numerous diseases. This reliable text informs you about the pathophysiologic underpinnings of the symptoms and signs of the aforementioned disorders that are frequently seen in clinical practice. Each chapter begins by introducing the condition before turning to the pathology and dysfunctional physiology, which serves as a general grasp of etiology. The underlying disease mechanisms, their signs, and symptoms, as well as how these mechanisms indicate the likely natural product treatment, are all presented.

ACKNOWLEDGEMENT

There are countless people would like to thank for their help throughout my life, without whom I would not be who I am or doing what I do. For the sake of brevity here, I would like to acknowledge and thank those who have had the greatest impact on the success of this book. I thank those of you who have been helped me encouraged me to write the book. Besides, I would like to thank Bhumi Publishing for giving me such a nice opportunity to write and publish this book.

- Prof. (Dr.) S. M. Firdous
Editor-in-Chief

CONTENT

CHAPTER 1

HEART DISEASE: TYPES, BIOCHEMICAL CHANGES AND ROLE OF HERBS

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ABSTRACT

Cardiovascular diseases (CVDs) are a group of illnesses that include, among others, hypertension, peripheral vascular disease, coronary heart disease (CHD), heart failure, heart attack (myocardial infarction), and stroke. Vascular dysfunction is the primary cause of CVDs, which then causes organ damage. For instance, vascular dysfunction can cause a heart attack or a stroke in the brain or in the heart. Atherosclerosis, thrombosis, and high blood pressure are the main causes of vascular dysfunction (BP). Smoking, an unhealthy diet, diabetes mellitus, hyperlipidemia, raised levels of LDL cholesterol (LDL), suppressed levels of HDL cholesterol (HDL), and hypertension are all common risk factors for CVDs. The stated safety of herbal treatments, however, has not yet been thoroughly investigated. Therefore, the public's understanding of the safety of therapeutic herbs should be increased.

KEYWORDS: Cardiovascular diseases, coronary heart disease (CHD), heart failure, heart attack (myocardial infarction), stroke, and herbs

INTRODUCTION

The heart is a muscular, fist-sized organ that is located in the left side of the chest cavity. Up to 100,000 times a day, it beats as it continuously pumps blood. In addition to transporting carbon dioxide and other wastes to the lungs, kidneys, and liver for elimination, the blood that the heart pumps distributes nutrients and oxygen throughout the body. The coronary arteries and veins of the heart provide the organ with its own supply of oxygen. The hormones atrial natriuretic hormone (ANP) and B-type natriuretic peptide (BNP), which coordinate heart function with blood arteries and the kidneys, are produced by the heart, which also functions as an endocrine organ. Heart Disease refers to any disease that affects the heart [1-2]. The four most common types of cardiovascular disease are coronary heart disease (which includes heart attack and angina pectoris or chest pain), stroke, high blood pressure and heart failure. Other forms include rheumatic fever, rheumatic heart disease, congenital cardiovascular defects, arrhythmias,

bacterial endocarditis, cardiomyopathy, valvular heart disease, and diseases of pulmonary circulation, diseases of veins and lymphatics and other diseases of the circulatory system [3].

HEART DISEASE

Coronary Heart Disease

Coronary heart disease (CHD) and Coronary artery disease (CAD) are the most common forms of heart disease. They are usually part of a systemic cardiovascular disease (CVD) a narrowing of arteries in the heart and throughout the body over time due to a build-up of fatty deposits that form plaques (atherosclerosis). The amount of blood carried by the arteries can be greatly reduced by this narrowing, which also reduces the amount of oxygen delivered to the tissues. When the majority of the blood flow is lost to a particular area of the heart, as the coronary blood arteries gradually constrict, symptoms can cause periodic chest discomfort (angina), which gets worse in frequency and intensity with time. An acute narrowing of the coronary artery can cause chest pain to develop at rest or with little effort (termed unstable angina), or it may even result in the death of a section of the myocardium or a heart attack (myocardial infarction). These types of acute onset of chest pain are referred to as acute coronary syndrome [4].

Pathophysiology of Myocardial Infarction [5]**:**

- Atherosclerosis**:** It is the disease primarily responsible for most acute coronary syndrome cases. Approximately 90% of myocardial infarctions result from an acute thrombus that obstructs an atherosclerotic coronary artery.
- MI is most often caused by rupture of an atherosclerotic lesion in a coronary artery. This causes the formation of a thrombus that plugs the artery, stopping it from supplying blood to the region of the heart that it supplies.

Mechanisms and Consequences of Plaque Rupture:

Coronary plaques with a high concentration of lipids and a thin fibrous top are often tiny and nonobstructive. At the location of plaque rupture, activated macrophages and T-lymphocytes are thought to release metalloproteases and cytokines that weaken the fibrous cap, making it susceptible to tearing or eroding under the shear stress of the blood flow.Plaque rupture reveals subendothelial collagen, which serves as a site of platelet adhesion, activation and aggregation. This results in:

1. The release of substances such as thromboxane A2 (TXA2), fibrinogen, 5-hydroxytryptamine (5-HT), platelet activating factor and ADP, which further promote platelet aggregation.
2. 2. The clotting cascade is activated, causing fibrin to develop and the occlusive thrombus to spread and stabilize. Around sites of coronary artery disease, the endothelium frequently

becomes compromised. Because of this, thrombomodulin and prostacyclin levels are depleted, which increases thrombus formation. Additionally, when endothelial-derived relaxing factors are absent, some platelet-derived factors, such as TXA2 and 5-HT, have a greater propensity to promote vasoconstriction.

3. Heart failure: The body retains fluid, and organs, for example, the kidneys, begin to fail this may promote the development of local vasospasm, which worsens coronary occlusion.

Complications of a Heart Attack

Heart Failure

Heart failure can occur when there is a significant loss of heart muscle, which reduces the heart's capacity to pump blood to the body's tissues.

Ventricular Fibrillation

Ventricular fibrillation can also be caused by injuries to the heart muscle. Ventricular fibrillation is a condition in which the heart stops beating and no longer pumps blood to the brain and other regions of the body. It happens when the regular, regular electrical activation of heart muscle contraction is replaced by erratic electrical activity. In the event that the blood flow to the brain is not restored within five minutes, permanent brain damage and death may result.

The majority of heart attack-related deaths are brought on by ventricular fibrillation, which develops in the heart before the attack sufferer can get to an emergency care.

Cardiopulmonary resuscitation (CPR) initiated within five minutes of the beginning of ventricular fibrillation can prevent ventricular fibrillation-related deaths. The person must breathe, and external chest compressions must be applied to squeeze the heart and make it pump blood.

Risk Factors for Atherosclerosis and Heart Attack

Increased blood cholesterol, high blood pressure, smoking, diabetes mellitus, being male, and having a family history of coronary heart disease are all risk factors for atherosclerosis and heart attacks. While male gender and family history are inherited traits, other risk factors can be altered by alterations in lifestyle and medication.

1. **High blood cholesterol (hyperlipidemia):** Because cholesterol is the main component of the plaques that are produced in artery walls, a high blood cholesterol level is linked to an increased risk of heart attack. When linked with specialized proteins called lipoproteins, cholesterol can be dissolved in the blood, just like oil, but not without doing so. (Cholesterol in the blood would solidify if it did not combine with lipoproteins.) Very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins are the three types of lipoproteins that contain cholesterol in the blood (HDL).

The "bad" cholesterol that builds up in arterial plaques is the cholesterol that is coupled with low-density lipoproteins (LDL cholesterol). As a result, having high levels of LDL cholesterol increases your risk of having a heart attack.

The "good" cholesterol that eliminates cholesterol from arterial plaques is the cholesterol that is coupled with HDL (HDL cholesterol). The risk of heart attack has been demonstrated to be reduced by interventions that reduce LDL cholesterol and/or raise HDL cholesterol (such as weight loss, diets low in saturated fats, regular exercise, and medication).

2. **High blood pressure (hypertension):** Atherosclerosis and heart attacks are both prone to high blood pressure. The risk of a heart attack is increased by high blood pressure in both the systolic (when the heart beats) and diastolic (when the heart is at rest) phases. It has been demonstrated that medication-assisted hypertension management can lower the risk of heart attack.
3. **Tobacco use (smoking):** Chemicals found in tobacco and tobacco smoke damage blood vessel walls, hasten atherosclerosis development, and raise the risk of heart attack.
4. **Diabetes (diabetes mellitus):** Accelerated atherosclerosis is linked to both insulin-dependent and non-insulin-dependent diabetic mellitus (types 1 and 2, respectively). Therefore, patients with diabetes mellitus are more likely than non-diabetic subjects to experience reduced blood flow to the legs, coronary heart disease, erectile dysfunction, and strokes earlier in life. Diabetes patients can reduce their risk by closely monitoring their blood sugar levels, engaging in regular exercise, managing their weight, and adhering to healthy foods.
5. **Male Gender:** Men are more likely than women to develop coronary heart disease and atherosclerosis at all ages. According to some scientists, this disparity is partially explained by the fact that women have higher blood levels of HDL cholesterol than males do. As men and women age, this gender disparity does, however, become less pronounced.
6. **Family History of Heart Disease:** Heart attack risk is higher in people with a family history of coronary heart disease. A family history of early coronary heart disease, such as a heart attack or sudden death before age 55 in the father or another first-degree male relative, or before age 65 in the mother or another female first-degree female relative, increases the risk.

Diagnosis of Heart Attack

Electrocardiogram

The electrical activity of the heart is captured by an electrocardiogram (ECG). Heart attacks typically cause abnormal electrical activity, which can be used to pinpoint the heart muscle regions that are starved of oxygen and/or that have died. When a patient exhibits typical heart attack symptoms (such severe chest pain) and heart attack-related ECG alterations, a secure

diagnosis of heart attack can be made swiftly in the emergency room, and treatment can begin right once. The diagnosis of a heart attack may be less certain if a patient's symptoms are hazy or unusual, and if there are pre-existing ECG abnormalities, such as those from previous heart attacks or irregular electrical patterns that make interpretation of the ECG challenging. The diagnosis in these people might be made just hours later by looking for high cardiac enzyme levels in the blood.

Blood Tests

Proteins called cardiac enzymes are released into the circulation by failing heart muscles. The amounts of these cardiac enzymes, which can be detected in the blood, include troponin, creatine phosphokinase (CPK) or creatine kinase (CK), particular sub-fractions of CPK (more specifically, the MB fraction of CPK), and other enzymes. Several hours after the start of a heart attack, the blood levels of these cardiac enzymes are frequently increased. In addition to helping to confirm the diagnosis of a heart attack, a series of enzyme blood tests over a 24-hour period also help to determine how much heart muscle has died because of changes in the levels of the enzymes over time.

Treatment

As in all heart diseases, controlling blood pressure (reducing hypertension) is a primary concern. Drugs, such as digoxin, which helps the heart increase contractions, and antiarrhythmics, such as procainamide, which help synchronize the contractions, may also be used, depending on how the heart is reacting. Other medications may also be prescribed, including beta blockers, ACE inhibitors, anticoagulants, anti platelet medicines and drugs that dissolve or split up blood clots (thrombolytic medications). Sometimes, medical procedures are needed, such as angioplasty or coronary artery bypass grafting.

Ischaemic Heart Disease

Ischaemic Heart disease (IHD) or myocardial ischaemia often manifests as a result of coronary artery disease and causes a reduction in the blood supply to the cardiac muscle.

Hypertensive Heart Disease

Hypertensive heat disease is described as heart disease that occurs as a result of high blood pressure. It may lead to the development of coronary heart disease, cardiac arrhythmias, hypertensive cardiomyopathy, left ventricular hypertrophy and congestive heart failure

Heart Failure or Congestive Heart Failure

Heart failure, also known as congestive heart failure (CHF), makes the heart less efficient in pumping blood throughout the body and less able to fully fill or empty the chambers. Blood backs up as a result, producing fatigue, edema, and shortness of breath in the legs, hands, feet,

lungs, and liver. Heart valve damage, which can be congenital or the result of an infection, high blood pressure (hypertension), coronary artery disease, or a history of a heart attack can all gradually weaken the heart over time and cause heart failure. Heart failure may be brief if the cause is transient, but it often is a chronic condition that gets worse over time and frequently gets better following therapy.

Cardiomyopathy

Heart muscle disorder known as cardiomyopathy. It can be congenital or the heart's reaction to poisons or pressure from the outside world. The size of one or more of the heart's chambers may grow due to dilation of one or more of them (dilated cardiomyopathy). Other times, one or more of the heart's walls may thicken (hypertrophic cardiomyopathy). Occasionally, aberrant material may build up in the heart's wall and cause cardiomyopathy by decreasing the flexibility of the ventricle walls (restrictive cardiomyopathy).

DRUGS INDUCED MYOCARDIAL INFARCTION:

ISOPROTERENOL INDUCED MYOCARDIAL INFARCTION [6]

Isoproterenol (ISO) induced myocardial necrosis is well known standard model to study the beneficial effect of many drugs on cardiac dysfunction. ISO is a β-adrenergic agonist that causes severe stress in myocardium and necrotic lesions in the heart muscles.

- Interaction of ISO with β-receptors leads to activation of adenyl cyclase, enhancing cAMP synthesis. cAMP is responsible for ISO-actions in the body, including metabolic processes. cAMP is considered a second messenger. Such messenger functions depend on its capacity to activate protein kinases. Activated protein kinases in turn interact with various enzymes or proteins by phosphorylation.
- ISO is probably due to a primary action on the sarcolemmal membrane, followed by stimulation of adenylate cyclase, activation of Ca^{2+} and Na^{+} channels, exaggerated calcium inflow and excess of excitation-contraction coupling mechanism leading to energy consumption and cellular death.
- Occurrence of intracellular calcium overload results in depletion of high energy phosphates caused by the activation of calcium-dependent ATPases as well as impairement of mitochondrial energy production.
- Calcium induced high energy phosphate exhaustion is considered to be a crucial point in the etiology of catecholamine-induced myocardial fiber necrosis
- ISO induced myocardial injury involves membrane permeability alterations, which brings about the loss of functions and integrity of myocardial membranes.

- Catecholamine-induced lipolysis increased myocardial oxygen requirement, unrelated to unrelated to myocardial mechanical activity. Thus, relative hypoxia caused by hyperlipidemia and hemodynamics contributes to isoproterenol induced myocardial necrosis.

The triggering factor in relative hypoxia, altered membrane permeability or Ca^{+2} overloads is cAMP (Figure 1).

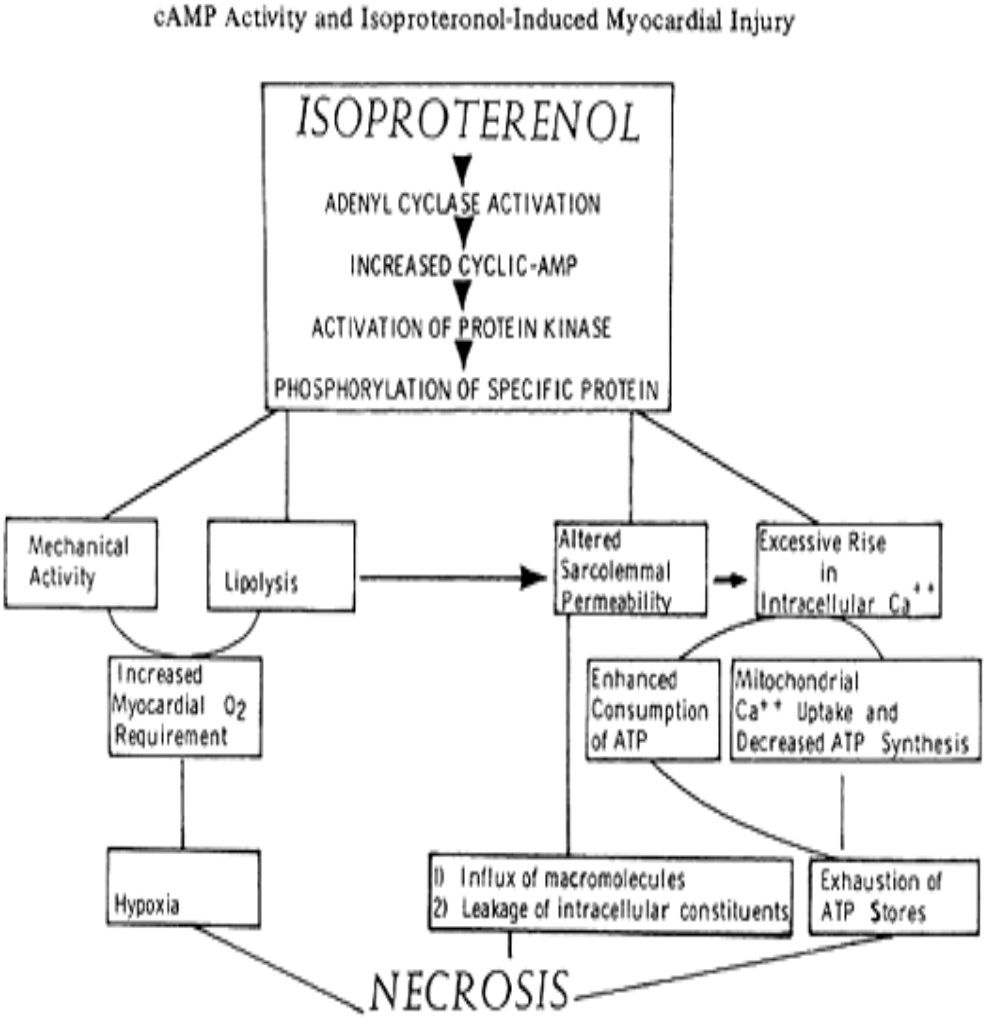

Figure 1: Events leading to myocardial infarction by isoproterenol

Mechanism for the role of free radicals in catecholamine induced cardiomyopathy [7]:

- The mechanism proposed to explain isoproterenol induced cardiac damage involves generation of highly cytotoxic free radicals through auto-oxidation of catecholamine and has been implicated as one of the causative factor.
- The localization of highly unsaturated fatty acids in membranes makes the latter vulnerable to free- radical induced lipid peroxidation.

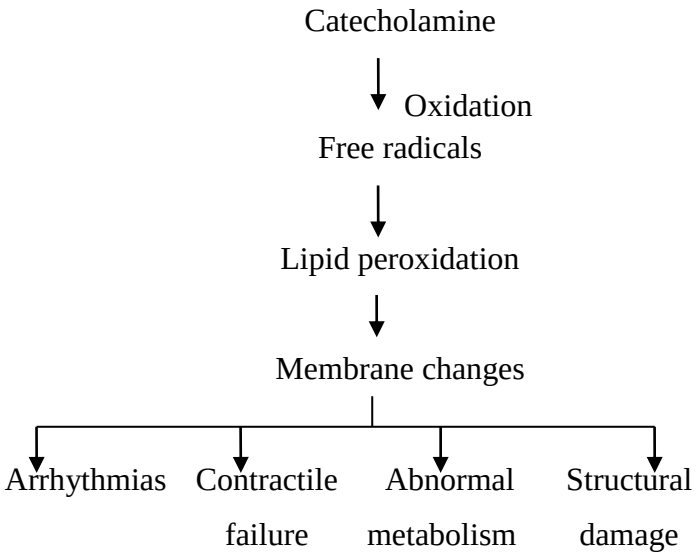

Figure 2: A generalized scheme for the role of free radicals in catecholamine induced cardiomyopathy

- Introduction of these peroxidation products in the membranes is known to affect semipermeable characteristics of the cellular and subcellular membrane barrier, thereby influencing physiological functions.
- The oxidative stress may be exerted through quinine metabolites of isoproterenol, which reacts with oxygen to produce ROS and interfere glutathione reductase, superoxide dismutase and ATP pumps.
- Administration of ISO raised LDL cholesterol and decreased HDL cholesterol level in the serum.
- An increase in concentration of total cholesterol and LDL cholesterol, and a decrease in HDL cholesterol are associated with raised risk of myocardial infarction. High level of circulating cholesterol and its accumulation in heart tissue is accompanied with cardiovascular damage.

DOXORUBICIN INDUCED MYOCARDIAL INFARCTION [8]

Doxorubicin, an anthracycline commonly used against a broad spectrum of human cancers has well known dose dependent cytotoxic effects. Although the mechanism underlying the severe cytoxicity of doxorubicin and other anthracyclines are not fully understood, there is evidence that drug toxicity may ensue through drug free radical formation and subsequent redox cycle with oxygen resulting in the generation of reactive oxygen species such as superoxide anion, hydroxyl radicals and hydrogen peroxide. Tissue with less developed antioxidant defenses such as heart is particularly susceptible to injury by doxorubicin induced oxygen radicals.

SIGNIFICANCE OF SERUM ENZYMES [9-10]

Certain tissue cells have distinctive enzymes that can only leave those cells and enter the blood when those cells are broken or destroyed. Significant amounts of these particular enzymes in the blood suggest the likely site of tissue injury.Cardiac enzymes are proteins that are in found the heart muscle. They do not circulate in the bloodstream. When damage occurs to the heart muscle, such as during a myocardial infarction (heart attack), cardiac enzymes leak into the bloodstream.

AST, ALT, SGOT, SGPT and ALP are abbreviations for proteins called enzymes which help all the chemical activities within cells to take place. Injury to cells releases these enzymes into the blood. They are found in muscles, the liver and heart. Damage from alcohol and a number of diseases are reflected in high values.

TRANSAMINASES (GOT AND GPT): AST/SGOT, ALT/ SGPT are also liver and muscle enzymes. They may be elevated from liver problems, hepatitis, excess alcohol ingestion, muscle injury and recent heart attack.

Glutamic-oxaloacetic transaminase (GOT)- Large levels of Glutamic-oxaloacetic transaminase (GOT) are found in the heart and liver, whereas smaller amounts are found in the skeletal muscle, kidneys, and pancreas. Within 10 to 48 hours, myocardial infarction can be identified using GOT levels. Arrhythmias, severe heart angina, liver damage, and other diseases are also associated with high GOT.

Reference Value: 8 – 20 IU/L

Glutamic-Pyruvic Transaminase (GPT) - The organs with the highest concentrations of Glutamic-Pyruvic Transaminase (GPT) include the liver, kidney, and skeletal muscle. GOT and GPT levels rise notably early in the disease when liver cells are destroyed. Transaminase levels increase in hepatitis many days before jaundice appears. The enzyme levels are particularly helpful in detecting early and mild biliary blockage and active cirrhosis alterations.

Reference Value: 10 – 40 IU/L

Alkaline Phosphatase (ALP) is an enzyme found primarily in bones and the liver. Expected values are higher for those who are growing (children and pregnant women) or when damage to bones or liver has occurred or with gallstones. Low values are probably not significant.

Reference Value: 4 – 11 KA

Lactic Dehydrogenase (LDH) is the enzyme present in all the cells in the body. Anything which damages cells, including blood drawing itself, will raise amounts in the blood. If blood is not processed promptly and properly, high levels may occur.

This enzyme catalyzes the reversible reaction between pyruvic and lactic acids.

Nearly all metabolizing cell types include LDH, however different cell types have distinct versions of the enzyme that can be identified. The heart, liver, red blood cells, kidneys, muscles, brain, and lungs are where the enzyme is most abundant.

LDH-1, LDH-2, LDH-3, LDH-4, and LDH-5 are the five parts or fractions that make up the entire LDH and are identified by numbers. The body uses each of these fractions, known as isoenzymes, primarily in one particular group of cells or tissues. The LDH isoenzymes test helps distinguish between liver illness, lung injury, anemia, heart attack, and other disorders that could produce similar symptoms.

LDH-1 is primarily present in the heart. LDH-2 is mostly linked to the body's defense against infection mechanism. LDH-3 is present in the liver and skeletal muscle, LDH-4 is present in the kidney, placenta, and pancreas, and LDH-5 is present in the lungs and other tissues. LDH-2 concentrations are typically higher than those of the other isoenzymes.

Elevated LDH isoenzyme levels are a hallmark of several illnesses. Indicators of heart attack or injury include LDH-1 levels above LDH-2; lung injury or illness is indicated by LDH-2 and LDH-3 elevations; and liver or muscle disease, or both, is indicated by LDH-4 and LDH-5 elevations. When all LDH isoenzymes increase at the same time, numerous organ injuries have occurred.

One of the most important diagnostic uses for the LDH isoenzymes test is in the differential diagnosis of myocardial infarction or heart attack. The LDH-1 isoenzyme level, however, is more sensitive and specific than the total LDH. Normally, the level of LDH-2 is higher than the level of LDH-1. An LDH-1 level higher than that of LDH-2, a phenomenon known as "flipped LDH," is strongly indicative of a heart attack.

Reference Value: 114 – 240 U/L

Creatine Phosphokinase (CPK or CK) is an enzyme which is very useful for diagnosing diseases of the heart and skeletal muscle. This enzyme is the first to be elevated after a heart attack (3 to 4 hours). If CPK is high in the absence of heart muscle injury, this is a strong indication of skeletal muscle disease.

Between ATP and ADP as well as between creatine and phosphocreatine, CPK catalyzes the reversible transfer of phosphate groups. Skeletal muscle, cardiac muscle, and the gastrointestinal tract are where the majority of the CPK is found. Immediately after muscle cells are damaged, CPK quickly enters the circulation. CPK initially appeared to be a good indicator of skeletal muscle or acute myocardial infarction (heart injury). Unfortunately, the CPK levels fluctuate dramatically and correspond with a number of other events, such as operations,

strenuous activity, falls, or deep intramuscular injections. CPK level measurements continue to offer important distinguishing diagnostic data.

Creatine Kinase – Total: An elevation in total CK is not specific for myocardial injury, because most CK is located in skeletal muscle, and elevations are possible from a variety of non-cardiac conditions.

Creatine Kinase - MB Fraction: Creatine Kinase can be further subdivided into three isoenzymes: MM, MB and BB. The MM fraction is present in both cardiac and skeletal muscle, but the MB fraction is much more specific for cardiac muscle: about 15 to 40% of CK in cardiac muscle is MB, while less than 2% in skeletal muscle is MB. The BB fraction (found in brain, bowel, and bladder) is not routinely measured.

Thus, CK-MB is a very good marker for acute myocardial injury, because of its excellent specificity, and it rises in serum within 2 to 8 hours of onset of acute myocardial infarction. A "cardiac index" can provide a useful indicator for early MI. This is calculated as a ratio of total CK to CK-MB, and is a sensitive indicator of myocardial injury when the CK-MB is elevated.

Reference Value: < 25 U/L

BLOOD FATS

Cholesterol is a fat-like substance in the blood which, if elevated has been associated with heart disease, stroke and atherosclerotic vascular disease. Some cholesterol is produced by the body, while another part is contributed through the diet. Cholesterol is a building block for sex hormones, cell membranes and bile acids

Total Cholesterol High cholesterol in the blood is a major risk factor for heart and blood vessel disease. Cholesterol in itself is not all bad; in fact, our bodies need a certain amount of this substance to function properly. However, when the level gets too high, vascular disease can result. Total cholesterol of less than 200 and LDL Cholesterol of 100 or less is considered optimal by the National Heart, Lung and Blood Institute.

As the level of blood cholesterol increases, so does the possibility of plugging the arteries due to cholesterol plaque build-up. Such a disease process is called "hardening of the arteries" or atherosclerosis.

Reference Value

Desirable: <200 mg/dl

Borderline-high: 200-239 mg/dl

High: 240 mg/dl

There are three major kinds of cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL).

LDL cholesterol - Because cholesterol deposits develop in the arteries when LDL levels are high, LDL cholesterol is referred to as "bad cholesterol." LDL cholesterol levels should be less than 130, 100 is ideal, and numbers over 160 are high risk. Two methods exist for reporting LDL. The most typical is a straightforward estimate derived from the results of the tests for total cholesterol, HDL, and triglycerides. It might read "LDL Calc." Although more expensive, a directly measured LDL cholesterol is typically more precise.

Reference Value

Desirable: <130 mg/dl

Borderline-high: 130-159 mg/dl

High: 160 mg/dl

HDL Cholesterol is 'good cholesterol' as it protects against heart disease by helping remove excess cholesterol deposited in the arteries. High levels seem to be associated with low incidence of coronary heart disease.

Reference Value

Low (major risk factor) : <35 mg/dl

High (negative risk factor): = 60 mg/dl

Triglyceride, a blood fat, has been linked to heart disease if it is increased, especially if it is over 500 mg. Pancreatitis is also related to high triglycerides. In addition to heart disease, triglyceride levels over 150 mg/dl may be linked to additional issues. How to reduce triglycerides: (1) weight loss if overweight; (2) a decrease in animal fats in the diet; (3) use of specific drugs that your doctor may prescribe; 4) Engage in routine aerobic exercise 5) Reduce your sugar and alcohol intake. Although sugar and alcohol are not fats, your body can convert them into fats and release those fats into your bloodstream. 6) Cut back on calories. When consumed in excess, carbs are transformed into triglycerides.

Reference Value

Normal <200 mg/dl

Borderline-high: 200-400 mg/dl

High: 400-1000 mg/dl

Very high: > 1000 mg/dl

Very Low Density Lipoprotein (VLDL) is another carrier of fat in the blood.

ROLE OF HERBS:

Cardiovascular diseases (CVDs) are a serious health burden that are becoming more and more common. They continue to be the principal global sources of illness and mortality. The use of medicinal plants is still a viable alternative therapy for a number of illnesses, including CVDs.

An extraordinary push is currently underway to include herbal remedies into contemporary medical systems. This urge is fueled by a number of factors, the two most important of which being the common perception that they are safe and their therapeutic promise of being more cost-effective than traditional modern medicines. The stated safety of herbal treatments, however, has not yet been thoroughly investigated. Therefore, the general public's understanding of medicinal herbs' safety, toxicity, possibly fatal side effects, and potential herb-drug combinations should be increased. Since the dawn of civilization, herbs have been employed as therapeutic agents, and several of their derivatives (such as aspirin, reserpine, and digitalis) have established themselves as cornerstones of modern pharmacology. Patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia have all benefited from herbal therapy for cardiovascular illnesses. However, many of the herbal medicines currently in use have not received thorough scientific evaluation, and some could have substantial adverse consequences and significant drug interactions. Clinicians should ask about these health practices for cardiac illness given the large prevalence of herbal usage today and be aware of the potential benefits and risks. To clarify the pharmacological actions of the many herbal treatments currently being used, more research is required.

Table 1: List of some herbal plant extracts with cardio protective property and their probable mechanism of action.

Plant	Model	Probable Mechanism of action
Bacopa[11] *monneira*	ISO induced MI in rats 30 days model	Antioxidant and antperoxidative properties.
Allium[12] *sativum*	ISO induced MI in rats 30 days model	Antioxidant property.
Momordica cymbalaria Fenzl [13]	ISO induced MI in rats 45 days model	Protective effect was confirmed by histological findings.
Mangifera indica [14]	ISO induced MI in rats 30 days model	Antioxidants, antilipidperoxidative, free radical scavenging, immunomodulatory, cardiotonic properties.
Cucumis trigonus Roxb[15]	ISO induced MI in rats 14 days model	Free radical scavenging activity.
Daucus carota Linn[16]	ISO induced MI in rats 30 days model	Antioxidant, antilipidperoxidative, free radical scavenging and inotropic property.
Muntingia calabura [17]	ISO induced MI in rats 30 days model	Membrane-stabilizing action.

Trichopus zeylanicus[18]	ISO induced MI in rats 30 days model	Antioxidant action.
Embelia ribe[19]	ISO induced MI in rats 42 days model	Anti oxidant property.
Lipistat[8]	Doxorubicin induced MI 30 days model	Lipid lowering and antioxidant properties.
Ocimum sanctum[20]	ISO induced MI in rats 30 days model	Antioxidant property.
Abana[21]	ISO induced MI in rats 7 days model	Membrane-stabilizing action.
Arogh[22]	ISO induced in rats MI 60 days model	Anti lipidperoxidative property.
Aegle marmelos[23]	ISO induced MI in rats 35 days model	Antioxidant property.
Erythrina stricta Roxb[24]	ISO induced MI in rats 30 days model	Cardio protective was confirmed by histipathological studies.
A.V. Circulo (AVC)[25]	ISO induced MI in rats 21 & 45 days model	Cardio protective due to its antioxidant property.
Zingiber officinale[26]	ISO induced MI in rats 20 days model	Antioxidant property.
Syzygium cumini[27]	ISO induced MI in rats 30 days model	Membrane-stabilizing action.

CONCLUSION:

Given the widespread use of herbal remedies, healthcare professionals should remember to ask about these medical practices while conducting clinical histories and keep up to date on any positive or negative consequences of these treatments. To better understand the pharmacological effects of the various cardiopotent herbal remedies and to encourage the future development of herbal medications that are therapeutically effective, study is constantly needed. Before the full potential of these kinds of medicines can be determined, however, additional government financing for such research is needed. For the interest of public health, legal oversight of the use of herbal medications with narrow safety margins should be implemented; this is particularly crucial for those herbs that have negative cardiovascular effects and drug interactions. Research-supported claims may eventually be made accessible to patients and doctors in a way comparable to allopathic medicines as more knowledge about the safety and efficacy of herbal medicines is gained through new clinical trials.

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CHAPTER 2

PEPTIC ULCER: PATHOPHYSIOLOGY AND ROLE OF HERBS

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ABSTRACT

Open sores known as peptic ulcers form on the inner lining of the stomach and the upper small intestine. Stomach pain is a peptic ulcer's most typical symptom. Gastric ulcers, which develop on the inside of the stomach, and duodenal ulcers, which develop on the inside of the upper part of the small intestine, are examples of peptic ulcers (duodenum). The bacteria Helicobacter pylori (*H. pylori*) infection and long-term usage of NSAIDs like and naproxen sodium are the two main causes of peptic ulcers. But compared to herbal remedies, these medications are more expensive and more likely to have negative effects. The best goals of treatment for peptic ulcer illness ought to be pain relief, ulcer healing, and postponing ulcer recurrence. In this review, we've tried to learn about some common medicinal plants that are reported to have effects against peptic ulcers, as well as some straightforward, all-natural approaches to treat ulcers with readily available herbs.

KEYWORDS: Peptic ulcer, Gastric ulcers, duodenal ulcers, NSAIDs and herbs

INTRODUCTION

A peptic ulcer is an erosion or sore in the wall of the gastrointestinal tract**.** Pepsin and other digestive enzymes, such as hydrochloric acid, are produced in the stomach. The stomach is covered in mucus, which shields it from acid. Prostaglandins, hormone-like compounds essential for muscle contraction and the inflammatory response, support lining defense. When these defenses are ineffective, pepsin and acid erode away at the lining to create an open sore known as an ulcer [1-3].

CAUSES OF PEPTIC ULCERS

- *H. pylori* is a urease-enzyme-producing bacterium that decreases the stomach's ability to produce mucus, making it prone to acid-damage and peptic ulcers
- Aspirin, non steroidal anti-inflammatory drugs (such as ibuprofen and naproxen), and newer anti-inflammatory medications (such as celecoxib [Celebrex]). Prostaglandins are

substances which are important in helping the gut linings resist corrosive acid damage. NSAIDs cause ulcers by interfering with prostaglandins in the stomach.

- Alcohol
- Stress - Physical (severe injuries or burns, major surgery) or emotional
- Caffeine
- Cigarette smoking
- Radiation therapy - Used for diseases such as cancer

ETIOLOGY AND PATHOPHYSIOLOGY OF ULCERS [4]

Acute peptic ulcers (stress)

Acute peptic ulcers are or stress ulcers are multiple, small, mucosal erosions, seen most commonly in the stomach but occasionally involving duodenum.

Etiology: These ulcers occur in following severe stress conditions and causes are

Psychological stress

- Physiological stress as in the following
  - Shock
  - Severe trauma
  - Septicemia
  - Extensive burns
  - Intra cranial lesions
  - Drug intake
  - Local irritants

PATHOGENESIS:

The possible hypotheses for genesis of stress ulcers are

- Ischemic hypoxic injury to the mucosal cells
- Depletion of gastric mucus barrier rendering the mucosa susceptible to attack by acid-peptic secretion

Pathological Changes

Acute stress ulcers are multiple. They are more common in anywhere in stomach and have a decreasing frequency by occurrence in first part of duodenum. They may be oval or circular in shape usually less than 1 cm in diameter. Microscopically the stress ulcers are shallow and do not invade the muscular layer. The margins and base may show some inflammatory reaction depending upon the duration of ulcers. The ulcers commonly heal by complete re-

epithelisation without leaving any scars. Complications such as haemorrhage and perforation may occur.

Chronic Peptic Ulcers (gastric and duodenal ulcers):

Gastric Ulcer:

Etiology: Gastric colonization with *Helicobacter pylori* asymptomatic but higher chances of development of duodenal ulcer. Disruption of mucus barrier is the most important factor.

Pathogenisis : Usually normal to low acid levels; hyperacidity if present is due to high serum gastrin and damage to mucus barrier is the significant factor

Pathological Changes: Most common among the lesser curvature and pyloric antrum and is grossly similar to duodenal ulcer. Histologically it is distinguishable from duodenal ulcer.

Grossly, peptic ulcers are commonly solitary (80%), small (1-2.5cm I diameter), round to oval and characteristically punched out.

Benign ulcers usually have flat margins in level with the surrounding mucosa. The mucosal folds converge towards the ulcer. The ulcer may vary in depth from superficial (confined to mucosa) to deep ulcers (penetrating into muscular layers).

Chronic duodenal ulcer never turns malignant, while chronic gastric ulcers may develop in less than 1%of cases. Malignant ulcers are larger, bowl-shaped with elevated and indurate mucosa at the margin.

Microscopically, chronic peptic ulcers have four zones:

1. *Necrotic zone*: lies in the floor of the ulcer and is composed of fibrinous exudates containing necrotic debris and few leucocytes.
2. *Superficial exudates zone*: lies underneath the necrotic zone.the tissue elements here show coagulative necrosis giving eosinophilic,smudy appearance with nucler debris.
3. *Granulation tissue zone*: is seen merging into the necrotic zone. It is composed of nonspecific inflammatory infiltrate and proliferating capillaries.

4. *Zone of cicatrization:* A thick layer of granulation tissue can be seen encasing the zone of cicatrization. It is made up of granulation tissue that is layered on dense fibrocollagenous scar tissue. The ulcer may be crossed by thrombosed or sclerotic arteries, which, should the ulcer erode, could cause hemorrhage.

Duodenal Ulcer:

Etiology: Most commonly as a result of H-pylori infection. Other factors include hypersecreation of acid-pepsin, association with alcohol cirrhosis, tobacco, hyperparathyroidism, chronic pancreatitis, genetic factors.

Pathogenisis: Mucosal digestion from hyperacidity is the most significant factor and protective gastric mucus barrier may be damaged.

Pathologic Changes: It is most common in first part of duodenum, often solitary, 1-2.5cm in size, and round to oval. Histologically, duodenal ulcer composed of 4 layers – necrotic, superficial exudative, granulation tissue and cicatrisation.

Symptoms of ulcers

Variable ulcer disease symptoms can occur. Numerous ulcer sufferers report quite minor or no discomfort at all. One to three hours after meals, as well as in the middle of the night, some people complain of upper abdomen burning or hunger ache. Food or antacids can frequently quickly ease these discomfort symptoms. Poor correlation exists between the intensity or existence of active ulceration and the pain of ulcer disease. Even after receiving full medical healing for an ulcer, some people continue to experience pain. Even though their ulcers recur, some people feel absolutely no pain. Unless a significant issue (such bleeding or perforation) happens, ulcers frequently appear and disappear on their own without the person ever realizing it.

Diagnosis of ulcers

The diagnosis of an ulcer is made by either barium upper GI X-ray or an upper endoscopy (EGD-esophagogastroduodenoscopy).

The barium upper GI X-ray is simple to carry out and causes no discomfort or risk. Orally taken barium is a chalky material. On X-ray film, barium can be seen tracing the contour of the stomach. Barium X-rays, on the other hand, are less reliable and may miss ulcers up to 20% of the time.

The stomach, esophagus, and duodenum can be examined with an upper endoscopy, which is more accurate but necessitates sedating the patient. The additional benefit of upper endoscopy is the ability to take tiny tissue samples (biopsies) to check for *H. pylori* infection. To rule out cancer, biopsies can also be viewed under a microscope. Duodenal ulcers are almost always benign, although stomach ulcers can occasionally be malignant. In order to rule out cancer, biopsies are frequently done on gastric ulcers.

Ulcer complications: Patients with ulcers generally function quite comfortably. Possibly, some ulcers can heal on their own without treatment. As a result, ulcer complications are the main issues caused by ulcers. Gastric obstruction, ulcer hemorrhage, and ulcer perforation are complications.

Patients with ulcer bleeding may experience weakness, orthostatic syncope (the feeling of fainting out when standing), black, tarry stools (melena), and blood vomiting (hematemesis). Intravenously replacing lost bodily fluids is the first step in treatment. Blood transfusions may be

necessary for patients who are bleeding severely or persistently. To locate the source of the bleeding and halt active ulcer bleeding with heated instruments, an upper endoscopy is performed.

Acute peritonitis is caused by the spilling of stomach contents into the peritoneal cavity as a result of ulcer perforation (infection of the abdominal cavity). These patients describe a rapid onset of excruciating abdominal discomfort that gets worse with any motion. The muscles in the abdomen stiffen and resemble boards. Usually, urgent surgery is necessary.

Increased abdominal pain, vomiting of undigested or just partially digested meals, decreased appetite, and weight loss are common symptoms of gastric obstruction in patients. The pyloric canal is typically where the obstruction arises. As it connects to the duodenum, the top portion of the small intestine, the pyloric canal is a naturally small portion of the stomach. Upper endoscopy is helpful in making the diagnosis and ruling out stomach cancer as the obstruction's etiology. Some individuals may benefit from intravenous anti-ulcer drugs such cimetidine (Tagamet) and ranitidine coupled with tube suction of the stomach contents for 72 hours to remove gastric obstruction (Zantac). Surgery is necessary for patients with persistent blockage.

Treatments available for peptic ulcers

Pain relief and the avoidance of ulcer complications like bleeding, blockage, and perforation are the two main objectives of ulcer management. Reducing risk factors is the initial stage of treatment (NSAIDs and cigarettes). Medication is the following step.

Antacids balance the stomach's natural acid. However, the duration of these medicines' neutralizing effects is brief, necessitating regular dosing. Maalox and Mylanta, which include magnesium, can lead to diarrhea, whereas amphojel, which contains aluminum, can lead to constipation. When antacids are stopped, ulcers frequently come back.

Histamine, a stomach protein, has been proven in studies to accelerate the production of gastric acid. Drugs called histamine antagonists (H2 blockers) are made to stop histamine from acting on gastric cells, which lowers the amount of acid produced by the stomach. Cimetidine, ranitidine, nizatidine, and famotidine are a few H2 blockers. H2 blockers have a limited role in eliminating *H. pylori* without antibiotics, notwithstanding their effectiveness in repairing ulcers. As a result, ulcers frequently come back after stopping H2 blockers. In general, even with prolonged use, these medications are well tolerated and have few side effects. Patients can complain of headaches, disorientation, fatigue, or hallucinations.

H2 blockers cannot match the effectiveness of proton-pump inhibitors like omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole in reducing acid secretion. Proton-pump inhibitors are more successful than H2 blockers for treating esophageal ulcers while being

equally effective at treating gastric and duodenal ulcers. Inhibitors of the proton pump are well tolerated. The most common side effects are headache, nausea, rash, diarrhea, and constipation.

Misoprostol and sucralfate are medications that fortify the stomach lining against attacks from digestive secretions that are acidic. The ulcer is coated with carafate, which aids in healing. The drug's negative effects are extremely minimal. Constipation and problems with other drugs being absorbed are the most frequent side effects. A prostaglandin-like molecule called Cytotec is frequently used to combat the effects of NSAIDs on ulcers. Diarrhea is a common side effect.

H. pylori is commonly present in the stomachs of persons who never experience pain or ulcers. Antibiotic combinations should be used to treat patients with ulcer disease and *H. pylori* infection. It might be quite challenging to totally remove *H. pylori*. Multiple antibiotics must be used in conjunction for treatment, often also with a proton-pump inhibitor, H2 blockers, or Pepto-Bismol. Tetracycline, amoxicillin, metronidazole, clarithromycin, and levofloxacin are among the antibiotics that are frequently utilized. The removal of *H. pylori* stops ulcers from recurring (a major problem with all other ulcer treatment options). The risks of receiving antibiotic treatment include allergic reactions, diarrhea, and occasionally severe antibiotic-induced colitis (inflammation of the colon).

The mechanisms by which peptic ulcers are formed are as follows [5] -

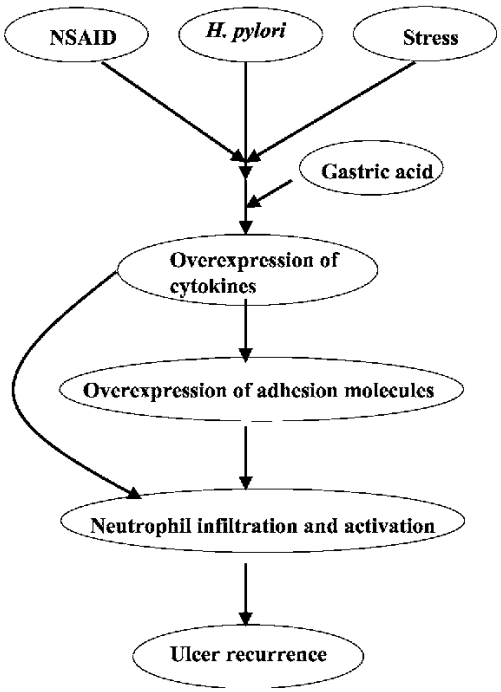

Figure 3: Mechanism of gastric ulceration

ROLE OF HERBS:

A common digestive system ailment is gastric ulcer. The majority of current treatment plans are based on Western medicine. However, multiple studies have shown that via different mechanisms, herbal remedies can successfully heal stomach ulcers in both people and diverse animal models. Much study covers the effectiveness, safety, and mechanisms of action of herbal remedies for healing stomach ulcers in both human and animal models. In humans and animal models, studies have shown that the efficacy of herbal medicines is equal to or greater than that of medications like omeprazole or cimetidine, and herbal medicines exhibit fewer side effects. The encouragement of mucous cell proliferation, anti-oxidation, and inhibition of stomach acid secretion and H(+)/K(+)-ATPase activity are some of the methods by which herbal medicines treat gastric ulcers. Some natural medications have antibacterial qualities as well. Utilizing herbal remedies could be a beneficial solution to heal human stomach ulcers successfully and with few side effects.

Table 2. List of some herbal plant extracts with antiulcerogenic property and their probable mechanism of action [6]

Plant	Model	Probable mechanism of action
Allophylus serratus Kurz	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Decreases acid secretion and peptic activity and increases mucin secretion.
Terminalia pallida Brandis	Histamine induced, alcohol induced, indomethacin induced	Decreases acid secretion and is potent antioxidant.
Desmodium gangeticum	Cold restraint, alcohol induced, aspirin induced pyloric ligation	Increases mucin secretion.
Ocimum sanctum Linn	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Decreases acid secretion and increases mucin secretion.
Hemidesmus indicus	Aspirin induced, pyloric ligation	Increase mucin secretion.
Asparagus racemosus Willd.	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Has no effect on acid and pepsin secretion, but increases mucin secretion.
Emblica officinalis Gaertn	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Decreases acid and pepsin secretion and increases mucin.

Azadirachta indica A Juss	Cold restraint, pyloric ligation, indomethacin induced, alcohol induced, histamine induced	Inhibits acid secretion and has antioxidant.
Centella asiatica Linn	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Has no effect on acid secretion, but increases mucin secretion.
Bacopamonniera	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Has no effect on acid secretion, but increases mucin secretion.
Bidens pilosa	Alcohol induced, pyloric ligation, indomethacin induced	Inhibits gastric acid and pepsin and stimulates mucus secretion.
Musa sapientum	Pyloric ligation	Increases mucin secretion.
Zingiber officinale[7]	Aspirin induced, pyloric ligation	Antisecretary activity.
Pterospermum acerifolium wild [8]	Aspirin induced, pyloric ligation, indomethacin induced	Inhibition of 5-LO enzyme, blockade of LTC4, LTD4 synthesis, free radical scavenging activity.
Ficus arnottiana miq [9]	Alcohol induced	Flavonoids have been reported for their antiulcerogenic activity and gastric protection.
Polyalthia longifolia[10]	Aspirin plus pylori ligation, HCl-Ethanol induced	Due to the presence of alkaloids and terpenoids it shows antiulcerogenic activity.
Entada phaseoloides[11]	Aspirin pylorous ligation method, HCl-Ethanol induced ulcer, stress induced ulcers.	Seeds of *entada phaseoloides* contain chemical constituents entadamide A, B & C, phaseoloides may likely be responsible for antiulcer activity.
Solanum surattense[12]	Aspirin induced, pyloric ligation	Antisecretory property.
Melia azedarach Linn [13]	Aspirin induced, pyloric ligation	Antisecretory property.
Digitrall [4]	Indomethacin induced	Antioxidant property.
Psidium guajava Linn 15]	Aspirin induced	Increase mucus secretion.
Gmelina arborea [16]	Cold restraint, alcohol induced, aspirin induced, pyloric ligation	Antisecretory and cytoprotective property.

Hingwashtak churna[17]	Alcohol induced, ibuprofen induced	Antioxidant property.
Naravelia zeylanica[18]	Aspirin plus pylori ligation, HCl – Ethanol, Water immersion stress	Antioxidant property.
Saraca indica[19]	Aspirin induced, pyloric ligation	Antisecretory property.
Nigella sativa[20]	Necrotizing agents (80% ethanol, 0.2 M NaOH and25%NaCl), indomethacin induced	Free radical scavenging and Antisecretory properties.

CONCLUSION:

Up to 10% of people worldwide are affected by the chronic condition eptic ulcer. Peptic ulcer development is influenced by the pH of gastric juice and a decline in mucosal defenses. The main factors affecting the mucosal resistance to damage are Helicobacter pylori (*H. pylori*) infection and non-steroidal anti-inflammatory medicines (NSAIDs). Proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, two common therapies for peptic ulcers, have been shown to cause side effects, relapses, and a variety of pharmacological interactions. In conclusion, herbal medications effectively treat stomach ulcers while having fewer side effects and a lower recurrence rate. A synergistic impact is shown when herbal remedies and traditional anti-gastric ulcer medications are combined. Consequently, herbal remedies alone or in conjunction with conventional medications could be useful.

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CHAPTER 3

DIABETES MELITUS: TYPES, PATHOPHYSIOLOGY AND ROLE OF HERBS

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ABSTRACT

The persistent metabolic condition Diabetes mellitus is a rapidly spreading global issue that has serious social, health, and economic ramifications. According to estimates, this illness affected 285 million people worldwide in 2010—roughly 6.4% of the adult population. If there are no improvements in treatment or control, this number is projected to rise to 430 million. The two main causes of the increase are aging and obesity. Additionally, it has been demonstrated that about 50% of alleged diabetics do not receive a diagnosis until 10 years after the commencement of the condition, indicating that the true prevalence of diabetes worldwide must be extremely high. Due to the current conventional medications' insufficient efficacy and unfavorable side effects, novel therapies are still in high demand. Natural remedies for diabetes are abundant in nature. The National Center for Complementary and Alternative Medicine states that there is yet insufficient solid data to back up the use of herbal supplements as successful type 2 diabetes therapy. Even if many of these supplements appear promising, you should not use herbal supplements to treat type 2 diabetes without first talking to your doctor. Herbal supplements can interact with other drugs and have negative effects.

KEYWORDS: Diabetes mellitus, health, obesity, and herbal supplements

INTRODUCTION

Diabetes mellitus is a group of metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The hyperglycemia is due to deficiency of insulin secretion or due to the resistance of body cells to the action of insulin. The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity. If diabetes mellitus remain untreated for long period of time leads to alteration in physiology and failure of organs like liver, kidneys etc. Diabetes mellitus may present with characteristic symptoms like weight loss, polydipsis, polyurea, polyphagia and blurred vision. The long-term effect of diabetes mellitus is retinopathy with loss of vision, nephropathy leading to renal failure,

peripheral and autonomic nephropathy with risk of foot ulcers and cardiovascular, cerebrovascular and peripheral vascular complications [1-3].

PREVALENCE OF DIABETES IN INDIA:

According to International Diabetes Foundation, India has more diabetic patients than any country in the world [4]. The current figure of diabetic affects more than 62 million Indians, which is more than 7.1% of India's Adult Population [5]. The disease an estimate shows that nearly 1 million Indians die due to diabetes every year. Onset of diabetes in Indian people at a younger age gives ample time to develop chronic vascular complications secondary to diabetes. Moreover, impaired glucose tolerance (IGT), which is a forerunner of diabetes, is also increasing, especially among the younger population [6]. Combination of genetic susceptibility with adoption of a high calorie, low-activity lifestyle of middle class people of India is the major causes of diabetes mellitus. In addition, according to American Diabetes Association, it has been reported that India will see greatest increase in people diagnosed with diabetes by 2030 [7,8].

CLASSIFICATION:

There are different types of diabetes mellitus, share hyperglycemia as a common feature but the pathogenic process involved in the development of hyperglycemia vary widely. The older classification systems dividing DM into primary (idiopathic) and secondary types, juvenile onset types, and insulin-dependent (IDDM) and non-insulin dependent (NIDDM) types, have become obsolete and undergone revision due to wide understanding of etiology and pathogenisis of diabetes mellitus [9].

As per American Diabetes Association the etiologic classification of diabetes mellitus is given below:

I. Type 1 diabetes

A. Immune mediated

B. Idiopathic

II. Type 2 diabetes

III. Other specific types

A. Genetic defects of β-cell function (eg; Glucokinase)

B. Genetic defects in insulin action (eg; Insulin resistaance)

C. Disease of pancreas (eg; Pancreatitis)

D. Endocrinopathies (eg; Cushing’s syndrome)

E. Drug or chemical-induced

F. Infections (eg; Congenital rubella)

G. uncommon form of immune-mediated diabetes (eg; “Stiff-man” syndrome)

H. Other genetic syndromes sometimes associated with diabetes (eg; Down's syndrome)

IV. Gestational Diabetes mellitus

Type I Diabetes Mellitus: It constitutes about 10% cases of diabetes mellitus. It was previously termed as juvenile onset diabetes (JOD) Due to its occurrence in younger age, and was called insulin dependent diabetes mellitus (IDDM) because these patients had absolute requirement for insulin replacement as treatment. However, in the new classification, neither age nor insulin dependence is considered as absolute criteria. Instead, based on underlying etiology, type 1 DM is further divided into 2 subtypes [9]:

Subtype 1A (immune-mediated) diabetes mellitus is characterized by desctuction of pancreatic beta cells by autoimmunity, which leads to deficiency of insulin.

Subtype 1B (Idiopathic) diabetes mellitus is characterized by deficiency of insulin with the development of ketosis. In this case patients are negative for autoimmune markers.

Type 2 Diabetes Mellitus: This type comprises about 80% cases of diabetes mellitus. It was previously called as non insulin dependent diabetes mellitus (NIDDM) or maturity-onset diabetes.

Type 2 diabetes mellitus mainly or predominantly affects older individuals, but it has been reported that it also occurs in obese adolescent children. Thus, the term maturity onset diabetes (MOD) is not appropriate. Moreover, many type 2 diabetes mellitus patients also require insulin therapy to control hyperglycemia or to prevent ketosis and thus are not truly non-insulin dependent contrary to its former nomenclature. Type-2 diabetes is strongly favored by genetic predisposition environmental factors such as excessive caloric intake, obesity with increased body fat in the abdominal (visceral) site, sedentary habit, etc. However, although it shows familial aggregation as well as a high concordance (80%) in monozygotic twins, its mode of inheritance is not fully understood. The risk of offspring and siblings of type-2 diabetic patients to develop the disease is moderately increased [9].

Gestational Diabetes Mellitus: GDM is any degree of glucose intolerance with onset or first diagnosis during pregnancy. About 4% pregnant women develop DM due to metabolic changes during pregnancy. Although they revert back to normal glycaemia after delivery these women are prone to develop DM later in their life [9]**.**

PATHOGENESIS

Pathogenesis of Type-1 Diabetes Mellitus [9]:

The basic phenomenon in type-1 DM is destruction of beta-cell mass, usually leading to absolute insulin deficiency. While type 1B DM remains idiopathic, pathogenesis of type 1A DM

is immune mediated and has been extensively studied. Currently, pathogenesis of type 1A DM is explained on the basis of 3 mutually-interlinked mechanisms:

1. *Genetic susceptibility:*

Type 1A DM involves inheritance of multiple genes to confer susceptibility to the disorder:

- It has been observed in identical twins that if one twin has type1A DM, there is about 50% chance of the second twin developing it, but not all. This means that some additional modifying factors are involved in development of DM in these cases.
- About half cases with genetic predisposition to type1A DM have the susceptibility gene located in the HLA region of chromosome 6 (MHC class II region), particularly HLA DR3, HLA DR4 and HLA DQ locus. It appears that in a HLA-associated susceptible individual, beta-cells act as autoantigens and activate CD4+ T lymphocytes, bringing about immune destruction of beta-cells.

2. *Autoimmune factors:*

Studies on humans and animal models on type 1A DM have shown several abnormalities:

- Presence of islet cell antibodies against GAD (glutamic acid decarboxylase), insulin etc, though its assay largely remained as research tool due to tedious method.
- Occurrence of lymphocytic infiltrate in and around pancreas islets termed insulitis. It chiefly consists of CD8+ T lymphocytes with variable number of CD4+ T lymphocytes and macrophages.
- Selective destruction of beta-cells while other islet cell types (glucagon-producing alpha cells, somatostatin producing delta cells, or polypeptide-forming PP cells) remain unaffected. This is mediated by T-cell mediated cytotoxicity or by apoptosis.
- Role of T cell-mediated autoimmunity is further supported by transfer of type 1A DM from diseased animal by infusing T lymphocytes to a healthy animal.
- Association of type1A DM with other autoimmune diseases in about 10-20% cases such as Graves' disease, Addison's disease, Hashimoto's thyroiditis, pernicious anaemia.
- Remission of type 1A DM in response to immunosuppressive therapy such as administration of cyclosporine A.

3. *Environmental factors:*

Epidemiologic studies in type 1A DM suggest the involvement of environmental factors in its pathogenesis, though none of them has been conclusively proved. In fact, the trigger may

precede the occurrence of the disease by several years. It appears that certain viral and dietary proteins share antigenic properties with human cell surface proteins and trigger immune attack on β-cells by a process of molecular mimicry. These factors include the following:

- Certain viral infections preceding the onset of disease e.g. mumps, measles coxsackie B virus, cytomegalovirus and infectious mononucleosis.
- Experimental induction of type 1A DM with certain chemicals has been possible e.g. alloxan, streptozotocin and pentamidine.

Pathogenesis of Type-2 diabetes mellitus [9]**:**

The basic metabolic defect in type-2 diabetes mellitus is either a displayed insulin secretion relative to glucose load (impaired insulin secretion), or the peripheral tissues are unable to respond to insulin (peripheral resistance).

1. *Genetic factors:*

- There is approximately 80% chance of developing diabetes in the other identical twin if one twin has the disease.
- A person with one parent having type-2 DM is at an increased risk of getting diabetes, but if both parents have type-2 DM the risk in the offspring rises to 40%.

2. *Constitutional factors:*

Certain environmental factors such as

- Obesity
- Hypertension
- Low physical activity

3. *Insulin resistance:*

One of the most prominent metabolic features of type-2 DM is the lack of responsiveness of peripheral tissues top insulin, especially of skeletal muscle and liver. Obesity, in particular, is strongly associated with insulin resistance and hence type-2 DM. Mechanism of hyperglycemia in these cases is explained as under:

- Resistance to action of insulin impairs glucose utilization and hence hyperglycemia.
- There is increased hepatic synthesis of glucose.
- Hyperglycemia in obesity is related to high levels of free fatty acids and cytokines (e.g. TNF-α and adiponectin) affect peripheral tissue sensitivity to respond to insulin.

The precise underlying molecular defect responsible for insulin resistance in type 2 DM has yet not been fully identified. Currently, it is proposed that insulin resistance may be possibly due to one of the following defects:

- Polymorphism in various post-receptor intracellular signal pathway molecules.
- Elevated free fatty acids seen in obesity may contribute e.g. by impaired glucose utilization in the skeletal muscle, by increased hepatic synthesis of glucose, and by impaired beta-cell function.

Insulin resistance syndrome is a complex of clinical features occurring from insulin resistance and its resultant metabolic derangements that includes hyperglycaemia and compensatory hyperinsulinaemia. The clinical features are in the form of accelerated cardiovascular disease and may occur in both obese as well as non obese type 2 DM patients. The features include: mild hypertension (related to endothelial dysfunction) and dyslipidaemia (characterized by reduced HDL level, increased triglycerides and LDL level).

4. *Impaired insulin secretion:*

In type 2 DM, insulin resistance and insulin secretion are interlinked:

- Early in the course of disease, in response to insulin resistance there is compensatory increased secretion of insulin (hyperinsulinaemia) in an attempt to maintain normal blood glucose level.
- Eventually, however, there is failure of beta-cell function to secrete adequate insulin, although there is some secretion of insulin i.e. cases of type 2 DM have mild to moderate deficiency of insulin (which is much less severe than that in type 1 DM) but not its total absence.

The exact genetic mechanism why there is a fall in insulin secretion in these cases is unclear. However, following possibilities are proposed:

- Islet amyloid polypeptide (amylin) which forms fibrillar protein deposits in pancreatic islets in longstanding cases of type 2 DM may be responsible for impaired function of beta-cells islet cells.
- Metabolic environment of chronic hyperglycaemia surrounding the islets (glucose toxicity) may paradoxically impair islet cell function.
- Elevated free fatty acid levels (lipotoxicity) in these cases may worsen islet cell function.

5. *Increased hepatic glucose synthesis:*

One of the normal roles played by insulin is to promote hepatic storage of glucose as glycogen and suppress gluconeogenesis. In type 2 DM, as a part of insulin resistance by peripheral tissues, liver also shows insulin resistance i.e. in spite of hyperinsulinaemia in the early stage of disease, gluconeogenesis in the liver is not suppressed. This results in increased hepatic synthesis of glucose which contributes to hyperglycaemiain in these cases.

Pathophysiology of diabetes mellitus:

Type-1 diabetes

The pathophysiological changes occur in type-1 diabetes due to severe insulin deficiency. In type-1 diabetes, decrease in insulin level and increase in glucagon level results in increase glycogenolysis and gluconeogenesis in the liver, with enhance hepatic glucose output (HGO). In addition, decrease in insulin activity results in reduced glucose utilization by peripheral tissue (especially muscles) as well as inactivation of lipolysis in the adipose tissue with increase free fatty acid (FFA) release. The latter, although they cannot be directly converted into glucose in man, favor gluconeogenesis in the liver. Combination of enhanced HGO and reduced glucose utilization results in hyperglycemia. In addition, FFA exerts anti-insulin effects at the muscle level, through the mechanism of the glucose-FFA cycle. This mechanism further results in resistance to insulin. In addition, hyperglycemia also favors glucose utilization by non-insulin dependent glucose transporters such as GLUT1 in gut, GLUT2 in liver, and GLUT3 in brain, and that in type-1 diabetes this glucose effect may be reduced, i.e. there may be 'glucose resistance' [10].

Type-2 diabetes

Type-2 diabetes is combination of insulin resistance and reduction in insulin secretion especially in the late stage. The metabolic alterations are less pronounced than those in type-1 diabetes. Due to insulin resistance (and to enhanced counter regulatory hormones), there is increased HGO (which contributes primarily to fasting hyperglycemia) and reduced peripheral glucose utilization. Due to activation of lipolysis and/or increase in fat mass or obesity results elevation of plasma FFA which cause insulin resistance via glucose-FFA cycle. Moreover, unlike type-1 diabetes, in type-2 diabetes glucose resistance may occur. It has been observed that in obesity and type-2 diabetes (as well as in acromegaly and Cushing's disease), in the post absorptive period, non-insulin mediated glucose uptake is a major determinant of glucose disposal and is similar in the different pathologies studied. On the other hand, the uptake rate of basal insulin-mediated glucose is reduced in insulin resistant states [10].

Insulin:

Insulin is the main hormone, which control the blood glucose level. Decrease secretion or production of insulin, often in combination with reduced sensitivity to its action or insulin resistance, results diabetes mellitus. The consequences of diabetes are dire-especially complications of atherosclerosis, kidney failure and blindness.

Insulin was the first protein for which an amino acid sequence was determined (by Sanger's group in Cambridge in 1955). It is a peptide hormone secreted by the pancreatic β-cells

of islets of langerhans in response to the rise in blood glucose levels. It consists of two peptide chains (A and B, of 21 and 30 amino acid residues, respectively) [11].

Biosynthesis of Insulin

Insulin is synthesized as a precursor preproiinsulin in rough endoplasmic reticulam. Preproinsulin is transported into the golgi apparatus. In golgi apparatus it undergo proteolytic cleavage first to proinsulin and then to insulin and then to C-peptide, a 31 amino acid polypeptide fragment of uncertain function. Insulin and C-peptide are stored in granules in β cells, and are normally co secreted by exocytosis in equimolar amounts together with smaller and variable amounts of proinsulin. The main factor controlling the synthesis and secretion of insulin is the blood glucose concentration. β cells respond both to the absolute glucose concentration and to the rate of change of blood glucose [12].

Insulin release

Insulin release from β cells of islets of Langerhans in two phases. In first phase insulin release in response to high level of blood glucose and in the second phase a sustained, slow release of newly formed insulin independently of sugar takes place [44]. The release of insulin in the first phase occurs in following steps:

- ✓ Glucose enters the β-cells through the glucose transporter, GLUT2.
- ✓ Glucose enter into glycolysis and the Krebs cycle
- ✓ An increased high-energy ATP molecules are produced by oxidation, leading to a rise in the ATP:ADP ratio within the cell.
- ✓ An increased intracellular ATP:ADP ratio closes the ATP-sensitive potassium channel (sulfonylurea receptor).
- ✓ This prevents potassium ions (K^+) from leaving the cell by facilitated diffusion, leading to a build-up of potassium ions, which makes inside of the cell more positive than the outside, results in depolarization of cell surface membrane.
- ✓ Depolarization cause opening of voltage-gated calcium channels which allow moving the calcium ions into the cells by facilitated diffusion.
- ✓ Increase in intracellular calcium ion results in phospholipase C which convert membrane phospholipid phosphotidyl inositol 4,5-bisphosphatidyl into inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG).
- ✓ IP_3 bind to receptor proteins in the plasma membrane of the endoplasmic reticulum (ER), which results release of calcium ions from ER and further intracellular calcium level.
- ✓ Other substances known to stimulate insulin release include the amino acids arginine and leucine, parasympathetic release of acetylcholine (via phospholipase

C), sulfonylurea, cholecystokinin (CCK, via phospholipase C) and the gastrointestinally derived incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

PHYSIOLOGICAL EFFECTS OF INSULIN:

Carbohydrate metabolism

Insulin influences glucose metabolism in most tissues, especially the liver, where it inhibits glycogenolysis (glycogen breakdown) and gluconeogenesis (synthesis of glucose from non-carbohydrate sources) while stimulating glycogen synthesis. Insulin prevents the conversion of glycogen into glucose in liver. Decrease in the insulin level increase in conversion of glycogen into glucose in the liver cells which excrete it into the blood [12].

Fat metabolism

Insulin increases the synthesis of fatty acids and triglycerides in the adipose tissue and liver cells. It prevents the breakdown of lipid (lipolysis), partly via dephosphorylation (and hence inactivation) of lipases. It also inhibits the lipolytic actions of adrenaline, growth hormone and glucagon by opposing their actions on adenylate cyclase [12].

Protein metabolism

Insulin increases the protein synthesis and also causes uptake of amino acids into muscles. It prevents the protein catabolism and oxidation of amino acids in the liver cells [44].

Autophagy

It decreased autophagy, decreased level of degradation of damaged organelles. Postprandial levels inhibit autophagy completely [13].

ROLE OF HERBS:

Due to the current conventional medications' insufficient efficacy and unfavorable side effects, novel therapies are still in high demand. Natural remedies for diabetes are abundant in nature. Herbal remedies were used to cure a variety of diseases even before the development of mainstream Western medicine. Western medicine today dominates "traditional" forms of medicine, including herbal medicine systems, due to emphasis on scientism and other complex factors. Although herbal medical systems are occasionally mistaken for being antiquated and unscientific, their longevity shows they can compete with Western medicines to some extent. Because of the diversity of the phytochemicals and bioactivities in the plant, using a medicinal herb, either alone or in conjunction with other herbs, can be considered a form of combination therapy. Consequently, by focusing on a variety of metabolic pathways and effectively having thousands of phytochemicals in one antidiabetic herb, it may have numerous advantages. This idea was backed by a study that showed a combination therapy of conventional medicine and

herbal medicine had a stronger (synergistic) effect than either drug alone. As a result, herbal medicine can support conventional therapy for T2D and offer hope for a cure [14].

Herbal remedies have always been used to treat illnesses and are still widely used today. Over 1200 plants have been identified among them as potential treatments for diabetes. 700 recipes and chemicals, together with more than 400 plants, have been scientifically tested for T2D treatment. The first-line treatment for T2D is metformin, which was created using a biguanide molecule derived from the anti-diabetic plant French lilac. Herbal medicines contain a variety of bioactive substances that can affect insulin synthesis, function, or both. The ability of specific herbs and phytocompounds to target insulin resistance, beta-cell function, incretin-related pathways, and glucose (re)absorption are the main mechanisms [15].

CONCLUSION:

Humans are severely morbidly and fatally affected by T2D, a sickness that has been known to man for many centuries. No treatments have been discovered despite substantial advancements in T2D and the creation of anti-diabetic medications. A very rich source of T2D treatments is medicinal herbs, which have a long history of usage in systems of complementary and alternative medicine. The processes by which herbal treatments for T2D are currently being better understood, and they are often thought to work by altering a number of metabolic pathways. Herbal treatments are effective treatment options for T2D due to their safety and variety of targeted effects. The benefit of a botanical extract is that if botanicals are effective at reducing risk factors and/or improving metabolism on a clinical level, these treatments are generally accessible and may thus be able to help the general public with regards to obesity and diabetes. Unfortunately, despite the fact that most common botanicals have a long history in traditional medicine, there are few conclusive scientific studies, especially when it comes to regularly enhancing glucose metabolism. Based on the information that is now available, there is not enough support for any specific botanical product to be actively advised for the treatment of high blood sugar or any associated risk factors. However, there are numerous ongoing investigations in which herbal remedies are reliable, as well as specific clinical studies.

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CHAPTER 4

DIABETIC COMPLICATIONS: AN OVERVIEW

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ABSTRACT

Diabetes mellitus is a significant contributor to morbidity and mortality as well as the early start of coronary heart disease. Retinopathy, nephropathy, and peripheral neuropathy are all side effects of diabetes. The current course of treatment includes changing one's diet, losing weight, exercising, using oral drugs, and taking insulin. The etiology of diabetes, which affects the cardiovascular, renal, neurological, and eye systems as well as the lower extremities, particularly the feet, has made significant strides in recent years. With strict glucose and blood pressure control, the advancement of diabetic retinopathy and nephropathy can be slowed down or even stopped. One of the key issues still generating serious impairment is neuropathy. There has been some success in the ongoing clinical trials and testing of various drugs to see how well they address the complications of diabetes, but more work needs to be done.

KEYWORDS: Diabetes mellitus, retinopathy, nephropathy, and peripheral neuropathy

INTRODUCTION

Diabetes is widely acknowledged as an epidemic that is just beginning to spread and that affects practically every nation, demographic, and economic system in the globe. The International Diabetes Federation estimates that 415 million people globally have diabetes in 2015, and that figure will rise to 640 million by the year 2040. Since an estimated 50% of diabetic patients are ignorant about their condition, they are more likely to experience diabetic complications. However, the price of managing diabetes can be prohibitive in terms of resources used and lives lost. Although diabetes was blamed for around 5.0 million deaths in 2015, more than 12% of global health spending that year went toward treating the condition [1].

Microvascular and macrovascular problems of diabetes are the two main categories, with the former having a significantly higher prevalence than the latter [2]. In contrast to macrovascular problems, which include cardiovascular disease, stroke, and peripheral artery disease, microvascular sequelae include neuropathy, nephropathy, and retinopathy. The goal of this chapter is to present a wide range of research and review papers that address current basic developments in our knowledge of diabetes complications.

COMPLICATIONS RELATED TO DIABETES:

Several complications are related to diabetes are-

Atherosclerosis in diabetic patients

In diabetic obesity low level of TNF-α secretion takes place which increase the secretion of leptin contribute to macrophages accumulation and addition of macrophages to the endothelial cell which is similar to that seen in atherosclerosis. TNF-*α* also cause increase in oxidative stress which result atherosclerosis [3].

Diabetic retinopathy

Diabetic retinopathy is a chronic ocular disorder and if it is remain untreated it results in activation of microglia cells which migrate toward dying neurons and release proinflammatory cytokines to further increase the damage. These findings suggest that any drug that reduces oxidative stress and inflammation might be effective to guard neurons in diabetic retinopathy. Generally quiescent microglia becomes activated during early diabetes. Proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and interferon-γ have been reported to activate microglia [4-6]. After activation microglia release glutamate, ROS, TNF-α, IL-1β, IL-6, vascular endothelial growth factor (VEGF), lymphotoxins, matrix metalloproteinase's (MMPs) and nitric oxide (NO). TNF-α, IL-1β, IL-6, and lymphotoxins alter the expression of vascular endothelial growth factors (VCAM) to recruit lymphocytes and macrophages to injury sites. TNF-α, lymphotoxins, NO and ROS can also directly kill cells. VEGF, NO and MMPs can weaken the blood retinal barrier (BRB), thus enhancing the infiltration of leukocytes into the retina. It is still unclear that why diabetes cause activation of microglia in retina, but it has been investigated that microglia activation may provide considerable insight into the pathogenesis of diabetic retinopathy. Cultured microglia has been used extensively to study microglia behaviour. Treatment of microglia or macrophage-like cells with advanced glycation end-products (AGE) or Amador albumin, high glucose or with endotoxins such as lipopolysaccharide (LPS) has been used as a model to simulate inflammation [7].

Diabetic and obesity

Many factors are linked to the development of insulin resistance with impaired glucose tolerance and type 2 diabetes and those factors are genetics, obesity, inflammation and environmental influences. Obesity and the activation of adipose tissue may increase the release of inflammatory cytokines which results in insulin resistance. A significant number of type 2 diabetes patients are obese and obesity is the risk factor for the development of type 2 diabetes [8]. Increase release of adipose tissue metabolites, cytokines, lipids, fatty acids also aid to develop insulin resistance [9]. Chronic inflammation is associated with obesity, insulin resistance, and type-2 diabetes is the group of metabolic pathologies known as metabolic syndrome [10].

It has been investigated that in a obesity-related model for the development of insulin resistance where adipocytes once activated release lipids, fatty acids and monocytes chemoattractant protein-1 (MCP-1) and proinflammatory cytokines. The release of cytokines cause local recruitment of monocytes within adipose tissue where monocytes differentiate into macrophages cause increase release in inflammatory cytokines and chemokines in the adipose tissue which further propagate to various tissues [9,10].

Diabetic nephropathy

Diabetic nephropathy is a progressive kidney disease and cause of end-stage renal disease all over the world. It is characterized by nephritic syndrome and diffuse glomerulosclerosis. The pathophysiology of diabetic nephropathy is not fully understood. Diabetic nephropathy is caused by both metabolic alterations (hyperglycaemia and possibly hyperlipidaemia) and haemodynamic alterations (systemic and glomerular hypertension). Inflammation, endothelial dysfunction, and oxidative stress, are also plays major role in the development of diabetic nephropathy. It is one of the main causes of morbidity and mortality in patients suffering from diabetes [11].

Cytokines play a major role in diabetic nephropathy. Pleiotropic actions of many inflammatory cytokines trigger several different cellular responses depending on diverse factors such as, cell type, timing and context. Cytokines act synergistically and can markedly amplify their effects, and stimulate the expression of other cytokines and their receptors [12].

Moreover, O°_2 in diabetes cause activation of different pathways involved such as polyol pathway flux, increase formation of advanced glycation end products (AGEs), increase expression of receptor for AGEs (RAGE), activation of protein kinase C (PKC) isoforms, and over activity of hexosamine pathway. ROS production also cause defective angiogenesis due to ischemia and also activates certain proinflammatory cytokines such as TNF-α and IL1β promotes a long lasting epigenetic changes that drive presistant expression of proinflammatory genes after glycemia is normalized.

It has been investigated that TNF-α and IL1β expressed in glomerular basement membrane of diabetic rats [13]. This finding indicates that inflammatory cytokines plays a major role in diabetic nephropathy [14].

Role of inflammatory cytokines in complications related to diabetes:

Inflammatory cytokines in vascular complications

Hyperglycaemia induces the expression of the PKC pathway. This results in the development of complications through altered gene expression and/ or protein function, thus contributing to cellular dysfunction and damage [15]. A well-described pathway for the development of diabetic vascular complications involves activation of the diacylglycerol (DAG)-

PKC pathway [16]. Elevation of DAG and activation PKC were reported in the different cells isolated from human and animals exposed to high glucose [17]. Several processes may underlie the increased formation of DAG, including the induction of oxidants, such as H_2O_2, and the accumulation in AGEs. PKC-β is the isoform of PKC is considered to play major role in the development of complications in the organs such as retina, kidney, heart and the vasculature. Activation of PKC-β in the vasculature has been associated with increase in the basement matrix protein synthesis, activation of leukocytes, endothelial cell activation and proliferation, smooth muscle cell contraction, endothelial permeability, aactivation of cytokines, transforming growth factor- β (TGF-β), VEGF and angiogenesis [18,19].

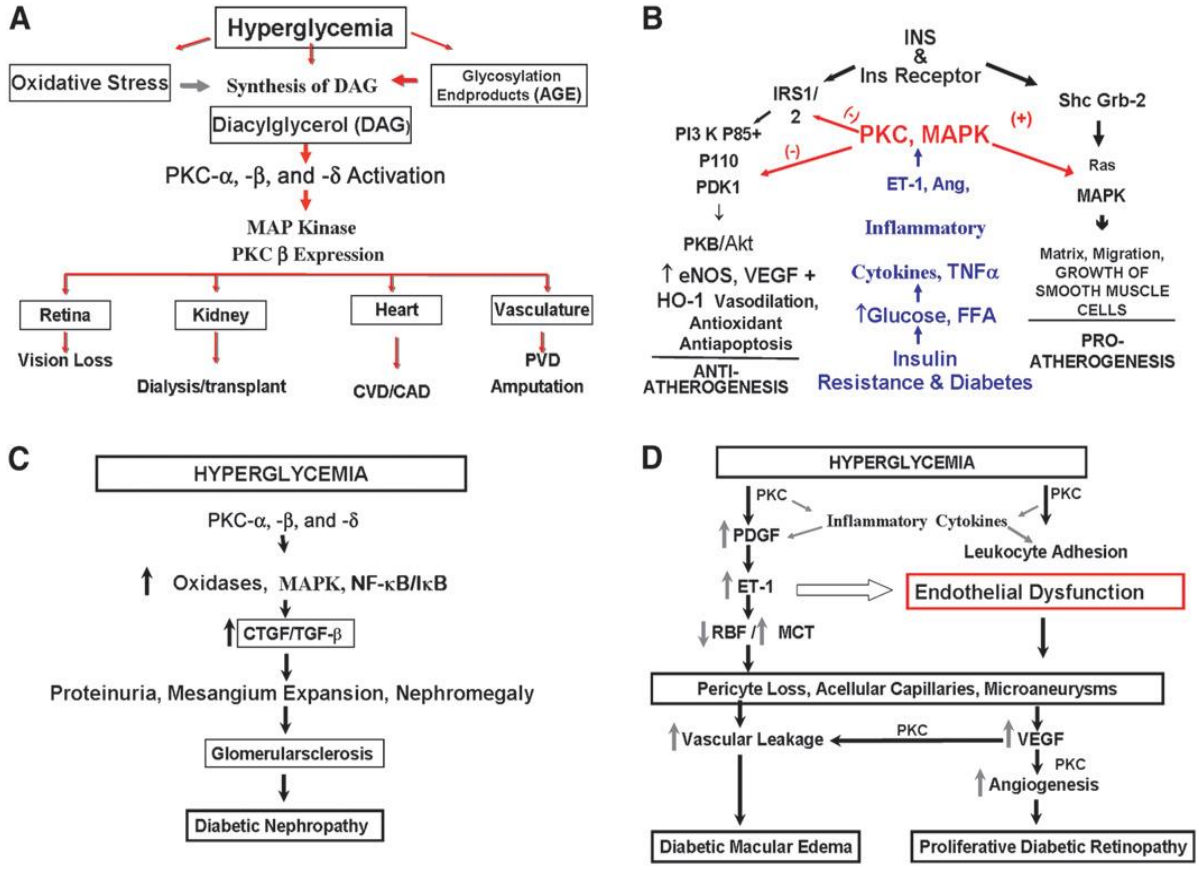

Figure 1: Vascular complications associated with diabetes

Vascular complications occur due to increase in PKC and MAPK activity in cardiovascular tissues in the presence of selective insulin resistance. Under normal physiologic conditions, insulin interects with its respective receptors and cause activation of phosphoinositide-3 kinase (PI3K) pathway that inhibits atherogenesis and has antiatherogenic effects and MAPK-activated path- way that promotes cellular growth and enhances atherogenesis two main pathways in cardiovascular tissue (Figure 1). Increase in glucose and free fatty acids level also leads to an elevated release of proinflammatory cytokines and altered

regulation of PKC and MAPK activity. PKC inhibits the PI3K pathway and increase atherogenesis by decrease in antiatherogenic NO production and decrease endothelium-dependent vasodilation. Loss of perycyte, formation of acellular capillaries, and microaneurysms also occur this type of pathological alteration in the retina increase vascular leakage and diabetic macular edema (DME), increase VEGF and angiogenesis results proliferative diabetic retinopathy [18,19].

Inflammatory cytokines in diabetic nephropathy

IL-18:

IL-18 is a potent inflammatory cytokine that induces interferon, which in turn induces functional chemokine receptor expression in human mesangial cells. It also leads to production of other inflammatory cytokines (including IL-1 and TNF-α), up regulation of ICAM-1, as well as apoptosis of endothelial cells. IL-18 is expressed in renal tubular epithelial cells. Recent studies demonstrated that infiltration of monocytes, macrophages and T cells are the potential sources of IL-18. It has been reported that serum and urine of diabetic nephropathy patients have more amount of IL-18 than normal individuals. In addition, urinary excretion of microglobulin, a marker of tubulointerstitial injury, is also positively associated with serum IL-18. Moreover, in another study serum and urinary concentration of IL-18 has been correlated with the albumin excretion rate, as well as with changes in albuminurea during the study period [20-24].

IL-1:

In experimental models of diabetic nephropathy, renal expression of IL-1 increases, which is related to subsequent expression of chemo tactic factors And adhesion molecules. IL-l enhances the synthesis of ICAM-1 and vascular cellular adhesion molecule-1. In addition, this cytokine induce transient expression of E-selectin by endothelial cells. IL-1 is also involved in the development of abnormalities in intraglomerular hemodynamic related to prostaglandin synthesis by mesangial cells. Treatment of glomerular mesangial cells with recombinant human IL-1 induces prostaglandin E2 synthesis and the release of a phospholipase A2 activity. In addition, pretreatment of resting mesangialcells with this cytokine results in an amplified secretary prostaglandin E2 response to angiotensin II. Furthermore, *in vitro* has been demonstrated that IL-1 is directly increases vascular endothelial cell permeability [25-28].

IL-6:

IL-6 also plays an important role in the development of diabetic nephropathy. It has been reported that serum of type 2 diabetic patients with nephropathy contains higher level of IL-6, which suggests that IL-6 is involved in the pathogenesis of diabetic nephropathy. In that study, it was observed that cells infiltrating the mesangium, and tubules were positive for mRNA encoding IL-6. Furthermore, they found a relationship between the severity of

diabeticglomerulopathy and expression of IL-6 mRNA in glomerularcells (mesangial cells and podocytes), which indicated that IL-6 affect the dynamic of extracellular matrix surrounding those cells. Recent studies in type 2 diabetic patients demonstrated that IL-6 also involved in basement membrane thickening which is crucial lesion of diabetic nephropathy [29,30].

TNF-*α*:

TNF-α is a pleiotropic inflammatory cytokine that is mainly produced by monocytes, macrophages, and T cells.as like other cytokines the expression and synthesis of TNF-α is not limited to hematopoietic cells. Thus, mesangial cells, glomerular cells, endothelial cells, dendritic cells, and renal tubular cells are able to produce TNF-α. TNF-α can be stored within cells in a proactive form, and the TNF-α–converting enzyme can rapidly increase levels of the active cytokine [31].

Inflammatory cytokines and obesity in diabetes mellitus

It has been investigated that in a obesity-related model for the development of insulin resistance, where adipocytes once activated, release lipids, fatty acids and monocytes chemoattractant protein-1 (MCP-1) and proinflammatory cytokines like TNF-α and IL-1 [64]. Increase in proinflammatory cytokines like TNF-α and IL-1 cause the activation the IKKb/NF-kB pathway. Several studies have been demonstrated the critical role of the IKKb/NF-kB pathway in the development of insulin resistance. It has been demonstrated that the heterogeneous deletion of IKKb in an obese mice model fed with high-fat over 23 weeks postnatally gives protection from development of insulin resistance. In addition, in a clinical study of young obese no-diabetic adults, treatment with salsala, a non-acetylated slicylate a known disruptor of the IKKb/NF-kB pathway, improved insulin sensitivity. In that study, salsalate also able to reduce free fatty acid and increases the serum anti-inflammatory cytokines such as adiponectin and C-reactive protein (CRP) [31].

NF-κB is an important regulator of cellular responses and it is categorized as a “rapid acting” primary transcription factor. NF-κB does not require any new protein synthesis or any transcription factors like c-jun, STATs, or nuclear hormone receptors for its activation. And because of this it is a first responder to harmful cellular stimuli. Known inducers of NF-κB activity are highly variable and include reactive oxygen species (ROS), tumor necrosis factor alpha (TNF-α), interleukin 1-beta (IL-1β), bacterial lipopolysaccharides (LPS), isoproterenol, cocaine, and ionizing radiation. Receptor activator of nuclear factor kappa B (RANK), which is a type of TNF receptor, is a central activator of NFκB [31] (Figure 2).

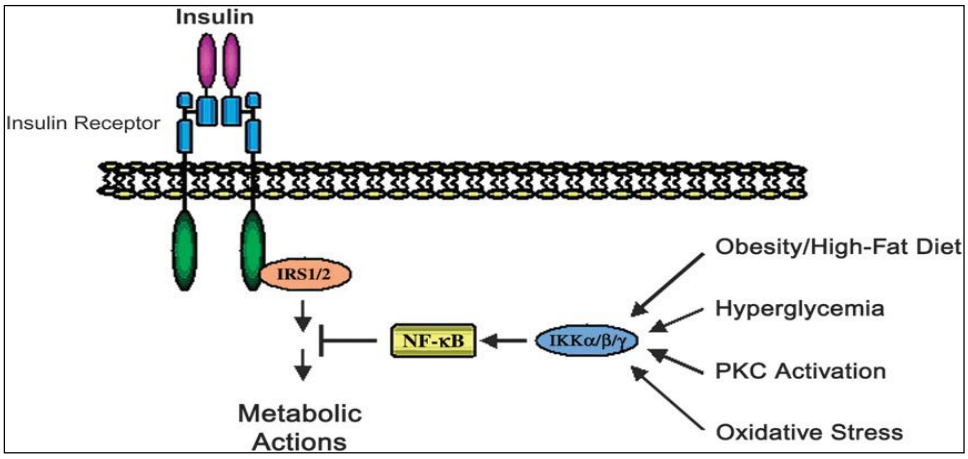

Figure 2: Activators of IKK/NF-kB pathway inhibit insulin signalling

IKK = IkB kinase; IRS = insulin receptor substrate

CONCLUSION:

Kidney failure, blindness, and amputations are some of the most common microvascular consequences, yet existing treatments only slow the course of the disease. Reduced glomerular filtration rate, a sign of impaired kidney function, is also a significant risk factor for macrovascular events like heart attacks and strokes. There have been numerous new treatments for diabetes complications evaluated in clinical trials, with generally underwhelming outcomes. Which pathways in diabetic complications are essentially protective rather than destructive, in terms of their influence on the underlying disease process, is still not completely known. Additionally, it appears that formerly isolated pathways have important interactions with one another that worsen disease. It's interesting to note that some of these routes could not just be important in difficulties. Furthermore, new areas of research that deserves more study as potential future treatment targets will be identified.

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CHAPTER 5

CHEMICAL-INDUCED RENAL COMPLICATIONS ANS ITS HERBAL TREATMENT: AN OVERVIEW

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ABSTRACT

By 2040, kidney illnesses are anticipated to rank as the sixth greatest cause of mortality. Kidney injury is brought on by a number of physiological failures that are categorized as pre-, intra-, and post-renal causes. Pre-renal factors include things like diabetes, liver disorders, rhabdomyolysis, and intestinal microbiota, whereas post-renal causes include things like lithiasis, or blood clots in the ureters, prostate cancer, urethral blockages, prostate elongation, and urinary tract infections. Plants are employed in traditional medicine for a variety of purposes, including as antioxidants, anti-inflammatories, diuretics, and anticancer agents. Scientific evidence is needed to substantiate some plants' nephroprotective properties because the mechanism of action of some of the plants that have been empirically employed is still unknown.

KEYWORDS: kidney, traditional medicine, antioxidants, anti-inflammatories, diuretics, and nephroprotective

INTRODUCTION TO KIDNEY

The kidneys are bean-shaped organs, each about the size of a fist. They are located near the middle of the back, just below the rib cage, one on each side of the spine. The kidneys are sophisticated reprocessing machines. Every day, a person's kidneys process about 200 quarts of blood to sift out about 2 quarts of waste products and extra water. The wastes and extra water become urine, which flows to the bladder through tubes called ureters. The bladder stores urine until releasing it through urination. Wastes in the blood come from the normal breakdown of active tissues, such as muscles, and from food. The body uses food for energy and self-repairs. After the body has taken what it needs from food, wastes are sent to the blood. If the kidneys did not remove them, these wastes would build up in the blood and damage the body. The actual removal of wastes occurs in tiny units inside the kidneys called nephrons. Each kidney has about a million nephrons. In the nephron, a glomerulus-which is a tiny blood vessel, or capillary-intertwines with a tiny urine-collecting tube called a tubule. The glomerulus acts as a filtering

unit, or sieve, and keeps normal proteins and cells in the bloodstream, allowing extra fluid and wastes to pass through. A complicated chemical exchange takes place, as waste materials and water leave the blood and enter the urinary system. The kidneys do the major work of the urinary system. The main funtions of the kidneys include such as regulation of blood ionic composition, blood pH, blood volume, blood pressure, blood glucose level, maintenance of blood osmolarity, production of hormone and excretion of waste and foreign substance [1].

Functions of Kidney[2]:

Functions of the kidneys include the following:

Regulation of blood ionic composition: The kidneys help regulate the blood levels of several ions, most importantly sodium ions, potassium ions, calcium ions, chloride ions, and phosphate ions.

Regulation of blood pH: The kidneys excrete a variable amount of hydrogen ions into the urine and conserve bicarbonate ions, which are an important buffer of hydrogen ion in blood. Both of these activities help regulate the pH.

Regulation of blood volume: The kidneys adjust blood volume by conserving or eliminating water in the urine. An increase in blood volume increases blood pressure; a decrease in blood pressure.

Regulation of blood pressure: The kidneys are also help regulate blood pressure by secreting the enzyme renin, which activates the renin angiotensin aldosteron pathway. Increased renin causes an increase in blood pressure.

Maintainance of blood osmolarity: By seperately regulating loss of water and loss of solutes in the urine, the kidneys maintain a relatively constant blood osmolarity close to 300 milliosmoles per litre.

Production of hormones: The kidneys produce two hormones. Calcitriol, the active form of vitamin D, helps regulate calcuim homeostasis and erythropoetin stimulates the production of red blood cells.

Regulation of blood glucose level: Like the liver, the kidneys can use the amino acid glutamine in gluconeogenesis, the synthesis of new glucose molecules. They can then release glucose into the blood to help maintained a normal blood glucose level.

Excretion of wastes and foreign substances: By forming urine, the kidneys help excrete wastes substance that have no useful function in the body. Some wastes excreted in urine result from metabolic reactions in the body. These include ammonia and urea from the deamination of amino acids; bilirubin from the catabolism of hemoglobin; cretinine from the breakdown of creatine

phosphate in muscle fibers; and uric acid from the catabolism of nucleic acids. Other wastes excreted in urine are foreign substances from diet,such as drugs and environmental toxins.

RENAL FAILURE[3]:

The term renal failure primarily denotes failure of the excretory function of kidney, leading to the retention of nitrogenous waste products of metabolism in blood. In addition, there is failure of regulation of fluid & electrolyte balance along with endocrine dysfunction. The renal failure is fundamentally categorized into acute renal failure & chronic renal failure.

Acute Renal Failure

Acute renal failure is characterized by azotemia that progresses rapidly over several hours or days. It may or may not accompanied by oliguria & there is a sudden & reversible loss of renal function

Early recognition of ARF is critical, because it is often asymptomatic. It is detected by measuring serum creatinine level & is more specific than measurement of blood urea nitrogen (BUN). There are many causes of ARF which could be,

Pre renal ARF

It is due to under perfusion of kidney. It accounted for 21% of ARF cases. It can be thought of as "a good kidney looking at a bad world." It is quickly reversible with appropriate therapy.

Post renal ARF

It is caused by obstruction of urinary tract. It accounted for 10% of cases.

Intrinsic ARF

It is due to disease in parenchyma. It accounted for 69% of cases. Among the renal causes of acute renal failure, acute tubular necrosis is more common accounting for 85% of incidence. ATN occurs due to either ischaemia or toxins. The toxins can be either exogenous or endogenous. The exogenous agents are radiocontrast agents, cyclosporins, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen, & illegal abortifacients.

Chronic Renal Failure:

It is a syndrome characterized by progressive & irreversible deterioration of renal due to slow destruction of renal parenchyma, eventually terminating in death when sufficient no. of nephrons have been damaged. Various causes are glomerulonephritis, diabetes mellitus, chronic pyelonephritis, hypertension; antineoplastic agents like cyclophosphamide, viniristne, cisplatin etc.

Nephrotoxic Agents:

Drugs, diagnostic agents & chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents.

A) **Heavy metal**

Mercury, arsenic, lead, bismuth

B) **Antineoplastic agents**

Alkylating agents

Cisplatin, cyclophosphamide

Nitrosoureas: Streptozotocin, Carmustine, Lomustine & Semustine

Antimetabolites

High dose Methotrexate, Cytosine Arabinose, high dose 6-thioguanine, 5-flurouracil

Antitumour antibiotics

Mitomycin, Mithramycin, Doxorubicin

Biologic agents

Recombinant leukocyte and interferon

C) **Antimicrobial agents**

Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin

AmphotericinB

D) **Aminoglycosides**

Gentamicin, Amikacin, Kanamycin, Streptomycin

E) **Miscellaneous**

Radiocontrast agents, Non-steroidal anti-inflammatory agents: Ibuprofen, Indomethacin, Aspirin etc.

Mechanism of Various Drugs and Chemicals to Cause Nephtotoxicity:

Gentamicin induced nephrotoxicity:

Aminoglycosides are natural or semi-synthetic antibiotics with a heterocyclic structure formed by two or more aminosugars linked by glycoside bonds to an aminocyclitol ring[4]. Perhaps the most widely used drug in this category is gentamicin. Gentamicin is an aminoglycoside antibiotic, it is obtained from *Micromonospora purpurea*[5] and widely used for the treatment of bacterial infections. Apart from their beneficial effects, aminoglycosides induce nephrotoxicity in 10-20% of therapeutic cases. Therapeutic doses of gentamicin and other aminoglycoside antibiotics can produce nephrotoxicity in humans and animals and use of this class of antibiotics is known as one of the most common causes of acute renal failure, possibly due to increased renal uptake of the antibiotic, mainly by the proximal tubules.

Nephrotoxicity has been related to a selective accumulation of gentamicin in the renal cortex[6]. Gentamicin-induced nephrotoxicity is characterized by a decrease in the glomerular filtration rate and direct tubular injury. Aminoglycosides are nephrotoxic because a small but sizable proportion of the administered dose ('5%) is retained in the epithelial cells lining the S1 and S2 segments of the proximal tubule after glomerular filtration[7]. The accumulation of gentamycin in proximal tubular epithelial cells leads to membrane structural disturbance and cell death by reactive oxygen species involvement[8]. These antibiotics can stimulate the formation of reactive oxygen species involvement, which may be directly involve in membrane lipid peroxidation. Reactive oxygen species (ROS) produce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage.

Cisplatin induced Nephrotoxicity:

Cisplatin are the platinun containing compound. It gets converted to the active form in the cell, inhibit DNA synthesis and cause cytotoxicity almost like alkylating agents. But it's nephrotoxicity is serious, characterized by high blood urea nitrogen and increased serum creatinine levels[9]. Cisplatin induced nephrotoxity lipid peroxidation and oxygen free radical generation in kidney, and these effects damaged the kidney.

In cisplatin induced nephrotoxicity, S3 segment in proximal tubuli is a major location site of the renal damage. Role for p53 protein in tubularcell apoptosis are very important for cisplatin induced nephrotoxicity[10]. Reactive oxygen species, depletion of antioxidant enzymes and enhanced oxidative are involved in cisplatin-induced nephrotoxicity[11]. Cisplatin inhibits mitochondrial function and glutathione depletion which are strongly associated with the renal toxicity of this compound.

Paracetamol induced Nephrotoxicity:

Paracetamol, is most widely used in the world as an analgesic and antipyretic drug that is safe at therapeutic dosages[12]. It is known to cause hepatic necrosis and renal failure in both humans and animals when administered in overdoses. Renal damage and acute renal failure can occur even in the absence of liver injury. Renal insufficiency occurs in approximately 1–2% of the patients with an overdose of paracetamol. Paracetamol-induced renal insufficiency is consistent with acute tubular necrosis, an increase in the plasma creatinine level and a decrease in the glomerular filtration rate. Oxidative stress is reported to play a role in the pathogenesis of paracetomol-induced renal damage, as evidenced by an increase in the lipid peroxidation and the depletion of intracellular glutathione.

There are three pathways for acetaminophen metabolism; conjugation with sulfate, glucoronide and metabolism by cytochrome p450 oxidase enzyme system[13]. Metabolism by

cytochrome p450 enzyme system produces a metabolite, N-acetyl-p-benzoquinone imine which is toxic to liver and kidney. In therapeutic dose, this is rendered ineffective by reduced glutathione, an antioxidant compound in the liver and N-acetyl-p-benzoquinone imine reduced glutathione is excreted by kidney. In acetaminophen overdose, sulfation and glucoronidation pathways become saturated. The amount and rate of formation of N-acetyl-p-benzoquinone imine is greatly increased, depleting body's reduced glutathione stores and outstripping its capability to make new glutathione. N-acetyl-p-benzoquinone imine then binds covalently with cells causing their death, resulting kidney dysfunction.

Potassium dichromate Induced Nephrotoxicity:

Potassium dichromate ($K_2Cr_2O_7$) is a chemical compound widely used in metallurgy, chrome plating, chemical industry, textile manufacture, wood preservation, photography and photoengraving, refractory and stainless steel industries and cooling systems. $K_2Cr_2O_7$ is a hexavalent form of Cr and has been demonstrated to induce oxidative stress and carcinogenic in nature.

The kidney is the principal route of Cr excretion and it has been reported that acute exposure induces an increase in Cr kidney content on potassium dichromate-treated rat. Exposition to Cr(VI) produced anatomical lesions at the level of the proximal tubular cells and lipid peroxidation in human kidney. Reactive oxygen species are involved in Cr(VI)-induced cell injury[14]. Potassium dichromate are easily taken up by the cells and are subsequently reduced to Cr(III) species. This reduction generates free radicals, which play a major role in the adverse biological effects. Administration of potassium dichromate resulted in acute renal function alteration. Reactive oxygen species produce a wide variety of toxic effects including DNA damage and lipid peroxidation. Potassim dichromate-administration reflect its interaction with cell membrane, leading to altered cell membrane permeability functional integrity in the kidney[15].

Carbon Tetrachloride induced Nephrotoxicity:

Carbon tetrachloride (CCl_4), a lipid soluble, heavy, and non-flammable liquid is most widely used for experimental induction of hepato and nephrotoxicity. CCl_4 is an organic compound widely used as a dry cleaning solvent until it was recognized as a potent carcinogen. Administration of carbon tetrachloride causes an increase in lipid peroxidation products and a decrease in the activity of enzymes protecting lipid peroxidation in the kidney[16]. The trichloromethyl and trichloromethyl peroxy radicals are reported to enhance lipid peroxidation and protein oxidation, resulting in wide spread membrane damage and decrease in the activity of enzymes protecting lipid peroxidation in the kidney .Carbon tetrachloride administration resulted

in oxidative damage of proteins and their accumulation due to poor degradation by proteasomal and lysosomal pathways, causing metabolic dysfunction of kidneys lipid peroxidation and is believed to be one of the major causes of cell membrane damage.

Diabetic nephropathy:

Diabetic nephropathy is one of the most serious complications of diabetes mellitus and is the leading cause of end-stage renal disease. Renal complications are more severe, develope early and more frequently in type 1 (i.e. insulin dependent) diabetes mellitus(30-40%) cases than in type 2(non-insulin dependent) diabetes mellitus(about 20% cases). Glomerular hypertrophy and hyper filtration are early renal abnormalities in diabetes. The onset of clinical diabetic kidney disease is characterized by an abnormal increase in the urinary albumin excretion rate. Progression to overt nephropathy characteristically occurs over a period of years with the development of heavier proteinuria and subsequent fall in glomerular filtration rate. Excessive extracellular matrix deposition in the mesangium, thickening of the glomerular basement membrane and podocyte abnormalities, eventually resulting in podocyte loss, are characteristic histological features of the complications. A variety of clinical syndromes are associated with diabetic nephropathy that includes asymptomatic proteinuria, nephritis syndrome, progressive renal failure and hypertension. Streptozotocin, which produce diabetic nephropathy. The mechanism by which streptozotocin induced diabetic nephropathy are-

Oxidative stress has emerged as an important pathogenic factor in the development of diabetic nephropathy [17]. Reactive oxygen species (ROS) play an important role in oxidative stress. Increased ROS can cause cell abnormalities, reacting directly with nitric oxide (NO) to produce cytotoxic peroxynitrite and thus increase the reactivity of vasoconstrictors and modify extracellular matrix proteins. ROS also damage cells indirectly by stimulating the expression of various transcriptional factors such as NF-κB that are involved in inflammatory pathways. There is evidence that DM increases multiple pathways that lead to the increased generation of ROS; these pathways include protein kinase C-dependent activation of NADPH oxidase, enhanced glucose oxidation, hypertension, and advanced glycation end-products (AGEs). In renal cortex region advanced glycation end products are accumulates[18]. These advanced glycation end products play a role in the progression of diabetic nephropathy through impairment of matrix proteins. In streptozotocin induced diabetic nephropathy, increased Reactive oxygen species production are also responsible for cell membrane damage, enzymes inactivation, apoptosis, and endogenous antioxidant altered gene expression[19] and glomerular matrix proteins production are increased, the accumulation of which decreases the surface area for filtration leading to decreased glomerular filtration rate.

Table 1: Clinical Significance of serum biomarkers

Measurement	Clinical Significance	Normal Values
Blood Urea	It is widely used as screening test for the evaluation of kidney function[20]. It is estimated in the laboratory either by urease method or diacetyl monoxime(DAM) procedure. Elevation in blood urea may be broadly classified into three categories. a. Pre-renal: This is associated with increased protein breakdown, leading to a negetive nitrogen balance, as observed after major surgery, prolonged fevers, diabetic coma, thyrotoxicosis etc. In leukemia and bleeding disorders also, blood urea is elevated. b. Renal: In renal disorders like acute glomerulonephritis, chronic nephritis, nephrosclerosis, polycystic kidney, blood Urea is increased. c. Post-renal: Whenever there is an obstruction in the urinary tract(e.g. tumors, stones, enlargement of prostate gland etc.), blood urea is elevated. This is due to increased reabsorption of urea from the renal tubules.	10-40mg/dl
Total Protein:	Low total protein suggest a liver disorder , a kidney disorder, or a disorder in which protein is not digested or absorbed properly[21]. Low levels may be seen in severe malnutrition and with conditions that cause malabsorption, such as Celiac disease or inflammatory bowel disease. High total protein levels may be seen with chronic inflammation or infections such as viral hepatitis or HIV. They may be caused by bone marrow disorders such as multiple myeloma.	6.0 to 8.3 gm/dL

Serum Creatinine	Serum creatine concentration is increased in muscular atrophy and muscular dystrophy[22]. Excessive proteinuria results from impaired tubular creatine reabsobtion. Determination of creatinuria has a dianostic value only incase of atrophy and in muscle regeneration in myopathies. Creatine phophate undergoes spontaneous breakdown in muscle cells to form creatinine. The loss of water molecule from creatine results in the formation of creatinine. Creatinine is transferred to the kidneys by blood plasma, wherefrom it is eliminated from the body by glomerular filtration and partial tubular excretion. Serum concentration of creatinine primarily depends on glomerular filtration. As creatinine is endogenously formed and is not reabsorbed in the tubules, serum creatinine is a reliable indicator of glumerular function.	0.6-1mg/dl
Uric acid	Hyperuricemia may be conveniently divided into two major categories [23]. Symptomatic hyperuricemia is manifested by gout, nephrolithiasis, and uric acid nephropathy. A larger group of patients have asymptomatic hyperuricemia. Some of these patients will eventually become symptomatic. The risk of acute gouty arthritis increases with the level of serum uric acid and the duration of hyperuricemia. Acute fluctuations in serum uric acid may be associated with the precipitation of acute gouty arthritis. Sudden reductions in serum uric acid may accompany the introduction of antihyperuricemic therapy; hence, these patients often simultaneously begin prophylactic doses of colchicine. Nephrolithiasis may accompany gouty arthropathy or occur as an independent problem. Uric acid forms radiolucent stones or may contribute to the formation of calcium stones. In patients with gout, the risk of stone formation rises with the level of serum uric acid. Acute uric acid nephropathy results from the precipitation of uric acid crystals within the collecting tubules and ureters. It	6-7 mg/dl.

	is a severe form of acute renal failure and is classically associated with the chemotherapy of leukemias and lymphomas. It may also occur following strenuous exercise and epileptic seizures. Hyperuricosuria, aciduria, and urine concentration seem to act in concert to produce this syndrome. The diagnosis can be made by the demonstration of a uric acid to creatinine ratio greater than 1 in the setting of acute renal failure. Routine screening of hospitalized patients will identify a substantial number with elevated serum uric acid and no related symptoms. Most of these patients will remain asymptomatic throughout their lives. A complete discussion of the management of asymptomatic hyperuricemia is beyond the scope of this chapter. Suffice it to say that the weight of current evidence speaks against the normalization of uric acid in asymptomatic patients. Regardless of the level of uric acid, little seems to be lost by awaiting the onset of the first bout of arthritis or kidney stone. Hypouricemia Hypouricemia is commonly defined as a serum urate concentration of 2 mg/dl or less. A low serum urate concentration may result from decreased production or increased excretion. Quantification of urinary uric acid can facilitate a distinction between these two mechanisms. Patients with hypouricemia secondary to impaired production will have little or no urinary uric acid. Hypouricemia can be found in about 1% of hospitalized patients. In most cases the cause is related to drugs, including salicylates, allopurinol, x-ray contrast agents, and glyceryl guaiacholate. Forced diuresis, used mainly in the treatment of suicide-attempt patients and renal colic, may result in hypouricemia. Total parenteral nutrition can cause profound hypouricemia in some patients.	

Blood Urea Nitrogen	Blood urea nitrogen is a measure of the amount of nitrogen in the blood in the form of urea, and a measurement of renal function[24]. The BUN are screening tests of renal function. Because they are handled primarily by glomerular filtration with little or no renal regulation or adaptation in the course of declining renal function, they essentially reflect GFR. The BUN survives and is finding wide application in the nutritional management of critically ill patients. The urea nitrogen appearance (UNA) objectively lets the intensivist know whether the patient's nitrogen needs are being met. The UNA assessment requires the measurement of BUN at the beginning and end of the period of observation as well as the total urea excretion.	7 to 21 mg of urea nitrogen per 100 ml (7–21 mg/dL) of blood

HERBAL DRUGS IN RENAL PROBLEM:

Several disorders recognized as pre-, intra-, and post-renal variables, among others, have been treated historically using plants. Secondary metabolites, which have significant physiological advantages to prevent various diseases or provide protection against infections, have been linked to the therapeutic properties of plants. Numerous bioactive chemicals that are antioxidants, anti-inflammatory, diuretic, anti-cancer, and antibacterial are found in plants. Additionally, plant-derived nephroprotective compounds counteract conditions such glomerulonephritis, tubular necrosis, altered intraglomerular hemodynamics, and interstitial nephritis. An important understanding of how extracts or individual compounds interfere with molecular pathways to ameliorate kidney disorders has previously been provided by other research that addressed the use of plants and phytochemicals as nephroprotective agents.

Table 2: Plants investigated for nephroprotective activity:

Name of the Plant	Models	Probable Mechanism of Action
Aerva Lanata [25]	Gentamicin Induced nephrotoxicity in rats	Antioxidant, free radical scavenging property
Nigella Sativa[26]	Gentamicin Induced nephrotoxicity in rats	Antioxidant
Withania Somnifera[27]	Gentamicin Induced nephrotoxicity in rats	Antioxidant

Anthoxanthum Odoratum[28]	Paracetamol induced nephrotoxicity in rats	Antioxidant
Caesalpinia Bonduc[29]	Gentamicin Induced nephrotoxicity in rats	Free radical scavenging property.
Curcuma Longa[30]	Paracetamol induced nephrotoxicity in rats	Antioxidant
Carica Papaya[31]	CCl_4 induced nephrotoxicity in rats	free radical scavenging property
Ambrosia Maritima[32]	Potassium dichromate induced nephrotoxicity in rats	Anti lipid peroxidant activity
Boerhaavia Diffusa[33]	Paracetamol induced nephrotoxicity in rats	Antioxidant
Rosmarinus Officinalis[34]	CCl_4 induced nephrotoxicity in rats	Antioxidant
Salvia Miltiorrhiza[35]	STZ induced diabetic nephropathy in rats	Improve blood microcirculation
Kalanchoe Pinnata[36]	Gentamicin Induced nephrotoxicity in rats	Antioxidant
Digera Muricata[37]	CCl_4 induced nephrotoxicity in rats	Antioxidant, free radical scavenging property
Citrullus Colocynthis[38]	STZ induced diabetic nephropathy in rats	Increase in reduced glutathione, superoxide dismutase and GPx
Pongamia Pinnata[39]	Cisplatin Induced nephrotoxicity in rats	Antioxidant.
Salviae Radix[40]	Cisplatin Induced nephrotoxicity in rats	Anti lipid peroxidant
Cassia Auriculata[41]	Cisplatin Induced nephrotoxicity in rats	Antioxidant, free radical scavenging property
Razya Stricta[42]	Gentamicin Induced nephrotoxicity in rats	Anti lipid peroxidant activity
Ginkgo Biloba[43]	Gentamicin Induced nephrotoxicity in rats	Antioxidant

Drynaria Fortunei[44]	Gentamicin Induced nephrotoxicity in rats	Antioxidant
Tribulus Terrestris[45]	Gentamicin Induced nephrotoxicity in rats	Antioxidant

CONCLUSION:

A progressive loss of kidney function is a feature of chronic kidney disease, commonly known as chronic kidney failure. You may not have many signs or symptoms when chronic kidney disease is first developing. The goal of chronic renal disease treatment is to slow the development of kidney damage, usually by addressing the underlying cause. However, even stopping the source could not stop kidney disease from getting worse. According to the physiological pathway they use to cause kidney injury, pre-renal, intrinsic, and post-renal diseases and causes can all cause kidney disease. The primary finding from this review is that it expands the list of plants that are nephroprotective by taking into account plants with intrinsic effects or that can reverse nephrotoxicity.

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