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PII: S1044-579X(17)30171-2
DOI: http://dx.doi.org/doi:10.1016/j.semcancer.2017.06.011
Reference: YSCBI 1352

To appear in: *Seminars in Cancer Biology*

Received date: 9-2-2017
Revised date: 4-6-2017
Accepted date: 23-6-2017

Please cite this article as: Braicu Cornelia, Mehterov Nikolay, Vladimirov Boyan, Sarafian Victoria, Nabavi Seyed, Atanasov Atanas G, Berindan-Neagoe Ioana.Nutrigenomics in cancer: revisiting the effects of natural compounds.*Seminars in Cancer Biology* http://dx.doi.org/10.1016/j.semcancer.2017.06.011

Nutrigenomics in cancer: revisiting the effects of natural compounds

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Abstract

Nutrigenomics effects have an important role in the manipulation of dietary components for human benefit, particularly in cancer prevention or treatment. The impact of dietary components, including phytochemicals, is largely studied by nutrigenomics, looking at the gene expression and molecular mechanisms interacting with bioactive compounds and nutrients, based on new 'omics' technologies. The high number of preclinical studies proves the relevant role of nutrigenomics in cancer management. By deciphering the network of nutrient-gene connections associated with cancer, relevant data will be transposed as therapeutic interventions for this devastating pathology and for fulfilling the concept of personalized nutrition. All these are presented under the nutrigenomics canopy for a better comprehension of the relation between ingested phytochemicals and chemoprevention or chemotherapy. The profits from the nutrigenomics progress, with a particular focus on the coding and noncoding genes related to the exposure of natural compounds need to be validated. A precise attention receives the evaluation of the role of natural compounds in tandem with conventional therapy using genomic approaches, with emphasis on the capacity to inhibit drug resistance mechanisms. All these relevant nutrigenomics aspects are summarized in the present review paper. It is concluded that further nutrigenomics studies are required to improve our understanding related to the complex mechanisms of action of the natural compounds and for their appropriate application as gears in cancer therapy.

Key words: nutrigenomics, natural compounds, cancer

Introduction

Hippocrates, the father of modern medicine, asserted, "*Let the food be thy medicine and the medicine be thy food*". The classical validating examples are those related to the Asian diet (rich in soy, fish and green tea) associated with reduced incidence of breast cancer [1], the Mediterranean diet [2, 3] or red wine consumption related to decreased levels of cardiovascular diseases, a phenomenon known as the "French paradox" [4, 5]. A large number of epidemiological studies stipulate that a healthy diet, rich in fruit and vegetables protects our body against cancer and other chronic diseases such as cardiovascular pathology, diabetes and aging. All these findings are attributed to the huge amount of *plant secondary metabolites* responsible for flavor, taste and color. A giant class of natural compounds is retrieved in literature as *phytochemicals* and has been proven to have a wide assortment of beneficial effects in human health [6-9]. There are several options to achieve a diet rich in beneficial phytochemicals. The simplest approach is to select phytochemicals-enriched nutriments or other beneficial related nourishments, encompassing one or more health-promoting products [3, 7], retrieved under the name "functional food" fortified in essential nutrients that was proved to provide health benefits [10, 11]. Another option is to use products enriched in bioactive agents, commonly known as nutraceutics [9, 12]. These healthy promoting products derived from natural sources can be used in a concentrated formula as enriched extracts or as capsules, termed dietary supplement. The development of functional supplements is sustained by ***nutrigenomics***, allowing the identification of those bioactive natural compounds that sustain a healthy genome and are properly customized for each individual genotype and genome status. The phenomenon of crossing point concerning *Nutrients - Genes - Cancer* is multifaceted and needs to be deciphered, but recent advances in nutrigenetics as individual genetic "make-up" and nutrigenomics as the whole genes picture sustain it.

Cancer is a multifactorial and comprehensive disease, characterized by multiple genetic mutations and alterations of more solfeggios of pathways and mechanisms. It is mainly a heterogeneous manifestation of similar hallmarks with uncontrolled evolution, limited treatment potential and some degree of cure. The natural compounds are able to target several of the altered pathways, interfering during early tumorigenesis, but also during late carcinogenic steps, invasion, the

proangiogenic and the metastatic phase (luteolin treatment). Dietary natural compounds can influence cancer risk and tumour behavior. Around 30-40% of cancers are known to be influenced by diet, being related to cancer histological type, molecular subtype, tumor markers and prediction markers for response to therapy [13].

The vital role of nutrigenomics in cancer management is already ascertained. By clarifying the network of nutrient-gene-cancer connections associated with tumor pathology, relevant data can be integrated in therapeutic strategies and interventions for this deadly "game". A major aim is data integration into translational research. Nutrigenomics' main focus is to improve molecular understanding of the nutrition role in genomic communication and exchanges, including the individual genotype. The concentration stands at genomic, proteomic and metabolomics levels.

Despite many unknown mechanisms and a lack of clear understanding of the relationship between consumption and effects, these diets can be considered a synergism or even an additive effect as consequence of all the phytonutrients ingested, which makes them much more difficult to investigate. The topic remains highly debatable. This is mainly due to the wide diversity of study designs, the selection of the most relevant cell line or animal model, and the measured endpoint. Therefore, there is an urgent need for assessing the complex interconnections between diet and health status by investigating the protective role of natural compounds on human wellbeing. The obtained data should be connected with the complex environmental exposure. Consequently, simply consuming such healthy phytochemicals is not sufficient. Food supplies with native forms of these compounds can achieve the maximal antitumor effect. The problem is related to the high concentration of phytochemicals required for reaching the biological effect, impossible to be retrieved from natural sources. Furthermore, some studies show that the role of some natural compounds is still questionable [14]. Other works point that biological effects of health-promoting foods can be better explained by looking not at single constituents but at the complex, often synergistic, effects displayed by the mixtures of bioactive compounds present in the respective food products [15]. In the survey presented herein we discuss several types of natural compounds and their role in cancer, in the context of their nutrigenomics effects, revealed by genomic approaches.

Analyzing 'omics' for dietary nutrients exposure pattern: a closer look at a complex picture

Nutrigenetics is mainly focused on the evaluation of genetic and epigenetic alterations in response to a particular dietary component, which might lead to a change in the disease status [16, 17]. A broad variety of nutrients or phytochemicals affects the genetic and epigenetic mechanisms (Fig. 1). Noteworthy, some nutrients are important for the normal cellular methylation status. The mutational pattern evaluation implies sequencing based approaches, microarrays for gene expression, Nanostring or qRT-PCR for SNP (single nucleotide polymorphism) evaluation. Investigation of epigenetic alterations includes assessment of histone modification, DNA methylation, nucleosome organization, and methyl-binding proteins expression. Epigenetic variation can be considered by an extensive choice of technologies starting with the next generation sequencing, again microarray, pyrosequencing or a simple qRT-PCR-array panel using specific restriction enzymes [18].

A personalized diet in the future will be established based on a particular SNP-based test for dietary counseling. That important progress can be made based on the information retrieved from the new high-throughout 'omics' technologies. The integration of these data contributes to the advancement in the field of so-called "*personalized nutrition*" in such a way that it maintains healthy status of the body. That is how it might prevent disease apparition or could contribute to therapeutic strategies [16]. One example is that of the olive oil bioactive components (oleic acid, biophenols and vitamin E) able to modulate gene expression pattern with proven utility in chemoprevention [19, 20].

Nutrigenomics as a basic definition is a new science that studies the interaction between diet and genome. *Nutrigenomics* displays the interaction between the unique genetic signature and the exposome exposure (defined as entire environmental agents), including diet and in particular the environmental toxins.

Nutrigenomics is used for the evaluation of an altered genomic profile in response to dietary nutrients and for the development of novel strategies that can be applied in personalized nutrition and medicine.

Nutrigenomics was first named by Pelegrin in 2001 [21]. This investigation line was continued by Van Ommen and Stierum. One year later, a review paper

underlined for the first time the important role of nutrigenomics, in direct relationship with systems biology approaches and connected the nutrition and health status, in a multidisciplinary view [21]. Using systems biology tools, it has become feasible to assess the biological action of a natural compound in multiple metabolic pathways, including interactions with other nutrients, in relation to genotype, all aiming to achieve human health benefits.

Nutrigenomics has some degrees of similarity with pharmacogenomics; one difference is that pharmacogenomics uses synthetic chemicals whereas nutrigenomics applies to natural bioactive agents, where the transcriptomic profile is the key element. Dietary released agents act in a multifaceted mode and are linked to the presence of environmental factors causing genomic alterations. Nutrigenomics brings an important added value for cancer and other chronic diseases prevention.

Transcriptomics approaches are used for the analysis of genomic data generated related to nutrients and include standardized protocols for coding and non-coding (miRNAs, lncRNA, UCG) genes [22-24]. The most frequently exploited technologies for the evaluation of the transcriptomics signature consist of gene expression analysis, splicing genetic variants study, particularly SNPs by microarray and gene expression, single nucleotide variants profiling, post-transcriptional single nucleotide variants and fusion gene deletions by next generation sequencing (RNA-seq) [22, 23, 25]. Some of the microarray machineries allow not only the evaluation of transcriptomics pattern but also highlights different splicing or different genetic variants, particularly SNP. Recently Nanostring technology allows assessment of a custom panel of coding or non-coding transcripts, focused on a particular mechanism. Other alternatives are represented by PCR-array cards, which have a spotted panel of target molecules for a mechanism of action study, or simple variant is by using qRT-PCR [25]. Valid data and appropriate conclusions are obtained by bioinformatics tools [26].

The impressive data generated by transcriptomics approaches need to be validated. Different tools like proteomics and metabolomics analysis can be useful in this regard. ***Proteomics and metabolomics*** approaches have as a main goal to evaluate the protein composition or abundance and metabolic pattern in normal state and physiological status as related to xenobiotic exposure. Proteomics and metabolomics methods imply the utilization of throughput techniques based on mass spectrometry (MS) and nuclear magnetic resonance (NMR) [27]. These methods ensure high

sensitivity, accuracy and rapidity to determine thousands of proteins or metabolic products in a single experiment [26, 28]. *Proteomics* identifies the expression level of proteins of interest, posttranscriptional alteration, or particular protein-protein interaction, at a specific and precise moment in a biological system [28].

Metabolomics profiles metabolites and can be used to track the biochemical alterations in different cancer types. Metabolomics evaluates a variety of small molecules, like sugars and amino acids constituting the substrates or intermediates for a multitude of cellular processes. Proteomics and metabolomics changes are interconnected. They determine the role of different protein interactions responsible for physiological and pathological processes. These two approaches are used for the evaluation of the phytochemical's metabolism (quinones or semiquinones) [29], but also for the assessment of the whole proteomic cell pattern, particularly at the level of the tissue or the entire body [26]. They are very useful for the identification of metabolic alterations, particularly the Warburg effect retrieved in the case of cancer cells, characterized by a high glycolysis rate followed by lactic acid fermentation, requiring a high amount of glucose [30].

The use of *'omics'* allows to implement advanced protocols for the investigation of molecular alterations and to deliver reliable connection between medicine and nutrition. Natural compounds affect coding and non-coding genes and proteins, and their therapeutic role still need to be elucidated. Currently, preclinical tests are available, but these data still need to be analyzed and integrated [31].

Nutrigenomics methods evaluate the transcriptomics pattern alteration caused by these natural agents, leading to the identification of molecular targets related to prevention, delay of the cancer progression, or reducing the side effects caused by chemotherapy. This implies the use of the relevant functional genomic tools and an appropriate bioinformatics analysis to evaluate the effect of a nutritional stimulus [16, 17].

Biologically active phytochemicals in the genomic puzzle and their implications in cancer therapy

The *'omics'* technologies will shift the paradigm in our understanding of nutritional agents, allowing to see the full picture of the puzzle, not only some pieces. All cancers are characterized by molecular and cellular alteration. In the acquisition of

a malignant phenotype, the diet plays a major role. The integration of all the genomic data, solving the nutrition-genomic puzzle, will support implementing the concept of personalized nutrition (Fig. 2).

Phytochemicals are plant non-nutritive chemicals [32], being synthesized as a defense system and being responsible for the color, taste and aroma of fruit and vegetables [33]. Presently, there is a vast amount of phytochemicals described [33], being classified as polyphenols, terpenoids and thiols.

The ***flavonoids*** are represented by *flavones* (kaempferol and quercetin), *flavonoles* (apigenin and luteolin) [34], *isoflavone* (daidzein and genistein), *flavanones* (naringenin and hesperidin), *flavan-3-ols* (catechins and gallocatechins isomers) and *anthocyanins* [35]. Traditional medicine used for hundreds of years an extensive variety of plants, rich in flavonoids [36]. Epidemiological data available demonstrate that the consumption of citrus is beneficial due to the high amount of flavanones, mainly naringenin and hesperetin [37]. The flavones and isoflavone are considered to be phytoestrogens [34], being able to interfere with sex hormone-mediated molecular pathways [37, 38]. The flavonoids were proved to target oestrogen receptors in human breast cancer cells [39], or androgen receptors (AR) in prostate cancer [40]. A synthesis of their influence in the genomic puzzle is summarized in Table 1.

Many phytochemicals are certified to have anti-carcinogenic effect in preclinical and clinical studies. Flavonoids are candidates as genomic modulators in signaling pathways for breast [109, 110], colon [46, 54], liver [111, 112], prostate [113, 114], ovarian [115], and lung cancer [105] inhibition of invasion and metastasis. Moreover, an important progress has been done in deciphering the complex mechanism of action of these natural compounds at cellular and molecular level. Known mechanisms of action are summarized in Fig. 3.

Several meta-analysis represent interesting results encompassing nutrigenomics and cancer risk. A meta-analysis study reveals the protective effect of dietary flavonoids against ovarian cancer and a reduced risk of ovarian cancer except for flavones consumption [115]. A similar meta-analysis exposes that flavonoles and flavones are correlated with a reduced breast cancer risk, particularly among post-menopausal women [116]. Esophageal cancer risk was reduced by the ingestion of dietary intake of total flavonoids, anthocyanidins, flavanones, and flavones as recently

a meta-analysis indicated [117]. Therefore, these bioactive compounds represent a valuable source for the development of novel antitumor therapeutic strategies [6].

Chemoprevention and its stars: the natural compounds

A large category of foods including fruit and vegetables, cereals, nuts and cocoa or even different types of black and green tea, green coffee and red wine are studied in relation with cancer *chemoprevention* and chemotherapy. An impressive amount of plant-based food classes and dozen classes of phytochemicals are studied in cancer [118]. The major classes of bioactive phytochemicals used in cancer chemoprevention and therapy cover carotenoids, phenolic compounds, or phytosterols derivatives [119].

Chemoprevention was described in different epidemiological-based studies, underlining the relationship between a reduced cancer risk and an increased consumption of different classes of biologically active agents as functional food or enriched plant extracts formulated as nutraceutical [120]. An apparent disadvantage is related to the high doses required to achieve the biological activity and stability. Generally, some flavonoids exert a selective toxicity on tumor cells, and reduced or no effect on normal cells [83]. The side effects are very rarely retrieved, in preclinical and clinical studies, generally at very high doses and associated with carotenoids. An example is the case of carotenoids that were proven to have an important antioxidant effect in *in vitro* cell culture-based study. But once applied in *in vivo* models or clinical studies, their pro-oxidant activity became dependent on the redox potential of the carotenoid molecules as well as on the biological environment in which they acted [121]. Even the above mentioned pro-oxidant activity [102], in different biological systems might be responsible for therapeutic effects or unwanted side effects, like the formation of quinones or semiquinones generated by polyphenols oxidation [83, 122]. Also, it is still difficult to demonstrate what is most relevant for the shown biological activity, the bioactive agent or the oxidized product [83]. The biological effects, particularly the antitumor effects of phytochemicals are produced by integral processes related to absorption, transport, biotransformation, cellular and molecular action pathways, as well as to excretion mechanisms [16]. The effects are cell type specific and difficult to separate in high and low dose-dependent. This is the case of

estrogenic activity that is increased in bone cells and inhibited in breast cancer cells [123].

The main issue related to these natural compounds, is the pro-oxidant action at higher doses. Also the bioactive agents, act different in the presence of different environmental toxic or beneficial agents [124].

Plant-derived phytochemicals implication in genetic alteration

The most frequent genetic variations in humans are SNPs, used to map the human genome [125]. A recent progress is related to next generation sequencing approaches that allowed the identification of important genetic heterogeneity of the human population [126]. Until present, thousands of genetic regions were evaluated (over 16,000 SNPs). These multiple genetic variants influence the phytochemicals' biological activity [127]. Many plant phytochemicals interfere with the human genome, thus generating a broad assortment of genetic variants-determined responses.

A SNP or a haplotype is not always related to a specific disorder, but in most of the cases is negatively affected by the presence of the environmental toxic agents or positively affected by chemopreventive agents [18]. An increased interest was registered in the assessment of proofs related to SNP and diet interactions. SNP evaluation is able to serve as an important instrument for the impact of dietary habits in human health and disease prevention [16, 18, 30]. Significant interactions between phytochemicals and the antioxidant defense system, as well as with cellular metabolism (phase I/II detoxification system), are already known. SNPs play a significant role not only in cancer but also in inflammation, neurodegenerative diseases and metabolic disorders [128]. SNPs can lead to the alteration of key cellular pathways or can have an effect on the capacity to interact with natural phytochemicals [55, 125, 129].

The mechanism of SNPs impact is mainly caused through metabolic inefficiency, as in the case of the methylenetetrahydrofolate reductase gene (MTHFR). This gene is involved in the metabolism of folate and homocysteine blood homeostasis. Increased level of homocysteine is connected with cardiovascular diseases and colon cancer risks as a result of their nutritional requirement. The needs of folic acids supplementation are much higher due to the fact that choline is required as a methyl donor for MTHFR gene [126]. A key polymorphism is (677C→T)

causing the production of a variant of the methylenetetrahydrofolate reductase (*MTHFR*) gene, responsible for the synthesis of 5-methyl THF. It is connected with increased homocysteine concentrations, reduced global DNA methylation, or linked with much pathology like the neural tube defects and venous thrombosis [130].

Natural phytochemicals can act as chemopreventive agents and this consequence is related to their specific interaction with genes (that have different SNPs), either in the presence of a particular carcinogenic or anticarcinogenic agent, that can increase/decrease or have no beneficial effect. The cytochrome P450 (CYP), a phase I detoxification enzyme, is a major player in drug metabolism, including those associated to natural compounds. Increased number of particular SNPs were related with its catalytic activity [129]. The most important polymorphic CYPs were found to be 1A2, 2D6, 2C9 and 2C19. Thirty-four frequent allele variants retrieved for the Caucasian population have displayed an altered catalytic activity of this enzyme [129]. Another example is that related to the glutathione S-transferase P1 (GSTP1) gene, a phase II detoxification enzymes, that has been shown to have 10 promoter polymorphisms, grouped in 3 main haplotypes [131, 132].

Natural plant products, such as soy isoflavone, curcumin, resveratrol and tea polyphenols can modulate the repair potential or redox activities of APE1/Ref-1 or their capacity to interact with other mechanistic components. The presence of certain SNPs: Thr232 phosphorylated in Alzheimer disease; genetic variants of APE1/Ref-1, XRCC1 and XRCC3 in Parkinson disease; Leu104Arg, Glu126Asp, Asp148Glu, Asp283Gly and Gly306Ala in its Amyotrophic lateral sclerosis, can be a reason for unbalanced response to external and internal stimulus, leading to increased oxidative stress, or modified as a consequence of its interactions with phytochemicals [55].

EGCG physically interacts with the ligand-binding domain of AR (androgen receptors), leading to the modulation of transcriptional activation. Treatment with EGCG inhibits transcriptional activation by a mutant AR hotspot (T877A), having ectopically similar expression to the endogenous mutant AR. Moreover, EGCG represses methyltrienolone R1881-induced cell growth is observed in prostate cell lines and animal models [133]. AR play an important role in early and advanced prostate cancer. AR sustain cell growth, thus representing the major drug target [133].

EGCG can directly bind to TNF receptor associated factor (TRAF) [134], which is important in the regulation of tumorigenesis and invasion via the NFκB pathways [135]. It was also confirmed using molecular docking approaches that

EGCG probably interacts with TRAF6 at the Gln54, Gly55, Asp57 ILe72, Cys73 and Lys96 residues. Thus, the mutations at these loci could influence the EGCG proapoptotic effects via death receptors [134]. Catalase SNPs (G-844A, A-89T, and C-20T) were proved to be connected with a lower efficiency of diet for preventing the malnourishment of the elderly subjects. Catalase genotyping is a marker of the nutritional status [136].

Plant-derived phytochemicals as gene expression modulators beyond hallmarks of cancer

The transcriptomics profiling studies allow the biological significance evaluation of all these agents in different biological systems relevant for cancer development [137]. Several cancer–inducing mechanisms have been clarified using the genomic approaches. Nevertheless, the capacity to modulate signal transduction cascades and to activate transcription factors that antagonize with carcinogenesis mechanisms have attracted considerable interest. Transcription factors are binding to the response elements contributing to the triggering or inhibition of gene expression. Their direct or indirect mode of action allows targeting of a number of cancer-related signaling pathways. Integrating all this information together will lead to a better comprehension of the complex picture of the antitumor effect of phytochemicals in the post-genomic era. Data are summarized in Table 2.

Many nutrigenomics studies show the beneficial effect of natural compounds in combination with standard therapy, especially in the aspect of an increased chemotherapeutic efficacy. In rare cases present as activating the compensatory mechanism as in triple negative breast cancer [138], or stimulating drug resistance mechanism, like the chemoresistance induced by genistein treatment in HCC [139].

The natural phytochemicals are able to target a multitude of key genes in cancer hallmarks leading to carcinogenesis. The different proposed mechanisms for chemoprevention and anticancer activities of the natural phytochemical agents are summarized in Fig. 4. These include not only the antioxidant activity but also the inhibition of mitogen-activated protein kinase (MAPK), nuclear factor-κB (NFκB), activation of apoptosis (BCL-2 or p53) or autophagy, angiogenesis (Wnt/β-catenin), invasion and migration [140]. The complex effect of natural compounds is summarised in Fig. 5.

Antioxidant effect. The nutrigenomics added a multipart view on the antioxidant mechanism deciphering partially the complex role of natural phytochemicals in early events of chemoprevention or in chemotherapy processes. During the evolutionary process, the human body developed a comprehensive and sophisticated antioxidant system, composed of antioxidant enzymes (superoxide dismutase, catalase) and non-enzymatic molecules (glutathione) in order to cope with imbalanced production of reactive oxygen species (ROS). The later are produced in a high rate in response to some internal or external stimuli, a condition known as oxidative stress. Frequently the body antioxidant system is unbalanced and leads to oxidative damage of a wide range of biomolecules, including lipids, DNA/RNA or proteins. Recently a new group of polymeric oxidized flavanols, like the quinone produced by the oxidation of EGCG, captured the attention as a powerful antioxidants with an effective biological activity in cancer therapy [141]. The oxidized catechins containing a galloyl moiety to quinone are related to activation of electrophile-responsive element (EpRE), being connected to activation of glutathione (GSH) [29]. Therefore the induction of the pro-oxidant mechanism [142] is not always related to harmful effects. EGCG at doses higher than 50 µM have prooxidant effects, leading to the activation of autophagy and significant antitumoral effects [142]. EGCG doses lower than 100 µM act as inhibitor of transcription factors that sustain cell proliferation. Our experience showed that doses over 50 µM all catechins isomers acts as pro-oxidants [83, 122], such as quercetin (50 µM), which generates mitochondrial superoxide radical in cell culture [124].

The activation of reactive oxygen species (ROS) production is among the first events in cancer. The natural phytochemicals act as antioxidants and have the capacity to serve as scavengers of ROS and counterbalance reactivity caused by ROS during metabolic processes [143]. It was demonstrated that the ROS possess a dual role, being also an important cell signaling mediators through the activation of cytokines and hormones secretion or by regulating redox-responsive transcription factors [144]. Occasionally, the plant phytochemicals can exert a pro-oxidant effect, dependent on dose, time of exposure or on the association with metal ions (iron or copper) [145]. For example, resveratrol has the capacity to mobilize copper in lymphocytes, thus leading to the activation of the mechanism of DNA oxidative damage in leukemias and meanwhile triggering pro-oxidant mechanism [141]. Another example includes quercetin, which is able to activate ROS-dependent apoptotic mechanism via

Sestrin2/AMPK/mTOR in colorectal cancer cells [46, 141]. The classical example is represented by EGCG, a compound with a dual pro and antioxidant effect that even can induce DNA damage [146].

Genomic stability and non-genotoxic effects of dietary phytochemicals. Several phytochemicals proved to serve as health promoters. Their relationship to environmental toxicology, particularly for the maintenance of genomic stability correlates with increased ingestion of natural phytochemicals via ROS detoxifying mechanisms. A higher level of ROS is connected with some promutagenic lesions in DNA that can represent an early carcinogenic event. Algae extract rich in fatty acids, lutein, β-carotene and α-carotene was proved to protect against environmental genotoxic factors that cause ROS production [147]. The micronuclei and comet assay revealed that pelargonidin and chlorogenic acid have protective effect against genotoxic agents [148]. Similar data were obtained in the case of grape seed extract, enriched in resveratrol, ellagic acid (polyphenol produced in the large intestines of the human body and found in many foods, with cancer healing properties) and lycopene. All studies emphasize their importance in the activation of the DNA-repair pathways [149].

Detoxification mechanism. Usually, interrelated pathways can be found in the detoxification mechanism. The genomic "tools" represent a valuable instrument to study it in the context of human health. The phytochemicals can activate the cellular protection mechanism by targeting different stress-related proteins and transcription factors. The chemoprevention mechanisms are acting mainly via phase-I drug-metabolizing enzymes CYPs inhibition, followed by forced expression of phase II conjugating-enzymes [150]. The phenomenon is seen not only as altered expression level or a response to toxic injury but it also produces different SNPs that affect the reaction against the same compound. These classes of genes have an essential role in personalized nutrition [129].

An important player in the detoxification mechanism is nuclear factor erythroid-2-related factor 2 (Nrf2) that binds to Keap1 proteins, leading to the activation of cellular defense mechanism via the detoxifying/antioxidant enzymes. These genes are regulated through a consensus cis-element at the 5′-flanking promoter region, depicted in the literature under the name of antioxidant responsive element (ARE) or electrophile response element (EpRE), localized in the promoter region of regulated genes. This element produces a relevant answer in cellular defense against

oxidants and electrophiles agents [151]. Extensive research has been conducted both *in vitro* and *in vivo* and demonstrated the pivotal role of Nrf2 in the regulation of ARE-mediated gene expression. A plant extract enriched in EGCG was connected with an important activity of the phase II detoxifying enzymes via ARE in hepatic cells. EGCG induces a low activity of Nrf-2-ARE binding in lung cancer cells [150]. EGCG exposure was connected with an increased level of phase II detoxifying enzymes (GST and NQO) in an extensive number of cancer cells such as liver, breast and prostate cancer cells[151].

Inflammatory mediators. The main mechanism of natural phytochemicals to interfere with gene expression is via transcription factors, where a multitude of inflammatory mediators is activated [152]. The modern concept in cancer biology reveals a clear link between inflammation and oncogenesis. The tumor microenvironment contains a comprehensive list of these inflammatory mediators that are essential for tumor development, progression, invasion, and metastasis. Many different cell types, including immune inflammatory cells, serving as the main source of inflammatory cytokines, compose it. The later have pleiotropic effects on cells in the tumor microenvironment such as impaired apoptosis, increased proliferation, angiogenesis and invasion. The genomic studies using phytochemicals reveal their capacity to act on inflammatory mediators and activate transcription factors [144]. The dietary nutrients can interact and cause the suppression of MAPK, NFκB, COX-2, iNOS, STAT signalling or inflammatory cytokines, thus targeting the main inflammatory mechanisms related to cancer [153].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is one of the most well-known family of transcription factors in inflammation and cancer. Generally this pathway is activated by ROS or by inflammatory mediators and is inhibited by many polyphenolic compounds [154, 155]. NFκB inhibition by phytochemicals leads to a reduced cell proliferation or an increased sensitivity to chemotherapeutics such as CAPE [104, 154]. Resveratrol was observed to decrease the p-ERK expression and increase the p-JNK expression in nigrostriatal pathway injury mice model compared to the control group, but does not affect p38 MAPK proteins expression. The same treatment decreases IL-1β, TNF-α and IL-6 [156]. Also LPS-induced inflammation was reduced by resveratrol via inhibition of phosphorylation of NF-κB, CREB and MAPKs family in a mTOR-dependent manner in murine glial cells [157]. STAT pathways are proved to be altered in a wide range of

cancers and, represent very well-studied therapeutic target. The development of resveratrol-Caffeic acid hybrids, able to target STAT pathways, displayed good therapeutic efficiency once tested on breast cancer xenograft tumor models [158]. In lung cancer resveratrol targets STAT3 signalling pathway via induction of SOCS-1, and was able to act as a sensibiliser to therapy [159].

Apoptosis and cell cycle arrest. The genomic underpinnings of apoptosis and cell cycle regulation in normal and physiological status are modulated by phytochemicals. Disabled apoptosis is prone to genomic instability; therefore this is the main protective mechanism against the tumorigenesis, being centred to eliminate all the cells that are unwanted or genetically damaged [160, 161]. EGCG is a well-known natural compound that was demonstrated to have the capacity to induce apoptosis [138] and cell cycle arrest in many cancer cells without any effect on normal cells [161]. EGCG was able to target both intrinsic and extrinsic pathways irrespective of the presence or absence of the p53 gene in prostate [162], breast cancer [138], cervical cancer cells [163] or oral cancer cells [164]. In some cases, the EGCG treatment was connected with the activation of antiapoptotic genes BAG3, XIAP, RIPK2 [138]. These mechanisms responsible for resistance to therapy counteract with other therapeutic agents in order to achieve the maximal therapeutic efficiency and the minimal toxic effects [165]. TRAF6 (TNF Receptor-Associated Factor 6) plays an essential function in signalling transduction of the apoptotic mechanism and was overexpressed in melanoma. EGCG had a double role: EGCG treatment activated the apoptosis-related genes, but also those related to cell growth and metastasis. In another study it has been shown that resveratrol treatment is followed by up-regulation of Bcl-2 and downregulation of Bax [134].

Resveratrol guards normal cells against DNA damage and specifically activates apoptosis by modulating anti- and pro-apoptotic mediators. Resveratrol targets the p53 pathways and stresse-activated protein kinases [166]. The dual combination of curcumin plus resveratrol treatment, decreased the expression of Fas, FasL, Bax, Bcl2, and Apaf1 along with the inhibition of the main activated kinases (ERK1/2, p38 and JNK), thus emphasizing their important role in chemoprevention [111].

Autophagy. Autophagy is a critical mechanism for sustaining cytoplasmic and genomic integrity. It has been shown that the process is influenced by intracellular and extracellular stresses, including natural phytochemicals [167].

Autophagy is partially reversible, but once it becomes irreversible, always leads to cell death [168]. An increased autophagy flux might be connected with lysosomal membrane permeabilization and dysfunction of mitochondrial membrane potential, both leading to cell death via death receptors and caspase activation. By targeting DR5, EGCG was proved to activate the autophagy flux mechanisms, thus causing the TRAIL-induced apoptosis in TRAIL-resistant cells [167]. Another study emphases the importance of the EGCG-triggered autophagy for boosting the effect of doxorubicin in Hep3B cells [169]. Resveratrol induces autophagy and modulates cell death by targeting death-associated protein kinase 1 (DAPK1) in human dermal fibroblasts [170]. The same molecule was able to induce autophagy cell death via Cap (2+)/AMPK/mTOR in A549 lung cancer cells [171].

Genistein treatment was proved to induce autophagy-caused cell death in ovarian cancer cells. This has an important application in cancer therapy, preventing drug resistance caused by the altered apoptotic pathway [172]. A similar study on endometrial cancer cells treated with resveratrol reveals the capacity to modulate this process *via* ATG5 or ATG7. Another noteworthy fact is the capacity of CAPE to modulate drug resistance via autophagy. The relationship of the survival pathways MAPK, NFκB and autophagy still remains controversial [104]. This continues to be an intriguing point that needs to be deciphered in the context of system biology, based on latest genomics approaches.

Angiogenesis in the context of invasion and migration

Angiogenesis is the process of the formation of new blood vessels. This mechanism is absolutely essential in cancer progression; therefore, it represents an important target for the prevention of tumor growth and treatment. There is well known that the dietary components cannot be used as single therapy. There are some investigations that provide information on the ability of natural phytochemicals to modulate tumor angiogenesis, including some from our group [138, 173]. The inhibition of both VEGF and its related receptors was evaluated in a wide range of preclinical studies using natural phytochemicals [173]. Resveratrol inhibits angiogenesis, and is capable to inhibit VEGF (vascular endothelial growth factor) expression via HIF-1α [174]. From the other side, HIF-1α is inhibited by a wide range of natural compounds. EGCG significantly decreased HIF-1α expression and leads to the inhibition of angiogenesis as it is demonstrated both *in vitro* and *in vivo* studies. Also it inhibits EMT, invasion and migration on A549 lung cancer cells [91].

EGCG reduces tumor growth and suppresses carcinogenic molecular signals such as Notch1, MMP-2/9, and proliferating cell nuclear antigen on cell cultures study and animal models representative for cholangiocarcinoma [175]. In lung cancer preclinical studies, EGCG is shown to activate apoptosis, moreover it targets Wnt/β-catenin pathway and is associated with the self-renewal and maintenance of CSCs [44]. EGCG has a complex mechanism of action at the genomic level and modulates oestrogen related genes [176]. Daidzein and genistein have a significant impact on gene expression pattern in breast cancer cell lines [177]. However, these two phytoestrogens have reversed effect on gene expression in BRCA1 transient cells [178].

Phytochemicals and non-coding gene modulators

Non-coding RNAs genes (ncRNAs) are transcribed as small regulatory transcripts and the most relevant ones are represented by microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)[187]. These noncoding modulators have received an increased interest in the last years as biomarkers or therapeutic strategy [22, 188]. MicroRNAs (miRNAs) are small molecules involved in posttranscriptional gene regulation. These 19-25 nucleotides transcripts have the capacity to bind to the 3′-UTRs regions and finally lead to translation repression or mRNA degradation [187, 189]. It is worth mentioning that a single miRNA is able to target multiple genes, or an mRNA transcript can be targeted by multiple genes involved in cellular processes [22, 190, 191]. Long non–protein coding RNAs (lncRNAs) are another important class of transcripts. They are over 200 nucleotides in length and are related to the regulation of cellular mechanisms [24, 187, 188, 192, 193].

Based on their role in molecular processes, the non-coding genes are classified as oncogenic or tumor suppressors ncRNA [24, 187-189]. These sequences have important application in therapeutics, restoring the normal level of these transcripts re-establishing the physiological mechanisms [24, 189-191]. Natural phytochemicals are generally small molecules able to modulate the miRNA expression levels and to key regulatory networks, directly or indirectly (Table 3).

MiRNA regulation is influenced by natural phytochemicals. An extensive range of genomic studies demonstrated this fact. What is more, phytochemicals are able to target the miRNA pattern, this alteration being cell specific and influenced by

the administered dose. Using bioinformatics approaches targeted genes were identified to be related to the most frequently altered miRNAs or lncRNAs [190]. The mechanism of miRNAs regulation is mainly via targeting transcription factors or epigenetic mechanisms [194, 195]. Another possibility is to interfere with the biogenesis and maturation of miRNAs[25]. *In silico* modelling is useful for prediction of phytochemicals' interaction, but the validation of these prediction models is difficult. It was shown by ^{1}H NMR spectroscopy that resveratrol and EGCG directly bind to two miRNAs (miR-33a and miR-122) [188]. This specific mechanism of direct binding to target miRNAs represents a new avenue to explain the posttranscriptional mechanism related to antitumor effects [188]. Another *in silico* modelling showed that EGCG is a direct agonist of androgen signalling, followed by the overexpression of miR-330 and downregulation of miR-21 [133]. CTR1 (copper transporter 1), a transmembrane solute carrier transporter, is connected to intensification of the cellular uptake and sensitivity to cisplatin. EGCG was able to increase the expression level for CTR1 in lung cancer cells and xenograft mice [50]. The same gene was modulated in ovarian cancer, being connected with an increased accumulation of cisplatin, where miR-98 suppresses both CTR1 and the nuclear enriched abundant transcript 1 (NEAT1). Interestingly, both mechanisms are modulated by EGCG treatment [182].

Resveratrol treatment induced an altered miRNA pattern, containing 71 miRNAs overexpressed in lung cancer cells [196]. Resveratrol targeted apoptotic and cell cycle machinery by affecting tumor suppressor miRNAs (miR-125b-5p, miR-200c-3p, miR-409-3p, miR-122-5p and miR-542-3p) in breast cancer cells [87]. In colon cancer cells resveratrol treatment altered the expression of 46 miRNAs, most of them with oncogenic role, by targeting TGFβ pathways [197]. Treatment with genistein or daidzein had comparable effect on miRNA pattern as revealed by PCR-array evaluation, possibly due to the similar chemical structure and molecular interactions [198].

LncRNAs investigation gained increased interest due to their functional importance in pathological conditions. An increased number of studies demonstrated that lncRNAs are engaged in the regulation of various cellular processes. HOTAIR is a well-known upregulated oncogenic lncRNA in several cancer types. It interferes with PI3K/Akt signaling pathway and was proved to be downregulated by genistein, in breast cancer cells [69].

The capacity of resveratrol (25 μmol/L) to modulate ncRNA profile was shown in a profiling study in lung cancer cells. The bioinformatics analysis reveals 21 lncRNAs upregulated and 19 lncRNAs downregulated in the *in vitro* model. AK001796 was the most overexpressed in lung cancer tissue and cell line, and resveratrol was able to inhibit this lncRNA[88]. In prostate cancer cells genistein-induced inhibition of HOTAIR via modulating the overexpression of miR-34a [67]. It was demonstrated that ncRNAs play a significant role in drug resistance. Recently, EGCG showed the capacity to inhibit drug resistance via NEAT1/mir-98 crosstalk in lung cancer cells [50].

Phytochemicals proteomic and metabolomics alteration

The pro-oxidant effect can be also responsible for activation of the immune response [102, 141]. Generally, the pro-oxidant effect is difficult to be demonstrated after intestinal absorption except in the case of polyphenols, where some modifications of the polyphenol backbone can be seen. The novel proteomic and metabolomics approaches can be a good solution to solve this issue. Proteomic analysis revealed that EGCG leads to the alteration of the expression levels of various proteins (HSP27, porin, tropomyosin 3 isoform 2, prohibitin and keratin 5, 14, 17), in bladder cancer cells, that finally leads to apoptosis [203]. EGCG treatment was related to the inhibition of AKT kinase activity and the alteration in the expression levels of the main apoptosis related proteins, like Bcl-2, Bax and BAD [203].

A recent proteomic study using high-resolution mass spectrometry (MS) in tandem with TiO2 phosphopeptides enrichment and stable isotope labelling by amino acids (SILAC) permitted the identification of 1177 phosphorylation sites on 635 unique proteins. The bioinformatics analysis revealed novel-signalling components targeted by these compounds. These proteins were grouped in different classes of receptors, signal adaptors, protein kinases, protein phosphatase regulatory subunits, and transcription regulators at single or multiple sites [204]. Other study using micro-western array technology revealed that CAPE is modulating the antiproliferative pathway via cell cycle regulation, targeting Skp2, p53, $p21^{Cip1}$, and $p27^{Kip1}$ in prostate cancer cells [205].

P-glycoprotein (P-gp), multidrug resistance-associated proteins 2 and 3 (MRP2 and 3) and breast cancer resistance protein (BCRP) are efflux pumps that play

a key role in cancer chemoresistance and were proved to be modulated by polyphenols. Genistein (GNT) is well known as estrogen mimetic and was proved to exert its genomic properties via Estrogen-Receptors and Pregnane-X-Receptor (PXR) a key protein related to multidrug resistance genes. GNT in concentration of 1.0 and 10 μM was able to inhibit PXR and activate P-gp. The activation of MRP2 was observed only at 10 μM in HCC. In HCC cancer, genistein treatment was correlated with an increased resistance to therapy [139]. Therefore, phytochemicals **can increase or decrease cancer chemoresistance**, the effect depending of the cell type and exposure dose. Most of the studies report an increased therapeutic efficacy in the presence of these natural compounds, as it is presented in Table 4.

Phytochemicals as adjuvants in cancer therapy: myth or reality?

Latest discoveries in cancer therapy, particularly in preclinical models include a wide range of combination of low doses of natural phytochemicals with conventional therapies. Accordingly, most of the combinatorial strategies prove to have an additive or even a synergic effect, presented in Table 5. The most important to mention was the reduced toxicity caused particularly by chemotherapy or radiotherapy when used in combination with a natural bioactive agent.

EGCG, a relevant chemopreventive agent, when used in combination with standard chemotherapies, inhibit sphere formation, a particular phenotype responsible for drug resistance caused by the presence of cancer stem cells [112]. The biological activity of these compounds was relatively reduced. That is the case of the EGCG effect that induce a very low reduction of cell proliferation in a resistant HCC cell line, but when administered with Doxorubicine the antitumor effect is much higher even at lower doses [207, 208].

The synergic effect with classical chemotherapy in the case of EGCG or its related derivatives was observed in a wide range of human cell lines. Other examples are those related to the case of resveratrol, that inactivate the chemoresistance mechanism via inhibition of epithelial-to-mesenchymal transition (EMT) mechanisms, by decreasing the expression level for vimentin and slug, increasing the expression level for E-cadherin. In the same time, the down-regulation of NF-κB activation and the translocation at nuclear level and inhibition of MMP-9, caspase-3 was observed [209]. The same compound was proved to enhance 5-

fluorouracil chemosensitivity via inhibiting suppressed Notch1, Bmi1, Suz12, and Ezh2, connected with the upregulated self-renewal suppressive-miRNAs (miR-34a, miR-145, and miR-200c), the key pathways targeted by 5FUR [210].

Genistein treatment along with inhibition of miR-223 could reverse EMT phenotype and increase chemotherapeutic drug sensitivity to gentamicin in pancreatic cancer models [211]. Copper transporter 1 (CTR1) is a copper influx transporter, which promotes an important fraction of cDDP internalization in tumor cells, including in the case of lung cancer. It was proven that EGCG-induced CTR1 in NSCLC *in vitro* and *in vivo* via mir-98-5p and NEAT1, had as final effect an increased response to cisplatin [50]. In another study on ovarian cancer cell lines EGCG reduces the resistance to Cisplatin (cis-diamminedichloroplatinum, cDDP), mainly via CTR1, no other copper transporters were involved. These data were validated on xenograft animal models, and it was shown that EGCG is able to reduce the nephrotoxicity caused by cDDP [182]

In our opinion, the natural compounds could be considered as a good source for discovery of new therapeutic strategies in a varied range of pathologies outside cancer. The nutrigenomics and nutrigenetics approaches are valuable tools to see the whole picture of the puzzle starting with the deciphering of the form retrieved in natural matrices. Another important issue is the understanding the cellular and molecular mechanisms of action of a single agent or combination of these natural compounds. By applying computational tools to the analysis of the structure of natural compounds or their related derivate can be a beneficial resource for the next generation drug discovery [213]. Therefore, these modern methods are anticipated to validate proof of concept prior to become a reality.

Conclusion and perspectives

It is clear that these natural phytochemicals act as key signaling molecules as one might observe from the nutrigenomics pattern of these molecules. In spite of the increased number of investigations, the results remain inconclusive, and only few cases are implemented into clinical trials. These preclinical data are useful and can serve as a base for developing novel antitumor agents, with superior

pharmacologically and biologically active effects. The failure of some clinical trials can be justified by the lack of natural matrices retrieved in the natural source. The enriched plant extract can be delivered in a partially oxidized form, due to the low stability of these natural phytochemicals. The genomic investigation allows the biological elucidation of the capacity of phytochemicals to modulate transcriptomics profiles, which is a highly complex task. An important role in the validation of preclinical data on clinical trials is to consider the environmental risk factors that might affect the disease model making the validation on humans very difficult. The different toxic environmental exposure is a major component of genomic studies related to natural compounds as benefactors in cancer neoadjuvant chemotherapy. This might create a different response rate, or a combination of toxic agents with phytochemicals. An important role is played by epigenetic events and their relationship with transcription factors.

Prior to become a true daily reality, nutrigenomics is anticipated to validate proof of concept for its main identified mechanisms, and then to be implemented in clinical practice. Diverse pro/contra opinions were addressed to natural phytochemicals, based on genomics evaluation. These missing puzzle pieces make it difficult to assess whether a particular phytochemical has an overall positive or negative effect on cell proliferation. The further application of genomic approaches will elucidate the different molecular mechanisms targeted, and will allow the identification of the doses having chemopreventive/therapeutic or detrimental effects.

There is no doubt about the benefit of these natural compounds in human health and in the same time it is very difficult to ignore the controversial data due to the extensive range of experimental and preclinical models used for the evaluation the biological effect. These discrepancies can be reduced with the development of a natural product database and standardization of the protocols.

The process of novel drug discovery or drug design from natural products is based on the integration of nutrigenetics and nutrigenomics data. The natural compounds have multifaceted properties due to the heterogeneity of the different molecular structures that are retrieved from natural sources. In spite of all these difficulties it is important to introduce in daily practice the concept of personalized diet that supports the chemotherapeutic treatment.

Conflict of interest

There are no conflicts of interest that need to be declared.

Acknowledgements

This work is part of research grant No. 128/2014; PN-II-PT-PCCA-2013-4-2166 "New strategies for improving life quality and survival in cancer patients: molecular and clinical studies of the tumor genome in deuterium-depleted water treatment augmentation - GenCanD" and research grant No. 96/2014, PN-II-PT-PCCA-2013-4-0030 "Modulation of pro/anticarcinogenic effect of toxic chemical agents in breast cancer multitargeted therapy-CANCERTER-p53". Dr. Mehterov's work was partially supported by Project HO-18/2014, funded by Medical University of Plovdiv.

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Fig 1

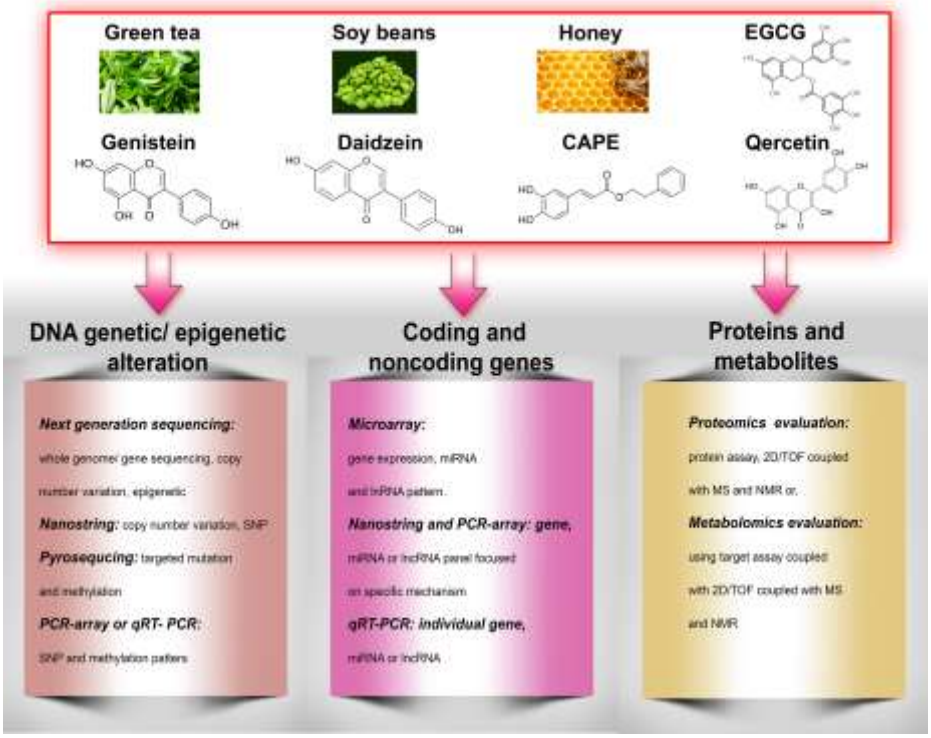

Fig 2

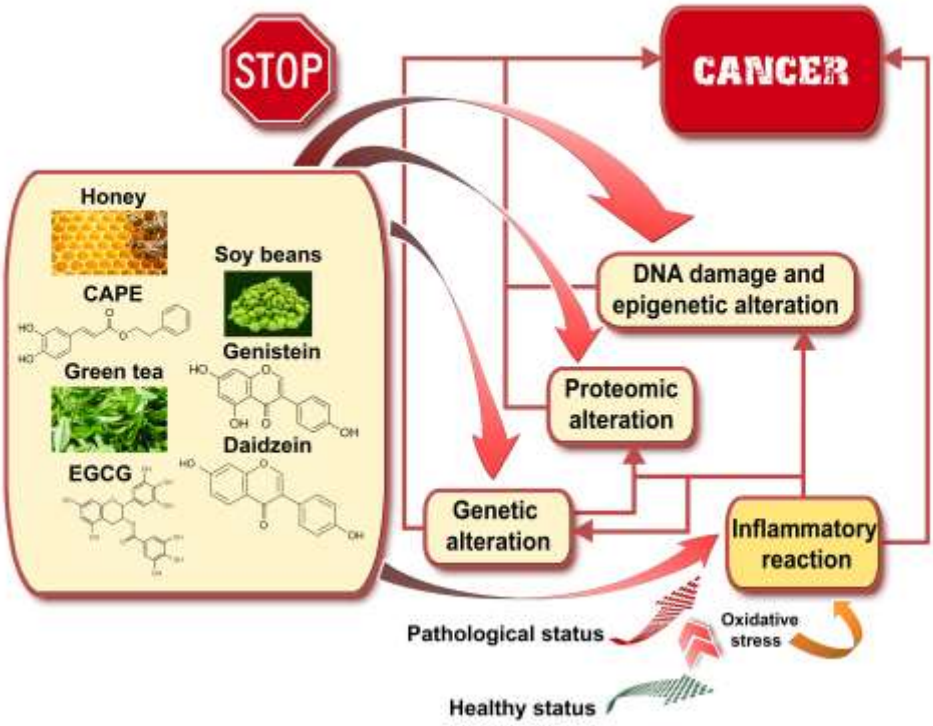

Fig 3

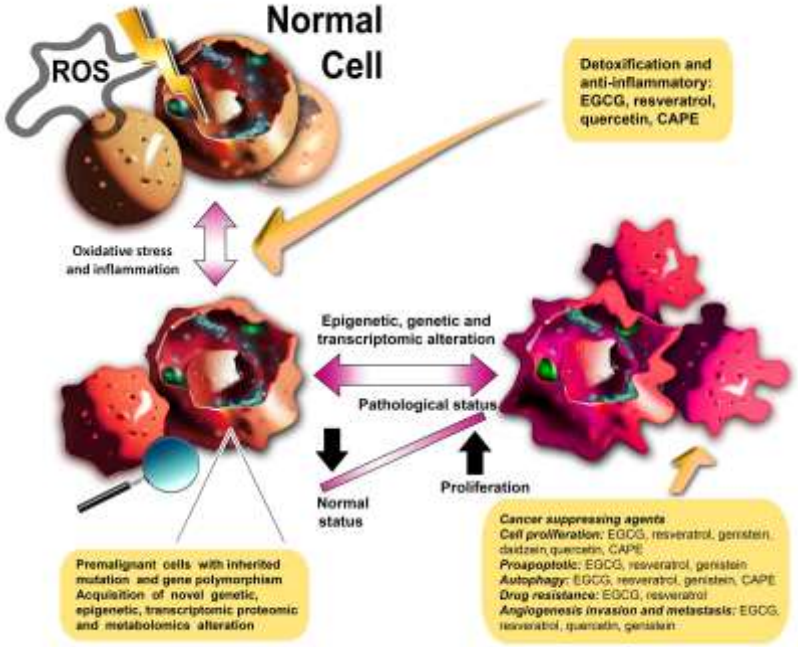

Fig 4

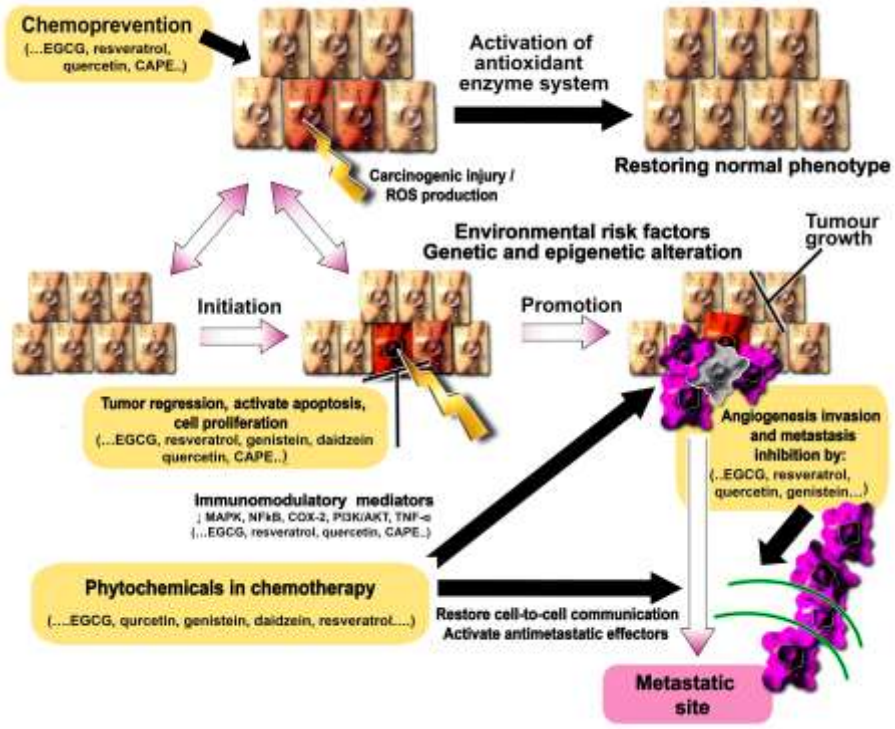

Fig 5

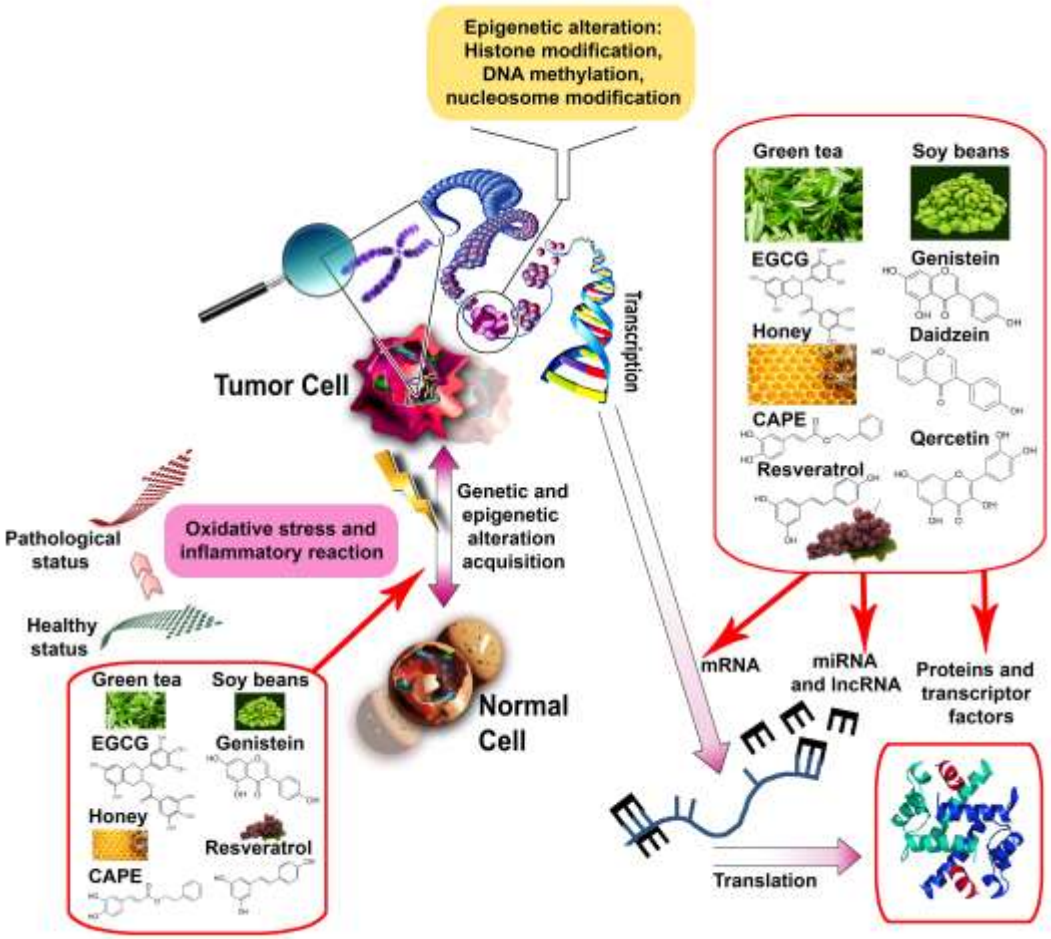

Table 1. The main application of phytochemicals in cancer prevention and treatment.

Class	**Subclass**	**Phytochemical**	**Genomic data related to antitumor effects**	**Biological source**	**Biological effects**	**References**
Polyphenols	Flavanols	Quercetin Kaempferol	Epigenetic regulation via NFκB signaling [41]; histone modification [42, 43] Gene expression: Wnt/β-catenin [44, 45], 2-AMPK-mTOR [46], HSP70[47] PI3K/Akt, TGFβ/Smad,	Seeds, citrus fruits, olive oil, tea, and red wine	Antioxidant, antiproliferative and antitumor effect	[36, 49]

			E-cadherin, cyclin D1, c-Myc, b-catenin and vimentin[45], p21, Twist and p38MAPK[48], Caspase 3, EGFR[48, 49] miRNA expression: mir-98[50], miR-151[51], let-7[52], miR-146a[48], mir-145[53], miR-27a[54] lncRNA: NEAT1[50] SNP: APE1/Ref-1 SNP[55]			
	Flavones	Apigenin Lutheolin	Epigenetic regulation: attenuated DNMT and HDAC activity [56] Target 5-cytosine DNMT; Histone H3 and H4 hyperacetylation [57] Gene expression: VEGF, PDGFβ[58], Akt/FOXO3a [59], Nrf2 [56], hTERT[60] MAPK[61] miRNA expression: miR-138[60]	Citric fruit	Estrogenic, anticarcinogenic, and antioxidant	[34, 37]
	Isoflavones	Genistein Daidzein	Epigenetic regulation: DNA methylation of GSTP1, RASSF1A, EPH2 and BRCA1 promoter[62], histone acetylation and	Soy beans, chick peas, alfalfa, peanuts	Estrogenic, anticarcinogenic and antioxidative	[38]

			demethylation activates tumor suppressor genes [57, 63], Gene expression: AR[62], ER[39], Akt, Cyclins[64], NFκB[62], Wnt/β-catenin[65], MMP2, -9, MT1-, MT2-, MT3-MMP and TIMP-1, -2 and -3[66] miRNA expression: miR-34[67], miR-155[68] lncRNA: HOTAIR[67, 69] SNP: APE1/Ref-1 SNP [55]			
	Anthocyanidins	Cyaniding Pelargonidin Petunidin	Epigenetic mechanisms: demethylate tumor suppressor genes through inhibition of DNMT1 and DNMT3B[70], regulate methylation of Wnt pathway genes[71], down-regulate the methylation of p53[72] Gene expression: ER, AR, Her-2[73], NFκB, COX-2, iNOS, PI3K/Akt, AP-1[64, 74], RAS/RAF/MAPK, MMP2 and MMP-9[75], TGFβ/Smad2	Red grapes, blueberries, cherries, strawberries, blackberries, raspberries, green and black tea, honey and	Anti-inflammatory and anticarcinogenic activity, cardiovascular disease prevention, obesity control, and diabetes alleviation properties	[77, 78]

			[76]	cocoa		
	Flavan-3-ols	Catechins Epicatechin Epigallocatechin gallate	Epigenetic regulation: histone modification [42], DNA methylation [42, 43], decrease transcription of DNMT1, DNMT3a, and DNMT3b methylation status of the promoter region of RARβ, decreased acetyl-H3, acetyl-H3K9 and acetyl-H4 levels in hTERT[79] Gene expression: Wnt/β-catenin[44], HIF-α[80], PI3K, MAPK, NFκB, HGF, IGF-1, VEGA, TNF-α[64] miRNA expression: mir-98[50], miR-151[51], let-7[52], miR-16[81], miR-210[80] lncRNA: NEAT1[50] SNP: APE1/Ref-1 SNP[55]	Green tea, chocolate, grapes	Antioxidant and anticarcinogenic effect, target altered epigenetic mechanisms	[82-84]
	Non-flavonoids	Hydroxycinnammic acids Stilbenoids (**resveratrol**, cinnamic acid)	Epigenetic regulation: DNMT1, prevents epigenetic silencing of the BRCA-1 gene[85] Gene expression: Cyclin A, B1 and E, Cdk1, TGFβ1/Smad[86],	Grapes, wine, blueberries, peanuts, raspberries	Antioxidant effects, antitumoral effects proapoptotic, antiproliferation, anti-	[91] [92, 93]

			Nrf[64] miRNA expression: miR-27a[54] miR-125b-5p, miR-200c miR-409-3p, miR-122-5p and miR-542-3p[87], miR-148a[86] lncRNA: AK001796[88], MALAT1[89], neat1, NEAT1, MIR155HG, MEG3, and ST7OT1[90]		inflammation and antiangiogenic effects	
Terpenoids	Monoterpenoids	Limonene, cantharidin	Gene expression: cytochrome c, caspase-9 and -3, NFκB, MAPK, TNF-α, IL-6, FOX3a BCL-2, PD-1/PD-L1 [94]	Essential oil, citric fruit, medicinal plants	Inhibit cell proliferation and invasion; anti-inflammatory effect; proapoptotic effect; antibacterial effects	[95]
	Sesquiterpenoids	Artemisinin and its derivatives		Medicinal plants		
	Diterpenoids	Oridonin, pseudolaric acid B, andrographolide, triptolide, tanshinone IIA		Medicinal plants		
	Triterpenoids	Celastrol, cucurbitacins, alisol, pachymic		Medicinal plants		

		acid				
	Tetraterpenoids	Carotenoids (alpha, beta and gamma carotene, lutein, zeaxanthin)		Tomatoes, carrots, corn, eggs, kale, spinach, red pepper, pumpkin, oranges, rhubarb, plum, mango, papaya, guava, papaya	Antioxidant, metabolic disorders, antitumoral effects	[96]
Phenolic acids	Hydrobenzoic acids	Gallic acid Ellagic acid Vanillic acid	<u>Gene expression:</u> COX, ATM, NF-κB and Akt, TNF-α [97] MAPK, IGF-1R and EGFR[98] <u>ncRNA expression and target genes:</u> miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR[99], miR-518b[100]	Grape seed, raspberries, blackberries, pomegranate, vanilla, green and black tea	Antibacterial effects, antioxidants, antitumoral effect	[101, 102]
	Hydroxycin	Ferulic acid, p-coumaric	<u>Epigenetic mechanism:</u> HDAC inhibitor and	Wheat bran,	Antioxidant, imune	

	namic acids	acid Caffeic acid and caffeic acid phenethyl ester (CAPE) Sinapic acid	induces hyperacetylation of histone proteins[103] Gene expression: Inhibit MAPKs NF-κB activation[104], target apoptotic genes cIAP- 1, cIAP-2 and XIAP [105] Bax, Bad, and procaspase, and the cleavage of PARP, and the BclXL [104], CASP8, FAS, FADD, p53, ZEB1, ZEB2, or TGFBB1[106]	cinnamon, coffee, honey, kiwi fruit, plums, blueberries	response modulator, antitumoral effect	
Phytosterols	Sitosterol Campesterol Stigmasterol		Gene expression: Caspase-3, BCL-2, MAPKs, AKT[107]	Nuts, seeds, legumes, wheat germ, whole grains, bran, fruit, vegetables	Reduce the risk for cardiovascular diseases, antitumoral effects	[107, 108]

Table 2 The main genomic alterations retrieved in tumoral cell lines upon exposure to natural phytochemicals.

Phytochemicals	Dose	Pathology	Preclinical model	End-point	Relevant mechanism	Relevant molecular target	Reference

EGCG	40 µM	Breast cancer	MCF-7	Microarray	Oestrogen driven processes in ER-positive breast cancer cells.	Overexpressed 1473 genes, downregulated 1844. Increased expression of two estrogen transcripts (pS2 and PR)	[176]
	20 µM	Triple negative breast cancer	Hs578T	Cell proliferation by xCELLigence System, flow cytometry, PCR-array	Targeting apoptosis but also activation of drug resistance genes	22 genes, of which 18 were upregulated and four downregulated, unspecific activation of pro-apoptotic genes BAG3, XIAP, RIPK2	[138]
	5 µg/mL	Cholangiocarcinoma	HuCC-T1 cells, tumor xenograft model	Cell proliferation, flow cytometry, western blot, IHC	Activated apoptosis, decrease invasion, and migration	Bax/Bcl-2, Caspase, and cytochrome C Notch1, MMP-2/9	[175]
	25-100 µM	Bladder cancer	SW780 cells and tumor xenograft	Cell proliferation, flow cytometry, western blot, qRT-	Decreasing cell proliferation, and migration activating	caspases-8, -9 and -3, Bax, Bcl-2 and PARP, NF-κB and MMP-9	[179]

			model	PCR	apoptosis		
	0-100 μM	Lung cancer	A549 and H1299 cells	Tumorsphere formation assay, flow cytometry, Hoechst staining, qRT-PCR, western blot	Decreasing CSCs markers, suppressing proliferation and inducing apoptosis	Wnt/β-catenin	[44]
	0-100 μM	Lung cancer	A549 cells	Cell proliferation, angiogenesis assay, invasion approach, qRT-PCR, ELISA	Modulate hypoxic mechanisms, inhibits angiogenesis	Downregulation of HIF-1α and VEGF expression	[180]
	25-100 μmol/L	Prostate cancer	PC-3 AP-1, Nrf2-knockout or C57BL/6J mice	Modulates gene expression responses to oxidative and electrophilic stresses	Microarray, qRT-PCR, microarray, luciferases assay,	Nrf2 and AP-1	[181]
	0-20 μM	Ovarian cancer	OVCAR3, SKOV3 and HEK-	qRT-PCR, MTT assay, colony assay	Drug resistance mechanism	CTR1	[182]

			293T	formation, Hoechst 33258 staining, measurement of platinum (Pt) accumulation in cells			
	0-100 μM	Oral cancer	Cal-27	Cell proliferation, microarray, western blot, invasion assay	Decreasing cell proliferation, and migration activating apoptosis, EMT	EGFR,MMP-2, ERK, JNK, p38 and AKT	[183]
	20 μM	Oral cancer	SSC-4	Cell proliferation, apoptosis assay, qRT-PCR, western blot,	Decreasing cell proliferation, and migration activating apoptosis	Activates the expression of the BAD, BAK, FAS, IGF1R, WNT11, and ZEB1 genes and inhibits CASP8, MYC, and TP53	[164]
	0-80 μM	Melanoma	SK-MEL-5, SK-MEL-28,	MTS assay, NF-κB gel shift assay, *in vitro* ubiqui	Activating apoptosis, reducing migration and invasion	Targets NFκB pathways effectors (IκBα, p-TAK1 p65 and	[134]

			A375, and G361, xenograft models	tination assay, western blot, qRT-PCR		p50), TRAF6	
Resveratrol	0-40 μM	Colorectal cancer	HCT 116 and HT-29	MTT test, qRT-PCR, western blot, western blot, cell cycle, assessment of Pgp and Pgp-ATPase activity	Drug resistance mechanism (p-glycoprotein pump), apoptosis and cell cycle	MDR genes, Bax, Bcl_2, Bcl-xl and p53	[184]
	0.1 – 200 μM	Endometrial cancer	Ishikawa cells	MTT assays, flow cytometry and annexin V staining, qRT-PCR, western blot, immunofluorescence,	Autophagy	Targeting autophagy ATG5 or *ATG7*	[185]
	100 μM	Cervical and	HeLa, SiHa and	MTT test, qRT-PCR, western	Apoptosis	PIAS3 correlated most	[186]

		squamous cell carcinoma	C33A	blot, tissue microarray		negatively with STAT3 nuclear translocation	
Daidzein	78.5 μM	Breast cancer	MDA-MB-231, MCF-7, MCF-10	Microarray	Pathways related to cellular communication, biodegradation of xenobiotics, lipid metabolism, signal transduction, and cell growth/death	169 genes with an altered expression level, involved in 24 total pathways, 17 pathways common to both ER− status and tumor status.	[177]
Genistein	18.5 μM	Breast cancer	MDA-MB-231, MCF-7, MCF-10	Microarray	Pathways related to communication, biodegradation of xenobiotics, lipid metabolism, signal transduction, and cell growth/deat	246 genes with an altered expression level 22 total pathways were dysregulated, 13 common to both ER− status and tumor status	[177]

					h		
	35-100 µM	Breast cancer	MDA-MB-231, MCF-7	Cell proliferation, flow cytometry, zymographic analysis of MMP-2 and -9, *in vitro* invasion assay, qRT-PCR	Reduce cell cycle progression and metastatic potential of cells	MMP-2, -9, MT1-, MT2-, MT3-MMP and TIMP-1, -2 and -3	[66]
Quercetin	10-50 µM	Triple negative breast cancer	MDA-MB-231 and MDA-MB-468	Cell proliferation test, wound healing assay, migration and invasion assay, qRT-PCR, western blot	Induced change in cell morphology and inhibited cell migration; induce MET via β-catenin	PI3K/Akt, TGF-b/Smad, E-cadherin, β-catenin cyclin D1, c-Myc, b-catenin and vimentin	[45]
	40 µM	Breast cancer cells	MCF-7 and MDA-MB-231	Cell proliferation test, apoptosis by flow cytometry, soft agar	Suppresses Twist leading to the induction of apoptosis	CyclinD1, p21, Twist and phospho p38MAPK	[48]

				colony formation assay, qRT-PCR, western blot, transmission electron microscopy			
	50 μM	Lung cancer	H460 cells	Microarray, Hoechst staining, trypan blue exclusion, and DNA fragmentation assays, caspase cleavage evaluation	Apoptosis activation, DNA fragmentation, cell cycle inhibition growth arrest, inhibit activation of NFκB pathways	TRAILR, IL1R, DFF45, FAS, IκBα, GADD45, $p21^{Cip1}$, NF-κB, IKKα	[177]
CAPE	0-25 μM	Pancreatic ductal adenocarcinoma	MIAPaCa-2 and PANC-1	Cell proliferation, western blot, apoptosis by tunel assay	Apoptosis and autophagy	Pro-apoptotic proteins Bax, Bad, and procaspase, and the cleavage of PARP, and the anti-apoptotic proteins BclXL and surviving	[104]

	10 μM	Ovarian cancer	A2780/ A2780 cis	MTT test, flow cytometry and qRT-PCR	Apoptosis and activated EMT related genes (ZEB1, ZEB2, or TGFBB1)	Activate pro-apoptotic genes (BAD, CASP8, FAS, FADD, p53)	[106]

Table 3. Plant-derived phytochemicals as miRNA and lncRNA modulators in cancer therapy.

Cancer type	Natural compound (dose)	Preclinical model	NcRNA targeted	Gene targeted by miRNA	Mechanism	Technology (microarray, NGS, RT-PCR)	Reference
Breast cancer	Resveratrol	MCF-7 and MDA-MB-231	MCF-7 cells: 37 miRNA with an altered expression level (eg. ↑: miR-542, miR-125b)	BCL-2, Cdks	Activation of cell death mechanism	PCR-array	[87]

			MDA-MB-231 cells: ↓25 miRNA 25 eg. miR-542, miR-200c Common miRNA in both cell line: ↑ miR-199a, ↓ miR-125b, miR-140, miR-20a				
	Genistein (0–50 μM)	MDA-MB-435, Hs578T and xenograft models	↓miR-155	FOXO3, PTEN, casein kinase, and p27	Proapoptotic and antiproliferative	qRT-PCR	[68]
	Genistein (0–80 μM)	MCF-7 Cells	↓HOTAIR	HOTAIR /p-Akt Signaling Pathway		qRT-PCR	[69]
	Quercetin	MCF-7 and MDA-MB-231, xenograft assays in nude mice	↑miR-146a	Caspase 3, EGFR	Activate apoptosis Mitochondrial pathways, and inhibiting invasion by inhibiting	qRT-PCR	[48]

					of EGFR		
	CAPE	MHCC97H and MDA-MB-231 and animal models	↑miR-148a miR-155 and miR-206	miR-148a down-regulates DNMT1	TGFβ/SMADs signal pathway, target stem-like properties	qRT-PCR	[86]
Prostate cancer	EGCG (20-40 μM)	LNCaP and 22R1 cells, xenograft models	↑ miRNA-330 and ↓ miRNA-21	AR	Androgen receptor signalling	*In silico* molecular modelling, qRT-PCR	[133]
	Genistein (25 μM)	PC3 and DU145	↑miR-34a, Top 5 lncRNA ↓: HOTAIR, LOC100287628, LOC145474, C6orf147, LOC100507165	miR-34 target HOTAIR	Tumorigenesis	Microarray, qRT-PCR	[67]
	Genistein (25 μM)	PC3 and DU145	↓miR-151	CASZ1, IL1RAPL1, SOX17, N4BP1 and ARHGDIA	Progression and metastasis of prostate cancer	qRT-PCR,	[51]
	Genistein (40	DU145 cells	DU145 cells ↓ miR-155, miR-	ERBB2, ERBB3,	Differentiation,	TaqMan miRNA	[198]

	μM) and daidzein (110 μM)	LNCaP cells	208b, miR-211, -376a and miR-411 LNCaP cells miR-494, miR-520g, miR-542 PC3L ↓ miR-125a, miR-125b and miR-15b; ↑miR-548b	VEGFA	signal transduction, cell maintenance	array and qRT-PCR	
	Genistein (25 μM)	PC3 and DU145	↓HOTAIR, ↑miR-34a	N/A	Knockdown using siRNA for HOTAIR decreased cell proliferation, migration and invasion and induced apoptosis and cell cycle arrest.	Microarray	[67]
Lung cancer	EGCG (0-10 μM)	NNK-induced mouse lung tumor	12 overexpressed and 9 downregulated miRNAs Top 5 ↑: miR-	AKT, NF-κB, MAPK	Activated apoptosis, decrease invasion, and migration	Microarray	[199]

			2137, miR-449a, miR-144, miR-486, miR-3107 Top 5 ↓: miR-696, miR-449c, miR-7a, miR-205, miR-450a				
	EGCG (0-40 μM)	H1299, H460 and A549 cells	↑ miR-210	HIF-1α	Inhibit proliferation and anchorage-independent growth via HIF-1α stabilization	Microarray, qRT-PCR,	[80]
	EGCG (0-50 μM)	A549, H460 and H1299	↑NEAT1, ↓ miR-98	CTR1	NEAT1 regulate CTR1 gene expression, Drug resistance mechanism	qRT-PCR	[50]
	Resveratrol (60-120	A549 cells	33 altered miRNAs (120 μM)	Target genes related to	Cell proliferation and	Microarray	[196]

	μM)		↑: miR-124, miR-183, miR-195, miR-339, miR-630 ↓: miR-1225, miR-139, miR-181d, miR-182, miR-196a, miR-206, miR-21*, miR-24-1*, miR-30c-1*, miR-32, miR-373, miR-383, miR-432, miR-503, miR-512, miR-518c*, miR-520d-3p, miR-548c, miR-550, miR-574-3p, miR-593, miR-622, miR-623, miR-663, miR-765, miR-769, miR-885-3p, miR-886-3p	apoptosis, cell cycle regulation, cell proliferation, and differentiation	apoptosis		
	Resveratrol (25 μM)	A549 cells	21 lncRNAs were upregulated and 19 lncRNAs The most	lncRNA AK001796 regulates multiple cell-	Cell cycle	PCR array	[88]

			upregulated was AK001796	cycle-related genes			
	Quercetin (0-100 μM)	A549 Cells	miR-16	Claudin-2	Tight junction proteins, decreases claudin-2 expression mediated by up-regulation of miR-16 expression	qRT-PCR	[200]
Colorectal cancer	Resveratrol (0–400 μM)	HCT-116 cells	↑miR-200	E-cadherin, Vimentin and ZEB1	Target apoptosis, invasion, and switching of EMT to MET	qRT-PCR	[201]
	Resveratrol (0-100 μM)	SW480 cells	22 miRNAs overexpressed and 26 downregulated Top 5 ↑: miR-146b-5p, miR-1, miR-340, miR-615, miR-801 Top 5 ↓: miR-17, miR-21, miR-25,	TGFβR1 TGFβR2, PDCD4, PTEN, and SMADs	TGFβ signalling pathway	Microarray, mutagenesis assay	[202]

			or miR-92a-2, miR-30a				
	Resveratrol (0-50 μM)	LoVo and HCT116	↓MALAT1	Wnt/β-catenin	Wnt/β-catenin signalling, leading to the inhibition of invasion and metastasis	qRT-PCR	[89]
	Resveratrol and quercetin (1:1)	HT-29	↓miR-27a	miR-27a-ZBTB10-axis related to Sp downregulation	Apoptosis	qRT-PCR	[54]
Ovarian cancer	Quercetin (0-100 μM)	SKOV-3 and A2780	↑miR-145	Caspase-3	Extrinsic death receptor-mediated and intrinsic mitochondrial apoptotic pathways.	qRT-PCR	[53]
Hepatocellular cancer	EGCG (100 μM)	HepG2 cells	Microarray: ↑let-7, miR-16, miR-18b, miR-20a, miR-25,	BCL-2 target miR-16	miR-16 in mediating the apoptotic	Microarray, qRT-PCR	[81]

			miR-92, miR-93, miR-221, miR-320 ↓miR-10a, miR-18a, miR-19a, miR-26b, miR-29b, miR-34b, miR-98, miR-129, miR-181d Validate qRT-PCR by: ↑miR-16, let-7a, miR-221; ↓miR-18a, miR34b, miR-193b, miR-221, miR-222, miR-324		effect		
	Quercetin (31.25 μM)	HepG2 and Huh7 cells	↑miR-34a	p53, SIRT1	miR-34a plays an important role in the anti-tumor effects of quercetin in HCC, via p53/miR-34a/SIRT1	Microarray	[177]
Glioblastoma	Resveratrol (1 μM)	U251 and U87	↑ NEAT1, MIR155HG, MEG3, and	N/A	Genotoxic stress-induced ce	qRT-PCR	[90]

			ST7OT1		ll death		
Melanoma	EGCG (5 μM)	B16 cells Nude mouse xenograft studies	Let-7	HMGA2	Tumour progression	Microarray and qRT-PCR	[52]

Table 4. Relevant examples related to the alteration of proteomic and metabolomic pattern by natural compounds.

Phytochemicals	Dose	Pathology	Preclinical model	End-point	Relevant mechanism	Relevant protein target	**Reference**
EGCG	0-100 μM	Urinary bladder carcinoma	TSGH-8301	Assay for mitochondrial membrane potential, proteomic analysis, Western blotting analysis, AKT kinase assay	Apoptotic BCL-2 AKT, and HSP27 pathways and	Bcl-2, Bax, BAD and p-BAD, p-BAD	[203]
	5-20 μM	Colon cancer	HCT116	MTT test, apoptosis assay, western blot	EGCG sensitized TRAIL-induced apoptosis via death receptors	Death receptors DR4 and DR5, Caspase-8	[206]
	25-	Colon	HCT1	ROS	ROS-related	Sestrin	[46]

Genistein	50 μM	Cancer	16	evaluation, MTT test, apoptosis assay, western blot	apoptosis in p53 mutant cells	2/AMPK/mTOR pathways	
	40 μM	Gastric cancer	SGC-7901 cells	Cell culture and SILAC labelling, protein digestion, Phosphopeptides enrichment using TiO2, SCX-LC–MS/MS analysis, phosphopeptides identification and quantitation, and phosphosites validation, Western blot analysis, immunoprecipitation	Phosphorylation of proteins	1177 phosphorylation sites on 635 unique proteins; among them, 320 phosphorylation sites on 222 unique phosphopeptides representing 215 non-redundant proteins. GPCRs, DCC, NCK1, TNK2, BTK, TP53BP1, BCLAF, MAX and MAG.	[204]
	40 μM	Ovarian cancer	A2780 cells	MTT test, apoptosis assay, microscopy,	Activation of apoptosis and autophagocytosis	Activation of caspase-9 and cleaved Caspase-9 (p37/35	[172]

				western blot		fragments), reducing the phosphorylation of Akt	
	1-10 μM	Hepatocellular cancer	HepG2 cells	MTT test, apoptosis assay, microscopy, western blot, qRT-PCR	Increased multidrug resistance, modulate Sorafenib cytotoxicity	Target MRP2, PXR and P-gp	[139]
Caffeic acid phenethyl ester (CAPE)	0-40 μM	Prostate cancer	LNCaP 104-R1 cells, nude mice	Micro-Western Array, cell proliferation, Western blot analysis, soft agar colony formation, cell cycle, qRT-PCR	Induced cell cycle arrest and growth inhibition Via a regulation of Skp2, p53, $p21^{Cip1}$, and $p27^{Kip1}$.	Skp2, Cdk2, Cdk4, Cdk7, Rb, phospho-Rb S807/811, cyclin A, cyclin D1, cyclin H, E2F1, c-Myc, SGK, phospho-p70S6kinase T421/S424, phospho-mTOR Ser2481, phospho-GSK3α Ser21, but induced $p21^{Cip1}$, $p27^{Kip1}$, ATF4, cyclin E, p53, TRIB3, phospho-p53 (Ser6, Ser33, Ser46, Ser392), phospho-p38 MAPK Thr180/Tyr182,	[205]

						Chk1, Chk2, phospho-ATM S1981, phospho-ATR S428, and phospho-p90RSK Ser380	

Table 5. Some examples of phytochemicals used in combination with chemotherapeutics in cancer treatment.

Phytochemicals	Chemotherapeutic	Biological systems	Biological effect	Reference
EGCG	5-Fluorouracil	Colorectal cancer cells (HCT116 a1nd SW480 CRC cells)	targets cancer stem-like cells and enhances 5-fluorouracil chemosensitivity	[210]
	Taxol	Head and neck and breast carcinoma cells.	Synergistic growth inhibition inhibits activation of HER-2/neu and downstream signalling pathway; inhibits activation of the EGFR in carcinoma cells	[207]
	Taxol	Hepatocellular cells and HCC xenograft models	Synergic antiproliferative effect in BEL-7404/DOX cells and animal models	[208]
	Doxorubicin	Hepatocellular cells (Hep3B cells)	Chemotherapeutic effect of doxorubicin increased in the presence of EGCG, mainly via autophagy inhibition.	[169]
	Cisplatin	Lung cancer cells (A549, H460 and H1299) cells, cDDP-	EGCG-mediated CTR1 induction via NEAT1/hsa-mir-98-5p crosstalk reducing	[50]

		resistant A549 nude mouse xenograft model	cisplatin resistance; p53 was elevated by silencing of miR-98-5p as response to EGCG	
	Cisplatin	Human ovarian cancer OVCAR3, SKOV3 cells and human embryonic kidney HEK-293T cells; OVCAR3 ovarian xenograft model in nude mice	Cisplatin enhances the sensitivity of the ovarian cancer cells to cisplatin via CTR1, confirmed by *in vivo* studies	[182]
	Gefitinib	Oral squamous cell carcinoma, CAL-27	Synergistic action on metastatic effect via EGFR, MMP-2 and MAPK signalling	[183]
Green tea and quercetin	Doxacetal	PC-3 xenograft prostate tumours	EGCG leads to an enhanced inhibition of PC-3 xenograft tumor growth, activation of apoptosis, Downregulation of tumor growth factors (VEGF, EGF, NGF-β, SCF, TNF-α)	[186]
Quercetin	Doxorubicin	Triple negative breast cancer (MDA-MB-231 and MDA-MB-468)	Decrease the motility induced by doxorubicin; increased the anti-tumor activity of doxorubicin by inhibiting the migratory ability of TNBC cells, via modulation of β-catenin and its target genes (cyclin D1 and c-Myc)	[45]
Genistein	Gemcitabine	Pancreatic cancer cells (AsPC-1 GR and BxPC-3 GR), nude mice	Synergistic reversal effect of EMT induced by miR-223 inhibitor and genistein in pancreatic cancer models	[211]

	Soranifeb	Hepatic cancer cells	Increased resistance to soranifeb, by activated P-gp and MRP2 at transcriptional and transcriptional level	[139]
Daidzein	Gemcitabine	Lung cancer cells (A549 and H460 cells)	Chemosensitizes the response to Gemcitabine via suppression of HSP70 expression, and an increased cell death, via caspase-3 and caspase-9 activation	[47]
Resveratrol	Doxorubicin	Breast cancer cells (MCF-7 and MDA-MB-231 cell lines)	Chemosensitizes doxorubicin in combination, through inhibiting breast cancer cells proliferation and invasion, and inducing apoptosis via suppression of chronic inflammation and autophagy.	[212]
	Doxorubicin	Human glioma cell lines (U251 and U87)	GAS5, MEG3 and ST7OT1 are up-regulated in leading to the activation of apoptosis	[90]
	Doxorubicin	Colorectal cancer cells (HCT 116 and HT-29)	Activating apoptosis and ameliorating P-glycoprotein activity	[184]
	5-Fluorouracil	Colorectal cancer cells (HCT116, SW480) and their corresponding isogenic 5-FU-chemoresistant derived clones (HCT116R, SW480R)	Chemosensitization to 5-fluorouracil through up-regulation of intercellular junctions, EMT and apoptosis	[209]

Caffeic acid phenethyl ester	Doxacetal and paclitaxel	Prostate cancer cells (PC-3, DU-145 and LNCaP)	CAPE-induced inhibition of AKT phosphorylation was more prominent in cells expressing ER-α (PC-3) compared to LNCaP. Increase chemotherapeutic effects via targeting ER-α and ER-β abundance	[113]