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Review

# Phytochemicals as Epigenetic Modulators in Chronic Diseases; Molecular Mechanism

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## Abstract

Phytochemicals are bioactive plant-derived compounds with significant antioxidant, anti-inflammatory, and epigenetic modulatory properties, offering promising avenues for the prevention and management of chronic diseases. Chronic conditions such as cancer, cardiovascular, neurodegenerative, metabolic, and autoimmune disorders often involve oxidative stress, inflammation, and epigenetic dysregulation. Evidence from *in vitro* and *in vivo* studies indicates that phytochemicals, including flavonoids, carotenoids, phenolic acids, organosulfur compounds, and terpenes, can attenuate oxidative damage by enhancing endogenous antioxidant defenses, modulate inflammatory signaling pathways such as NF- $\kappa$ B and Nrf2, and influence gene expression through the regulation of DNA methylation, histone modifications, and non-coding RNAs. Specific compounds—such as hesperidin, genistein, phloretin, lycopene, caffeic acid, p-coumaric acid, anacardic acid, allyl mercaptan, silybin, artemisinin, and geraniol—demonstrate multi-targeted actions, reversing aberrant epigenetic marks and restoring cellular homeostasis. By simultaneously acting on redox balance, inflammatory mediators, and epigenetic regulators, these natural compounds provide a mechanistic basis for chemoprevention and adjuvant therapy. However, translation into clinical applications requires rigorous trials to assess bioavailability, synergistic effects, and safety in humans. Understanding the molecular mechanisms of phytochemical action may advance novel, integrative strategies for chronic disease prevention and health promotion.

**Keywords:** phytochemicals; anti-oxidant activity; epigenetic mechanisms; anti-inflammatory activity; chemoprevention

## 1. Introduction

Phytochemicals are plant secondary metabolites, produced to act as defense molecules against external pathogens and stress induced by environmental factors [1]. They have a great chemical diversity ranging from low molecular-weight compounds, with single aromatic-ring structure, as phenolic acids to large, complex molecules as proanthocyanidins and ellagitannins [2,3]. The natural occurring compounds possess antiviral, antifungal, and antibiotic properties, along with photoprotective function and participate in plant metabolism and survival process under biotic and abiotic stress [4].

For centuries, plant-derived treatments were used to heal and alleviate acute and chronic conditions including diabetes, depression, hypertension, hypercholesterolemia, insomnia and inflammation [5,6]. According to WHO, the primary health care of almost 70-80% of world population still depends on traditional medicines based mostly on medicinal plant extracts [7].

In the past decades scientific data illustrated that natural bioactive compounds found in fruit, vegetables and medicinal plants are biocompatible with cellular and molecular target sites and often induce less toxicity to normal cells, than chemical synthetic drugs [8,9]. Several preclinical studies have reported that many phytochemicals with anti-inflammatory, anti-oxidant and anti-proliferative properties can prevent cancer initiation and development by triggering apoptosis and activating antioxidant enzymes [10,11]. Moreover, the phytochemicals can impact cellular and molecular processes by acting as substrates, cofactors or inhibitors in biochemical and enzymatic reactions. They also function as ligands, either activating or blocking cell surface or intracellular receptors, scavengers of reactive oxygen species or other toxic chemicals, and enhancers of nutrient absorption and stability [11–14]. However, the chemopreventive potential of phytochemicals, despite promising preclinical research, has not been successfully translated into clinical practice.

Nowadays, there is mounting evidence indicating that many chronic conditions such as cancer, metabolic, neurodegenerative and autoimmune disorders are triggered by epi-genetic dysregulations [15]. Epigenetic alterations can occur due to exposure at various environmental factors, such as air pollution, chemical pollutants, electromagnetic radiation and life style (e.g. alcohol consumption, poor nutrition, smoking and lack of physical activity) [16]. Generally, epigenetic refers to heritable changes in gene expression that do not involve alteration to the DNA sequence itself [17]. These changes are primarily mediated through specific mechanisms: DNA methylation (typically associated with gene silencing); post-translational modification of histone proteins (such as acetylation, methylation, phosphorylation, etc), non-coding RNAs, including microRNAs and long non-coding RNAs, which regulate gene expression post-transcriptionally [18,19].

Bioactive food components can trigger protective epigenetic changes throughout life, with early nutrition playing a particularly crucial role. These epigenetic modifications, influenced by diet and other environmental factors, can affect gene expression and potentially impact health outcomes, including the risk of chronic diseases, across a lifespan [20].

Early identification of epigenome abnormalities that may onset various pathologies and the possibility of eradicating them by using natural bioactive compounds from diet represent a new approach in prevention. The capacity of phytochemicals to modulate the epigenetic mechanisms, by reversing the aberrations related with onset and development of diverse diseases is intensively studied. All these factors can impact the epigenome and consequently might influence gene expression and biological processes

Therefore, a deeper understanding of the molecular mechanisms through which plant-derived compounds exert antioxidant and anti-inflammatory effects is needed to clarify their impact on human health. Further research into these mechanisms is crucial for developing new therapeutic strategies and promoting overall well-being.

This review aims to introduce the role of phytochemicals as natural bioactive compounds capable of modulating key molecular and epigenetic mechanism involved in the prevention and management chronic diseases. It highlights their antioxidant, anti-inflammatory, and gene-regulatory functions, emphasizing the potential of plant-derived compounds to influence human health by reversing or preventing pathological processes triggered by environmental and lifestyle-related factors. Furthermore, this review seeks to present current scientific evidence on chemopreventive properties of phytochemicals and to underscore the need for further research to translate these findings into effective clinical application.

## 2. Epigenetic Dysregulations in Chronic Diseases

In the past decades, many scientific reports have highlighted the essential role of the altered expression and function of epigenetic-regulatory proteins in the onset and development of various chronic diseases [21].

Epigenetic mechanisms are the main regulators of gene expression through chemical modifications of DNA, histones and RNA. For example, the transformation of a condensed chromatin region (heterochromatin), which is transcriptionally inactive into euchromatin as transcriptionally active structure, is achieved through the addition of methyl or acetyl groups to histone proteins. The addition of these chemical radicals along with gene's promoter demethylation can loosen the chromatin structure, making DNA more accessible to the transcriptional machinery [22,23].

Enzymes that regulate epigenetic modifications are categorized into "writers," "erasers," "readers," and "remodelers" based on their functions [24]. Writers are adding the specific chemical groups on DNA or RNA bases or histone's amino acids, whereas erasers are acting in reverse by removing these modifications. For instance, DNA methyltransferase (DNMT) catalyzes the addition of methyl groups to form 5-methylcytosine (m5C) in gene's promoter DNA sequence [25], whereas the ten-eleven translocation (TET) enzymes initiate DNA demethylation process by converting m5C into other derivatives, such as 5-hydroxymethylcytosine (5hmC), [26]. Typically, transcriptionally active genes exhibit a lower methylation pattern, whereas inactive genes or with a lower expression level are heavily methylated. Readers are proteins that recognize and bind to these chemical modifications, such as the methyl-CpG-binding domain (MBD) which is able to recognize 5mC [27]. The reader proteins are dynamically influencing chromatin status and by recruiting or collaborating with other protein complexes are regulating gene expression [28].

Remodelers such as SWI/SNF family, which possess DNA-stimulated ATPase activity are involved in nucleosome disruption with a crucial role in chromatin accessibility. They achieve this by disrupting nucleosomes and either moving or removing them from key regulatory regions like enhancers and promoters, thus influencing gene expression [29]. Furthermore, there are unique classes of epigenetic regulators, represented by non-coding RNAs (ncRNAs) which directly bind to various genomic regions or specific RNA sequences to modulate gene expression [30].

The long non-coding RNAs (lncRNAs) have a variety of functions and importantly they can interact with proteins, DNA sequences, RNAs regulating directly or indirectly the whole epigenetic machinery, by affecting gene expression and chromatin organization [31,32].

When epigenetic regulators, either epigenetic enzymes or ncRNAs expression, become imbalanced—by being excessively active or insufficiently functional—they disrupt cellular homeostasis and could induce the development of diseases [33]. Consequently, by investigating these individual epigenetic alterations such as DNA methylation, histone modifications and ncRNAs dysfunctional expression, represents a promising opportunity for chronic disease therapy, fueling the creation of targeted treatments [34,35]. As an example, the abnormal epigenetic mechanisms are present at various stages of cancer development, including initiation, progression, invasion, migration, and chemotherapy resistance. DNA methylation patterns are changes with hypermethylation of specific tumor suppressors and hypomethylation of oncogenes promoters, which drives tumor development [36]. The silencing of tumor suppressor and DNA repair genes leads to the disruption of normal cell proliferation and differentiation and fostering the malignant phenotype of tumor cells [37]. Moreover, DNA methylation loss in oncogene promoter regions, and extensive demethylation of DNA repetitive sequences, compromises the chromatin stability, facilitating tumor development. [38].

For metabolic disorders the physiological conditions, the pre-existence of genetic mutations and also the exposure to environmental factors, such as dietary patterns can significantly influence the epigenome [39]. Several studies have shown that in mice feed with high-fat diet the hypermethylation of the promoters of genes like Rac family small guanosine triphosphate hydrolase (GTPase), PPAR $\alpha$  and others is linked with retinal damage and microangiopathy in diabetic retinopathy models [40,41].

Diet-induced epigenetic modifications can affect future generations, heightening their susceptibility to metabolic diseases, including diabetes, non-alcoholic fatty liver disease and others. Furthermore, diet-related epigenetic changes have been observed impacting the function of epigenetic regulators enzymes along with their cofactors, such as TET enzymes and  $\alpha$ -ketoglutarate ( $\alpha$ -KG) derived from the tricarboxylic acid (TCA) cycle, in metabolic disorders [21,42]. This disruption further impairs epigenetic regulation and accelerates disease progression.

Thus, the reversible characteristics of epigenetic modifications that regulate the activation or inhibition of enzymes may serve as promising targets and valuable tools for understanding cellular and biological processes.

### 2.1. Oxidative Stress Impacting Epigenetic Mechanisms

The most studied property of plant-derived natural compounds is their antioxidant capacity. The scavenging of reactive oxygen species (ROS) is thought to be an effective measure to depress the level of oxidative stress in cells.

ROS are represented by free radicals such as hydrogen peroxide, hydroxyl radical ( $\text{OH}^-$ ), peroxy radical ( $\text{ROO}^-$ ), superoxide anion radical ( $\text{O}_2^-$ ), and singlet oxygen, among others, which are necessarily produced in the human body as a result of normal physio-logical occurring processes, and also by exposure to environmental stressors. Oxidative stress emerges when the balance between the levels of ROS exceeds and cellular antioxidant defense system is overwhelmed [43].

Oxidative stress is a key modulator of the cellular environment, often leading to alterations in gene expression via epigenetic modifications. The imbalance between pro-oxidant species and antioxidant defenses can lead to changes in DNA methylation patterns, histone modifications, and non-coding RNA expression, which collectively impact chromatin structure and gene transcription. For instance, oxidative stress induces the formation of 8-oxo-2'-deoxyguanosine (8-oxo-dG), a DNA lesion that recruits repair machinery but also affects the local methylation status, potentially silencing tumor suppressor genes or activating oncogenes [44]. Such oxidative DNA damage has been linked to disrupted DNMT activity and subsequent global DNA hypo-methylation [45].

Multiple lines of scientific evidence have linked oxidative stress process to pathophysiology associated with various diseases including cancer [46,47]. The ROS can effectively induce DNA damage by nucleotide alterations, DNA strand breakage and mutations within genome of normal cells and thus promote further disease related transformation. Moreover, ROS are able to activate certain transcription factors including NF- $\kappa$ B, cyclooxygenases (COX), p53, HIF-1 $\alpha$ , PPAR- $\gamma$ ,  $\beta$ -catenin/Wnt, and Nrf2, that leads to the expression of over 500 different genes, including growth factors, pro and anti-inflammatory cytokines, cell cycle regulatory molecules. [48,49]. Moreover, Nrf2, a crucial transcription factor that acts as a master regulator of cellular defense mechanisms against oxidative stress, electrophiles, and other harmful substances, is capable to influence epigenetic mechanisms by modulating histone acetylation and deacetylation [50]. This activity reshapes the cell's epigenetic landscape, impacting gene expression in response to oxidative stress [51].

Besides, the ROS can influence the DNA methylation pattern by directly oxidizing the catalytic site of DNMTs or by reducing the availability of the DNMT cofactor S-adenosyl methionine, SAM [52]. Cellular ROS levels themselves have been suggested to be the subject of epigenetic modulation. Thereby, ROS-generating systems of mitochondria and, including different subunits of the NOX complex, as well as antioxidant enzymes such as SODs and catalase, have been reported to be epigenetically regulated by different mechanisms [53]. ROS can modulate the activity of other epigenetic regulators such as histone acetyltransferases (HATs) and histone deacetylases (HDACs), influencing the histone acetylation epigenetic mechanism and thus inducing dysregulated gene expression in cancer and cardiovascular disorders [52].

Phytochemicals are highly bioactive molecules, yet a particular class, namely phenolics (phenolic acids, flavonoids), are the most abundant and exert the highest anti-oxidant activity in cellular environment [53,54].

Different mechanisms underlie the antioxidant capacity of phytochemicals, including the free-radical scavenging, hydrogen atom donation, ferric or cupric ions chelation, single oxygen quenching, and acting as a substrate for superoxide and hydroxyl radicals (Figure 1) [11,55]. The antioxidant activity of phytochemicals relies also on their capacity to inhibit essential enzymes responsible to the endogenous production of reactive oxygen species (ROS) such COXs, cytochrome P450 (CP450), lipoxygenase (LO), NADPH oxidase (NOX), nitric oxide synthases (NOSs) and xanthine oxidase (XO) [56]. The production of these enzymes is increased during inflammatory conditions; thus, inhibiting them can prevent ROS over-production, thus mitigating the associated cellular damage and inflammatory [57]. Since mediators of inflammation play key role in various pathologies, like cancer, metabolic and neurodegenerative disorders, the natural bioactive compounds might exert simultaneously anti-oxidant and anti-inflammatory activities [58].

In the view of recent scientific reports, the main molecular mechanism of phytochemicals acting to reduce cellular oxidative stress is by activating the Nrf2 pathway, which boosts antioxidant defense systems and diminishes inflammation [59,60]. Phytochemicals activate the Nrf2 pathway to combat oxidative stress primarily by modifying Keap1, the central negative regulator of Nrf2, or by promoting phosphorylation of Nrf2. Under normal conditions, Nrf2 is bound to Keap1 in the cytoplasm, which leads to its ubiquitination and degradation [61]. When phytochemicals induce oxidative or electrophilic stress, they cause conformational changes in Keap1 or directly modify it, leading to the release of Nrf2. Freed Nrf2 then translocate to the nucleus, where it forms heterodimers with Maf proteins and binds to antioxidant response elements (AREs) in the DNA. This binding initiates the transcription of various antioxidant and detoxification genes, such as heme oxygenase-1 (HO-1), glutathione-S-transferase (GST), and NAD(P)H quinone dehydrogenase 1 (NQO1), which enhance cellular antioxidant defenses and reduce oxidative damage [62,63].

At the same time, the phytochemicals influence epigenetic processes acting as epigenetic modulators primarily inhibiting the key epigenetic enzymes, including DNMTs, HDACs, HATs, BETs [64].

Moreover, the phytochemicals can directly donate the methyl group and act as co-substrates in DNA, RNA or histone methylation process or indirectly by affecting the methyl pool [25].

The combined action, as anti-oxidants, anti-inflammatory molecules and epigenetic modulators the phytochemicals represent valuable candidates for disease prevention and treatment through coordinated regulation of redox balance, inflammation process and epigenetic mechanisms(Figure 1).

## 2.2. Epigenetic Dysregulations in Inflammation Process

Inflammation is a highly dynamic and tightly regulated biological response, essential for defending the body against infections, injuries, and other harmful stimuli [65]. However, when the mechanism of controlling inflammation becomes dysregulated, the results can be chronic inflammatory states that contribute to wide range of diseases, from autoimmune disorders to cancer and cardiovascular pathologies [66]. Epigenetic mechanisms are increasingly recognized for their essential role in inflammation. They act as modulators of normal inflammatory responses by fine-tuning the protein expression and also as drivers of pathological inflammation when disrupted [67].

Epigenetic dysregulation is increasingly recognized as a critical factor in modulating inflammation and immune responses. DNA methylation plays a dual role, either suppressing or activating key pro-inflammatory genes. Aberrant activity of DNA methyltransferases (DNMTs) can lead to inappropriate methylation patterns that sustain chronic inflammation by silencing anti-inflammatory genes. For example, DNMT3B has been shown to hypermethylate promoter regions of tumor suppressor genes, thereby contributing to sustained inflammatory signaling [45].

During an inflammatory response, immune cells such as macrophages, dendritic cells, and lymphocytes undergo rapid changes in gene expression [68]. This transcriptional reprogramming is orchestrated in part by epigenetic modification, which enable these cells to quickly activate or repress large sets of genes in response to signals like cytokines, pathogen-associated molecular patterns

(PAMPs), or damage-associated molecule patterns (DAMPs) [69–71]. Epigenetic control not only dictates which genes are expressed, but also how quickly and intensely cells react to danger signals [72].

Multiple epigenetic modifications may occur in a large number of diseases connected or related to inflammatory processes. For instance, the most investigated class of diseases, cancers, are often associated with epigenetic deregulation, that can occur at tumoral stroma or in immune cells. Epigenetics includes a series of reversible modifications that do not include gene mutations, which are strongly modulated by internal environment, mainly that is located close to the tumoral processes. In this way the pro-inflammatory surrounding the tumor can be responsible for the induction of epigenetic modifications [73,74].

Yang [75] analyzed the implications of epigenetic modifications – DNA methylation, chromatin remodeling, regulation of non-coding RNAs, histone changes – during the progression from chronic inflammation to colorectal cancer. The study also outlined the accelerating effects of such changes on the activation of cancer signaling pathways. Among these, of notable impact appear to be NF- $\kappa$ B, and STAT3 pathways. A similar analysis was provided by Pandareesh et al., for the case of prostate cancer, with an almost identical distribution and interaction between epigenetic factors, tumor environment and pro-inflammatory environment. [76].

When epigenetic controls mechanism malfunction, the balance between pro-inflammatory and anti-inflammatory pathways can be disrupted [71,77]. For instance: aberrant DNA methylation patterns may silence anti-inflammatory genes (e.g. IL-10) or abnormally activate pro-inflammatory ones, such as IL-6 or TNF- $\alpha$  [78–80]. Moreover, histone modification can alter chromatin accessibility, maintain certain genes in a persistently active state, even in the absence inflammatory stimuli, for example, increased histone acetylation of NF- $\kappa$ B target gene promoters has been linked to sustained inflammation in rheumatoid arthritis and inflammatory bowel disease [81–83]. Notable, non-coding RNAs, such as miR-155 or miR-21 are often overexpressed in chronic inflammation and can modulate immune cell differentiation, cytokine production, and apoptosis resistance [84,85]. The eraser proteins HDACs inhibition leads to increased histone acetylation, opening chromatin and facilitating the expression of anti-proliferative and regulatory genes like p21 [86,87]. The p21 gene plays a multifaceted role in cellular processes. It acts as a cyclin-dependent kinase (CDK) inhibitor, primarily inhibiting CDK2 and CDK1, which are crucial for cell cycle progression [88]. This inhibition leads to cell cycle arrest, particularly at the G1/S and G2/M transitions, preventing uncontrolled cell division and promoting genomic stability after DNA damage. Beyond cell cycle regulation, p21 also influences the cellular environment through the secretion of bioactive molecules, contributing to immunomodulatory functions and potentially aiding in the resolution of inflammation [89].

Histone modifications further contribute to inflammation-driven gene expression. Pro-inflammatory cytokines like TNF- $\alpha$  and IL-6 are regulated by dynamic histone acetylation and methylation at their promoter regions, with histone acetyltransferases (HATs) enhancing expression and histone deacetylases (HDACs) serving as brakes on transcription. Natural polyphenols such as resveratrol and quercetin have been shown to modulate these enzymes, reducing pro-inflammatory histone marks while enhancing the expression of anti-inflammatory genes [90].

Non-coding RNAs, especially microRNAs (miRNAs), play a pivotal role in fine-tuning inflammation. For instance, miR-146a suppresses NF- $\kappa$ B signaling, a master regulator of inflammation. Under oxidative stress conditions, miR-146a expression can be epigenetically downregulated, leading to sustained inflammation [44]. This highlights a complex interplay between ROS, epigenetic mechanisms, and inflammation.

Interestingly, dietary polyphenols may exert protective effects on inflammation also, through modulation of Nrf2, that coordinates antioxidant responses and modulates inflammatory pathways. By activating the Nrf2-ARE pathway, compounds like curcumin, sulforaphane, and EGCG (epigallocatechin gallate) can upregulate antioxidant genes while simultaneously downregulating pro-inflammatory mediators [51]. This dual action highlights their potential as epigenetic modulators in chronic inflammatory diseases.

Furthermore, recent evidence from a clinical study suggests that polyphenol-rich diets can alter epigenetic aging markers in immune cells, indirectly influencing inflammation status [91]. Such interventions might slow down immunosenescence and mitigate inflammation-associated disorders.

Notably, such epigenetic changes can affect not only immune cells but stromal and epithelial cells within the inflamed microenvironment, contributing to persistent tissue remodeling and fibrosis [74].

Another field of major interest is coronary artery disease, where, on one hand, disease progression, in which epigenetic changes – such as histone methylation, phosphorylation and acetylation, play key roles. Besides these, the lncRNAs, miRNAs and circRNAs are also involved in epigenetic processes, and help the regulation of gene expression in response to environmental factors and lifestyle. Such modifications in de-regulation of genes regulating vascular function, inflammation, lipid metabolism or oxidative stress [92,93].

Collectively, this epigenetic modification can act as a form of inflammatory memory, locking cells into a pro-inflammatory state even after the initial trigger has passed [69]. This phenomenon is especially evident in chronic diseases like atherosclerosis, rheumatoid arthritis, and asthma, where immune cells show persistent activation profiles [94].

A defining feature of epigenetic regulation is its plasticity of epigenetic marks that are not static and can be influenced by environmental exposures [95]. Factors such as smoking, diet, psychological stress, pollution, infections, and gut microbiota derived metabolites can all modify the epigenetic landscape [96,97].

For instance, short-chain fatty acids like butyrate, produced by commensal bacteria, can inhibit HDACs and thereby affect gene expression in immune cells [98]. Similarly oxidative stress resulting from environmental pollutants can trigger histone modification that amplifies inflammatory gene transcriptions [99,100]. These influences suggest that chronic exposure to harmful environmental factors may not only trigger inflammation but may epigenetically fix it into the biology of the tissues [101,102].

Even subtle lifestyle factors, such as circadian rhythm disruption or chronic low-grade stress, may modulate the expression of inflammatory genes through epigenetic routes [103]. These influences suggest that chronic exposure to harmful environmental factors may not only trigger inflammation but may epigenetically fix it into the biology of the tissue [104].

Of interest is also the fact that natural compounds, for instance naringenin and naringin (pharmacologically active in anti-cancer and anti-cardiovascular diseases, displaying anti-oxidant and anti-inflammatory activities), are also involved in epigenetic mechanisms, thus broadening the mechanisms in supporting restoration of health [105,106].

Overall, the integration of dietary components, oxidative stress, and epigenetic alterations forms a complex network that modulates inflammation. Targeting these pathways through nutraceuticals offers a promising avenue for managing chronic inflammation-related diseases.

The reversibility of epigenetic marks makes them attractive targets for novel therapeutic strategies. Drugs that inhibit DNMT1 or HDACs are already being explored in cancer therapy but they show promise in treating chronic inflammatory diseases as well. By reprogramming immune cells epigenetically either to reduce their inflammatory potential or restore tolerance such intervention could offer more precise and durable solution than broad spectrum immunosuppressants [107]. For example, HDAC inhibitors may promote the expression of p21 and other regulatory genes, helping to dampen persistent inflammation. Similarly, DNMT inhibitors could potentially reactivate silenced anti-inflammatory genes or detoxifying enzymes like GSTP1, restoring homeostasis in chronically inflamed tissues [108].

### 3. Phytochemicals as Antioxidant, Anti-Inflammatory Agents with Epigenetic Modulator Capacities

Chronic inflammation and oxidative stress are fundamental contributors to the pathogenesis of numerous non-communicable diseases, including cardiovascular disorders, cancer,

neurodegenerative conditions, diabetes, and autoimmune syndromes. Oxidative stress arises from an imbalance between reactive oxygen species and the antioxidant defense system, which may induce also the inflammation by elevating the levels of pro-inflammatory mediators and cytokines. These two pathological states are tightly interconnected and often exacerbate one another, creating a self-perpetuating cycle of tissue damage and immune dysregulation [109,110].

In recent years, phytochemicals found in fruit, vegetables, herbs, and medicinal plants have gained significant attention for their ability to counteract oxidative and inflammation damage. These compounds include flavonoids, phenolic acids, terpenoids, alkaloids, and organosulfur compounds, many of which possess strong radical-scavenging capabilities and modulate inflammatory signaling pathways such as NF- $\kappa$ B, Nrf2, PI3K/Akt, and MAPKs (Table 1) [111,112].

Unlike conventional pharmaceuticals, phytochemicals often have multi-target potential, by modulating cellular processes simultaneously, with lower toxicity profiles. For instance, flavonoids enhance antioxidant enzymes activities, such as SOD, CAT, GSH, while simultaneously inhibiting pro-inflammatory mediators like TNF- $\alpha$ , IL-6 and COX-2 through suppression of transcription factors and kinases [113–115]. These mechanisms not only alleviate oxidative stress but also reduce systemic and local inflammation, contributing to disease prevention and adjunctive therapy. Notably, flavonoids represent a structurally diverse class of compounds-including flavonols, flavones, flavanones and anthocyanidins each with distinct bioactivities and tissue selectivity [116]. This diversity allows them to modulate also a broad range of molecular targets implicated in inflammation, oxidative damage, and metabolic imbalance [117]. The phytochemicals multi-target capacity supports their potential in disease prevention and adjunctive therapy.

In Table 1 are presented the phytochemicals with in vitro demonstrated anti-oxidant, anti-inflammatory and potential epigenetic modulator capacities.

**Table 1.** Example of phytochemicals with antioxidant, anti-inflammatory activities and epigenetic modulator capacity, investigated in vitro.

Class of compound	Phytochemicals	Type of study	Antioxidant	Anti-inflammatory	Epigenetic modulator	References
	Hesperidin	MCF-7 (50 $\mu$ M)	Increases activities of SOD, CAT, GSH; reduces lipid peroxidation; Activates Nrf2	Reduces expressions of TNF- $\alpha$ , IL-6 expression	Inhibits DNMT1; hypo-methylation of p16 promoter	[118–120]
Flavonoids	Phloretin	RAW 264.7 macrophages (25 $\mu$ M); A549 cells	Inhibits ROS production and increases GSH activity	Suppresses NF- $\kappa$ B activation and reduces iNOS and COX-2 expression	Inhibits HDAC; increases histone acetylation, p21 expression	[121–123]
	Genistein	MCF-7, PC3, HL-60 cells	Increases antioxidant enzymes, reduces lipid peroxidation	Reduces pro-inflammatory cytokines (IL-6, IL-1 $\beta$ ) expression via NF- $\kappa$ B	Inhibits DNMT1, demethylates and reactivates tumor suppressor genes	[124–127]
Phenolic acids	Caffeic acid	Caco-2, HeLa cells (20 $\mu$ M)	Neutralizes free radicals and boosts	Inhibits pro-inflammatory cytokines and	Inhibits DNMT; DNA	[128–130]

			antioxidant enzymes	NF- $\kappa$ B activation	hypomethylation; gene reactivation	
	Coumaric acid	LPS-stimulated RAW 264.7 cells; MDA-MB-231 cells (30 $\mu$ M)	Free radical scavenger and increases SOD activity	Reduces NO production and COX-2 expression	Inhibits HDAC; increases histone acetylation	[131–133]
Terpenoids	Lycopene	HepG2, PC3 cells (10 $\mu$ M)	Reduces ROS and increases antioxidant enzyme activity	Inhibits COX-2 expression and lowers prostaglandin E2 levels		
	Silibinin	HepG2, DU145 cells (50 $\mu$ M)	Increases SOD and CAT activity; reduces lipid peroxidation	Inhibits pro-inflammatory cytokines and NF- $\kappa$ B activation	Inhibits DNMT and HDAC; hypomethylation and histone acetylation	[134–136]
Sesquiterpenoids	Artemisinin	HeLa cells (50 $\mu$ M)	Reduces oxidative stress by lowering ROS and activating Nrf2	Inhibits IL-1 $\beta$ , TNF- $\alpha$ , and COX-2 expression	—	[137]
Mono-terpenoids	Geraniol	RAW 264.7 macrophages (50 $\mu$ M)	Reduces ROS production and increases GSH activity	Suppresses NO, IL-6, and TNF- $\alpha$ production by inhibiting NF- $\kappa$ B	—	[138]
Organo-sulfur compounds	Allyl mercaptan	HUVEC, HT-29 cells (15 $\mu$ M)	Enhances antioxidant enzyme activity and reduces ROS	Inhibits adhesion molecules and reduces vascular inflammation	Inhibits HDAC; increases histone acetylation; gene reactivation	[139–142]

Hesperidin, a bioactive flavonoid predominantly found in citrus such as orange lemons has demonstrated significant antioxidant and anti-inflammatory properties, particularly in the context of breast cancer [143,144]. In vitro studies on MCF-7 breast cancer cells treated with 50  $\mu$ M hesperidin revealed an increase in antioxidant enzymes such as SOD, CAT, and glutathione, alongside a reduction in lipid peroxidation [145]. These effects are attributed to the activation of the Nrf2 signaling pathway, which plays crucial role in cellular defense against oxidative stress. Furthermore, hesperidin significantly decreased the expression of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 by inhibiting pathway, thereby modulating inflammation within the tumor microenvironment [146,147]. These findings underscore hesperidin's potential as therapeutic agent managing oxidative stress and inflammation in breast cancer models [148]. Beyond this antioxidant and anti-inflammatory activities hesperidin also exerts epigenetic modulatory effects. Studies have demonstrate that hesperidin can reduce global DNA methylation levels by inhibiting DNA methyltransferases (DNMTs) particularly in cancer models [149]. In vitro and in vivo models of

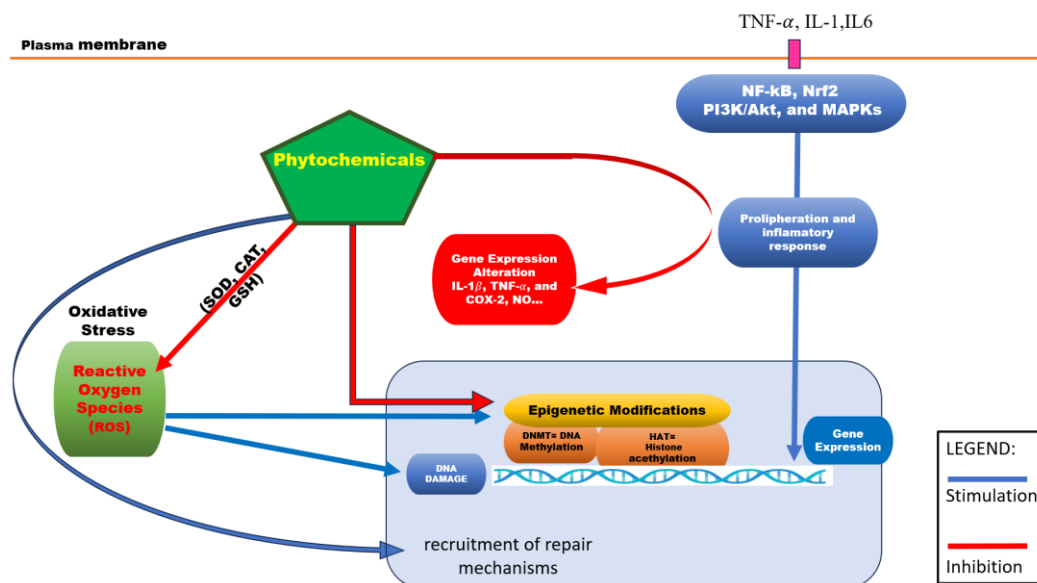
cancers have shown that hesperidin downregulates hypermethylation of repetitive DNA elements, such as KINE-1 and ALU sequences, and modulates microRNA expression, including the upregulation of tumor-suppressive miR-34a and downregulation of oncogenic miR-221 [150]. These epigenetic modifications contribute to the reactivation of tumor suppressor genes and the inhibition of oncogenic pathways, further supporting hesperidin's role in cancer and chemoprevention. These findings suggest that hesperidin supports human health through several interconnected mechanisms. By enhancing antioxidant defenses, reducing harmful inflammation, and influencing epigenetic processes that control gene activity, hesperidin shows great promise as a natural compound that could help prevent or support the treatment of cancer in an integrative approach.

Genistein is a naturally occurring isoflavone, it is predominantly found in leguminous plants, especially soybeans (*Glycine max*), where it exists mainly in its glycosylated form, genistin [151]. Genistein exhibits a spectrum of biological activities beyond its well known estrogenic and anti-cancer effects, including moderate antioxidant and anti-inflammatory actions, as well as epigenetic mechanisms regulator [152,153]. This compound exerts moderate but significant antioxidant effects, primarily by reducing ROS [57] and enhances the activities of antioxidant enzymes such as SOD, catalase CAT and glutathione peroxidase, largely via Nrf2 signaling pathway [154]. These effects stabilize redox balance and protect cellular components from oxidative damage especially under inflammation or tumorigenic conditions. In addition to its redox balancing effects, genistein demonstrated anti-inflammatory activity by downregulation the Nf- $\kappa$ B signaling pathway and suppressing the expression of pro inflammatory cytokines [155] such TNF- $\alpha$ , Il-6, and Il-1 $\beta$  [156].

Genistein also inhibits the activity of enzymes like COX-2 and iNOS, further reducing the inflammatory response [157]. This is particularly relevant in chronic diseases where low-grade inflammation plays a pathogenic role in atherosclerosis and arthritis. One of genistein most compelling biological features is its ability to modulate epigenetic mechanisms by inhibiting DNMTs, especially DNMT1, leading to reactivation of silenced tumor suppressor genes such as p16, RASSF1A and BRCA1 [158,159]. Recent findings also suggest that genistein can modulate the activity sirtuins and potentially interact with TET-enzymes, impacting DNA demethylation processes and metabolic-epigenetic crosstalk [160].

Phloretin, a dihydrochalcone flavonoid predominantly found in apples, has demonstrated notable antioxidant and anti-inflammatory properties (10.3390/molecules24020278). In vitro studies utilizing RAQ 264.7 macrophages treated with 25  $\mu$ M phloretin have shown a significant reduction in reactive oxygen species (ROS) production and an enhancement of intracellular GSH levels, indicating its potential in mitigating oxidative stress [161].

Furthermore, phloretin has been observed to suppress the activation of nuclear factor kappa B (NF- $\kappa$ B), a pivotal transcription factor in the inflammatory response. This suppression leads to the downregulation of pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Additionally, phloretin modulates the mitogen-activated protein kinase (MAPK) pathways, including extracellular signal-regulated kinase (ERK), c-Jun-n-TERMINAL KINASE (JNK), and p38 MAPK [162]. These findings are supported by Leet et al, which demonstrated that phloretin attenuates lipopolysaccharide-induced acute lung injury in mice via blockade of the NF- $\kappa$ B and MAPK pathways [163]. These pathways are integral to the production of pro-inflammatory mediators [161]. The combined modulation of these signaling pathways by phloretin suggests its potential application in managing chronic inflammatory conditions and cardiovascular diseases [164,165].



**Figure 1.** Role of phytochemicals in cell survival and metabolism. Phytochemicals act as homeostatic factors for cells: They intervene directly on ROS by modulation of SOD, CAT and GSH activity. At the same time, they promote recruitment of repair mechanisms to counteract the DNA damage done by ROS, thus promoting survival of the cells. Phytochemicals counteract the epigenetic effects of ROS by directly modulating DNA methylation and histone acetylation. Alongside these cell survival effects, phytochemicals interact with some extracellular proliferation and inflammation signals, by inhibiting their internal pathways, thus altering gene expression of NO, Cox2, IL1B, TNF- $\alpha$  and their subsequent pro-proliferative effects. .

In addition to these well-established antioxidant and anti-inflammatory actions, emerging evidence highlights phloretin's potential role as an epigenetic modulator. According to recent findings, phloretin can inhibit DNA methyltransferases (DNMTs), enzymes responsible for adding methyl groups to DNA and often involved in the silencing of tumor suppressor genes [45]. By modulating DNA methylation patterns, phloretin may help restore normal gene expression profiles that are disrupted in various chronic diseases, including cancer. Although further research is needed to clarify its impact on histone modification and microRNA regulation, these initial insights suggest that phloretin's health benefits extend beyond redox and inflammatory pathways to include epigenetic regulation of gene expression. Altogether, these multiple molecular action-combining antioxidant, anti-inflammatory, and epigenetic modulatory effects position phloretin as a promising candidate for managing chronic inflammatory diseases, metabolic disorders and cancer prevention.

Lycopene a lipophilic carotenoid found in tomatoes and watermelon acts, as a potent scavenger of ROS in HepG2 cells [166]. At a concentration 10  $\mu$ M lycopene reduced ROS levels and increased antioxidant enzyme activity [167]. Additionally, it inhibited COX-2 expression and decreased prostaglandin E2 synthesis, indicating an anti-inflammatory effect. Lycopene also modulates transcription factors such as AP-1 and STAT3, suggesting its potential for liver cancer prevention and hepatic inflammation reduction [168]. In addition to these well-established effects, lycopene also exerts epigenetic modulatory activity. According to recent findings, lycopene can influence DNA methylation patterns by inhibiting DNA methyltransferases (DNMTs). This inhibition may contribute to the reactivation of silenced tumor suppressor genes and the correction of aberrant gene expression associated with carcinogenesis. While further research is needed to fully elucidate its effects on histone modification and non-coding RNAs, these early insights suggest that lycopene contributes to regulation of gene activity through epigenetic pathways, adding a new layer to its chemopreventive potential [169]. Overall, these findings suggest that lycopene supports liver health through several complementary actions. By reducing oxidative stress, calming inflammation, and influencing gene activity through epigenetic mechanism, lycopene shows promise to reduce the risk of liver cancer. [45]

Caffeic acid, a hydroxycinnamic acid prevalent in coffee, fruits, and vegetables, has demonstrated significant antioxidant and anti-inflammatory properties, particularly within intestinal epithelial cells [169,170]. In vitro studies utilizing Caco-2 cells treated with 20  $\mu$ M caffeic acid have shown a notable reduction of ROS production and an enhancement of endogenous antioxidant enzyme activities, including SOD, CAT, and GSH [171,172]. These effects are primarily mediated through the activation of Nrf2 signaling pathway, which plays a crucial role in cellular defense against oxidative stress [173,174].

Moreover, caffeic acid has been observed to inhibit the activation of nuclear factor kappa B NF- $\kappa$ B, a key transcription factor involved in the inflammatory response [175]. This inhibition leads to a decrease in the secretion of pro-inflammatory cytokines, such as interleukin-8 (IL-8), thereby mitigating inflammation within the intestinal environment [176]. Additionally, caffeic acid modulates the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) signaling pathways, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK [177]. These pathways are integral to the regulation of cellular responses to oxidative stress and inflammation [178].

Collectively, these findings suggest that caffeic acid exerts protective effects against oxidative stress and inflammatory conditions in intestinal epithelial cells, highlighting its potential therapeutic applications in managing intestinal inflammation and related disorders [179].

These antioxidant and anti-inflammatory mechanism, caffeic acid has also been identified as a modulator of epigenetic processes.

Recent research highlights its capacity to influence DNA methylation and histone modifications, two key mechanism controlling gene expression without altering the underlying DNA sequence [180]. Specifically, caffeic acid has been shown to inhibit the activity of DNA methyltransferases (DNMTs), potentially reversing abnormal gene silencing associated with chronic diseases such as cancer and inflammatory disorders. Moreover, caffeic acid may impact histone acetylation and methylation states, further contributing to the regulation of genes involved in oxidative stress responses, inflammation and cellular homeostasis.

These findings show that caffeic acid protects intestinal cells not only by reducing oxidative stress and inflammation but also by helping restore healthy gene activity, making it a promising natural compound for managing intestinal disorders.

p-Coumaric acid, a naturally occurring hydroxycinnamic acid found in foods like red wine and balsamic vinegar, exhibits significant antioxidant and anti-inflammatory properties [181,182]. In vitro studies using lipopolysaccharide (LPS)-simulated RAW 264.7 macrophages have demonstrated that treatment with p-coumaric acid at concentration ranging from 10 to 100  $\mu$ g/mL effectively reduces the production of nitric oxide (NO) and suppresses the expression of pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) at both mRNA and protein levels [131,183].

The anti-inflammatory effects of p-coumaric acid primarily mediated through the inhibition of the nuclear factor kappa B (NF- $\kappa$ B) signaling pathway. Specifically, p-coumaric prevents the phosphorylation and subsequent degradation of I $\kappa$ B $\alpha$ , an inhibitor of NF- $\kappa$ B, thereby blocking the translocation of the NF- $\kappa$ B p65 subunit into the nucleus and reducing the transcription of pro-inflammatory genes [131].

Additionally, p-coumaric acid modulates the mitogen-activated protein kinase (MAPK) pathways by inhibiting the phosphorylation of extracellular signal-regulated kinase (ERK1/2) and c-Jun N-terminal kinase (JNK), which are crucial in the expression of inflammatory mediators [184].

Beyond its effects on macrophages, p-coumaric acid has been shown to exert protective effects against atherosclerosis. In studies involving THP-1 macrophages treated with oxidized low-density lipoprotein (ox-LDL) and LPS, p-coumaric acid at 20  $\mu$ M significantly inhibited lipid accumulation and foam cell formation. This effect is attributed to the upregulation of cholesterol efflux-related genes, such as ATP binding cassette transporter A1 (ABCA1), liver X receptor alpha (LXR $\alpha$ ), and peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), and the downregulation of lipid uptake

related genes, including lecithin-like oxidized low-density lipoprotein receptor-1 (LOX-1), cluster of differentiation 36 (CD36), and scavenger receptor class A1 (SR-A1). Furthermore, p-coumaric acid suppressed the expression of NF- $\kappa$ B, COX-2, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), indicating its potential role in mitigating inflammatory response associated with atherosclerosis. These findings suggest that p-coumaric acid hold promise as a therapeutic agent in managing oxidative stress-related inflammatory diseases, such as atherosclerosis, by modulating key. Inflammatory signaling pathways and promoting cholesterol homeostasis [185].

Anacardic acid, a phenolic lipid predominantly found in cashew nuts (*Anacardium occidentale*) and mango seeds, has gained attention for its potent neuroprotective properties, particularly in the context of neurodegenerative diseases such as Parkinson's and Alzheimer's [186].

In a study by Augusto et al (2020), purified anacardic acid (AAs) were administered at a dose of 50mg/kg in a rotenone induced mouse model Parkinson's disease. The treatment led to a significant reduction in lipid peroxidation and NO levels, alongside an increase in the glutathione (GSH)/oxidized glutathione (GSSH) ratio in both the substantia nigra and striatum regions of the brain. These changes indicate a restoration of redox balance and mitigation of oxidative stress-induced neuronal damage [187].

Furthermore, the study observed that AAs attenuated the activation of nuclear kappa B (NF- $\kappa$ B) and reduced the expression of pro-inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ). This anti-inflammatory effect was complemented by the downregulation of matrix metalloproteine-9 (MMP-9) and glial fibrillary acid protein (GFAP), markers associated with neuroinflammation and astrogliosis.

In addition to its neuroprotective and anti-inflammatory effects, anacardic acid also shows potential as a natural modulator of gene activity. Recent studies suggest that it can block the activity of histone acetyltransferases (HATs) particularly p300/CBP, enzymes that normally loosen chromatin structure to activate gene expression [188]. By limiting histone acetylation, anacardic acid may help turn down the expression of pro-inflammatory genes and other harmful pathways involved in neurodegenerative diseases. This ability to influence gene regulation adds another important layer to its protective action, complementing its antioxidant and anti-inflammatory effects. Together, these findings highlight anacardic acid as a promising natural compound that works on multiple levels to protect neurons and slow the progression of neurodegeneration. Allyl mercaptan, a sulfur containing compound derived from garlic (*Allium sativum*), has been shown to enhance the activity of key antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), while also reducing intracellular reactive oxygen species (ROS) levels in HUVEC cells treated at a concentration of 15 $\mu$ M. (<https://doi.org/10.1016/j.jff.2023.105657>

[189]. This antioxidant enhancement contributes to the perseveration of redox homeostasis in vascular endothelial cells [190].

In addition to its antioxidant effects, allyl mercaptan also inhibits the expression of adhesion molecules, such as ICAM1 and VCAM-1, and reduces vascular inflammation by preventing NF- $\kappa$ B nuclear translocation, a key event in endothelial activation. Although the precise molecular pathway remains under investigators, some studies have demonstrated that offer garlic-derived compounds like diallyl disulfide and diallyl trisulfide may act. Synergistically or more potently through NF- $\kappa$ B inhibition [191].

These findings support the therapeutic potential of allyl mercaptan as a candidate for endothelial protection and cardiovascular disease prevention, particularly in the context oxidative stress and inflammation [192].

Moreover, beyond its antioxidant and anti-inflammatory action, allyl mercaptan has been reported to exert epigenetic regulatory effects. According to findings from carcinogenesis ([141], allyl mercaptan can inhibit DNA methyltransferase DNMT activity, leading to hypomethylation of promoter regions in key genes involved in cell regulation, such as p21 WAF1. This epigenetic modulation results in the reactivation of tumor suppressor pathways and contributes to the control of cellular proliferation and apoptosis. Therefore, the protective role of allyl mercaptan in in vascular

endothelial cells may not only involve redox homeostasis and inflammation suppression but also the regulation of gene expression through epigenetic modifications, highlighting its complex mechanism of action in maintaining cardiovascular health.

Silybin, a flavonolignan extracted from *Silybum marianum* (milk thistle), is a widely recognized for its hepatoprotective, antioxidant, anti-inflammatory effects. In vitro studies on HepG2 cells have shown that silybin increase the activity of endogenous antioxidant enzymes, including SOD and CAT, while significantly decreased lipid peroxidation, thereby alleviating oxidative damage [193,194]. The compound also inhibits the activation of NF- $\kappa$ B, the key transcription factor regulating inflammatory cytokines [195]. As a result, treatment with silybin leads to reduced expression of TNF- $\alpha$ , IL-6, and iNOS, contributing to a pronounced anti-inflammatory effect. Moreover, it modulates JAK/STAT and TGF- $\beta$  signaling pathways, both of which play central roles in liver fibrosis and hepatocarcinogenesis [196].

Beyond its cellular effects, silibinin is under clinical investigation for its antifibrotic and chemoprotective potential, particularly in the context of chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD) and hepatoprotective carcinoma (HCC) [197]. Its multifunctional properties-spanning antioxidation, inflammation suppression, and fibrotic pathway interference-highlight its promise as a therapeutic agent in hepatic disorders [198].

In addition to these biological effects, silybin has also been shown to exert epigenetic regulatory activities. According to research [199] silybin modulates the activity of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), leading to changes in DNA methylation and histone acetylation status in liver cells. These epigenetic modification results in the reactivation of tumor suppressor genes and suppression of oncogenic pathways, contributing to its chemopreventive potential in hepatocarcinogenesis. Therefore, the therapeutic role of silybin in liver diseases may also involve the regulation of gene expression at epigenetic level, providing a broader mechanistic basis for its hepatoprotective and anticancer effects.

Artemisin, a sesquiterpene lactone extracted from *Artemisia annua*, has shown strong antioxidant, anti-inflammatory, and anticancer properties [200,201]. In HeLa cells treated with 50 $\mu$ M artemisinin, studies have demonstrated a significant reduction in ROS and enhanced expression of antioxidant enzymes such as a heme oxygenase-1 (HO-1) via activation of the Nrf2 signaling pathway [202,203].

In addition to its antioxidant effects, artemisin effectively inhibits NF- $\kappa$ B activation, resulting in the downregulation of pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and COX-2 [204,205]. These molecular effects contribute to the compound's ability to suppress the inflammatory tumor microenvironment and modulate immune responses.

Artemisinin also exerts pro-apoptotic activity, inducing mitochondrial membrane potential loss, caspase activation, and cell cycle arrest in various cancer cell lines, including breast, cervical, and colorectal cancers [206]. Moreover, its antiangiogenic properties, achieved through inhibition of VEGF-mediated endothelial cell migration and proliferation, make it a valuable candidate in anti-tumor therapy, particularly for limiting tumor neovascularization [207].

Due to this multimodal activity profile-antioxidant, anti-inflammatory, apoptotic, and anti-angiogenic, artemisin is increasingly regarded as a promising adjunct in oncological treatment and is currently under investigation in both preclinical and early-phase clinical studies [208].

Geraniol, a monoterpene found in rose and citronella essential oils, reduces ROS levels and increases GSH activity in RAW 264.7 macrophages (50  $\mu$ M). By inhibiting NF- $\kappa$ B, it decreases NO, IL-6, and TNF- $\alpha$  [209]. Geraniol also modulates P13K/Akt and MAPK pathways, with potential application in managing chronic inflammatory and metabolic disorders [210],[202]

These effects, recent research has uncovered an emerging role for geraniol in epigenetic regulation. A 2025 study demonstrate that geraniol can influence gene expression by modulating DNA methylation and histone acetylation levels, processes essential for controlling how genes are turned on or off [211]. Specifically, geraniol was found to inhibit the expression of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), enzymes that play key roles in

maintaining aberrant gene silencing in inflammation and metabolic dysfunction. Through this action, geraniol may help restore normal gene expression patterns, further supporting its protective effects at the molecular level. This evidence suggests that geraniol supports health by reducing oxidative stress and inflammation while also helping to restore healthy gene activity, making it a promising natural option for preventing chronic diseases.

Various classes of bioactive compounds including flavonoids (hesperidin, phloretin, silybin), carotenoids (lycopene), phenolic acids (caffeic acid, p-coumaric acid, anacardic acid), sulfur-containing molecules (allyl mercaptan), terpenes (geraniol), and sesquiterpene lactones (artemisinin)- have demonstrated strong antioxidant and anti-inflammatory activities in multiple in vitro studies,

Most of these phytochemicals enhance the activity of endogenous antioxidant enzymes such as SOD, CAT, and GSH, while reducing lipid peroxidation and ROS accumulation. These mechanisms contribute to cellular protection against oxidative damage.

Additionally, several compounds, such as hesperidin, lycopene, artemisin, and silybin, demonstrate antiproliferative effects through inhibition of NF- $\kappa$ B signaling and suppression of pro-inflammatory mediators like TNF- $\alpha$ , IL-6, COX-2, and iNOS. These bioactive compounds support potential roles as chemopreventive and therapeutic agents in inflammation-associated disease, including cancer, cardiovascular, and neurodegenerative disorders.

Moreover, several compounds, such as hesperidin, lycopene, artemisinin, and silibinin, demonstrate antiproliferative effects through inhibition of NF- $\kappa$ B signaling and suppression of pro-inflammatory mediators like TNF- $\alpha$ , IL-6, COX-2, and iNOS. These bioactivities support their potential roles as chemopreventive and therapeutic agents in inflammation-associated diseases, including cancer, cardiovascular, and neurodegenerative disorders.

Interestingly, some phytochemicals are able to regulate epigenetically the levels of NRF2, which acts as a master regulator of antioxidant response. As such the coupling NRF2 to the antioxidant response element sequences in promoters of genes results in mechanisms of antioxidant detoxification. Yates et al Phytochemicals documented to modulate NRF2 signaling act by reversing hypermethylated states in the CpG islands of NFE2L2 or Nfe2l2, via the inhibition of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), through the induction of ten-eleven translocation (TET) enzymes, or by inducing miRNA to target the 3'-UTR of the corresponding mRNA transcripts. To date, fewer than twenty phytochemicals have been reported as NRF2 epigenetic modifiers, including cur-cumin, sulforaphane, resveratrol, reserpine, and ursolic acid. (Bhattacharjee S, Dashwood RH. Epigenetic Regulation of NRF2/KEAP1 by [212] Bhattacharjee et al. provided a broader view of the action of phytochemicals on a broad array of disorders, including cancer and chronic diseases. A more focused insight is provided by Nurkolis et al (Journal of Agriculture and Food Research, Volume 21, 2025, [213], who focused on natural compound acting as epigenetic regulators in diabetes mellitus. As major actors were revealed curcumin, resveratrol, sulforaphane, genistein and quercetin.

Naturally occurring phytochemicals such as those mentioned above, along with other well studied compound like resveratrol [214], quercetin [215], apigenin [216] are commonly used in herbal extracts and show potential as complementary therapies in managing inflammatory diseases, cancer, and other chronic condition.

When these bioactive compounds are consumed from natural sources, they typically present alongside other related phytochemicals. This combination allows them to act on multiple regulatory pathways at the same time [217]. Additionally, these natural compounds can be combined with synthetic medicines to create more complex therapeutic strategies that target several disease mechanism simultaneously[218,219].

#### 4. Conclusions and Future Perspective

The preventive potential of phytochemicals is a rapidly growing area of research, with in vitro and in vivo studies demonstrating their ability to target multiple cellular and molecular pathways simultaneously, leading to enhanced biological effects. These natural bioactive compounds are

increasingly recognized for their roles in promoting health and preventing chronic disease. The majority of chronic diseases are characterized by early epigenetic dysregulations which might disturb the normal patterns of gene expression. The intrinsic factors like aging and genetic background alongside with extrinsic environmental factors (e.g. diet, pollution, radiation, stress) can significantly influence epigenetic mechanisms, ultimately impacting human's health.

The reversibility of epigenetic modifications and the ability to reset cellular homeo-stasis through compounds with epigenetic modulator capacity have opened new avenues for prevention interventions, particularly in aging, cancer, cardiovascular and metabolic disorders. Targeting these reversible changes with dietary bioactive compounds offers a promising approach to prevent diseases where early epigenetic abnormalities play a key role.

This review emphasizes that certain phytochemicals, including flavonoids, that possess both antioxidant and anti-inflammatory properties, and additionally, they can directly or indirectly inhibit the aberrant activities of epigenetic regulators. The underlying molecular mechanisms of phytochemicals multifaceted actions is incompletely unveiled, but certainly their capability to act through various epigenetic pathways, including DNA methylation, histone modifications and chromatin remodeling are potentially impacting a range of cellular processes.

The translation of preclinical data to preventive medicine is a challenging process requiring rigorous clinical trials, acknowledging individual variability in the gut microbiota and its impact on phytochemical metabolism. Long-term trials which should consider the synergistic effects of dietary phytochemicals, are also needed to evaluate overall efficacy and safety in humans, as the diet provides a combination of phytochemicals with specific cellular and organ-level actions.

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