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(REVIEW ARTICLE)

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Flavonoids as epigenetic modulators: A new frontier in disease prevention and therapy

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Abstract

Flavonoids, a diverse group of polyphenolic compounds found in plants, have garnered significant attention for their potential role in modulating epigenetic mechanisms and their implications in disease prevention and treatment. This review explores the multifaceted influence of flavonoids on key epigenetic processes, including, Non-coding RNA regulation histone modifications and DNA methylation. By targeting these mechanisms, flavonoids such as genistein, quercetin, epigallocatechin gallate (EGCG), and curcumin demonstrate promising therapeutic potential in combating diseases like cancer, neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes. The review highlights the ability of flavonoids to restore normal epigenetic patterns, suppress tumor growth, enhance neuroprotection, and regulate metabolic pathways. However, challenges such as limited bioavailability, translational gaps between preclinical and clinical studies, and the need for robust clinical validation remain. Despite these hurdles, flavonoids hold immense promise as adjuvants in epigenetic therapy and synergistic agents with existing drugs. This review underscores the importance of further research to fully harness the therapeutic potential of flavonoids as epigenetic modulators in disease prophylaxis and treatment.

Keywords: Polyphenols; Flavonoids; Epigenetics modulators; DNA methylation; Histone modification; mRNA and IncRNA; Cancer; CVS disease; Diabetes; Neurodegenerative diseases

1. Introduction

The term "epigenetics" refers to processes that control reversible inherited alterations in gene expression that do not result from modifications in the nucleotide sequence and are passed on through mitotic or meiosis cell division. It indicates that both the genotype and epigenotype both can affect the phenotype, with phenotype altering throughout development as a result of environmental factors. Epigenetic mechanisms can mediate how environmental conditions impact exposed individuals, thus serving as a connection between the gene expression and environment potentially influencing future health outcomes [2]. Currently, increasing evidence indicates that epigenetic modifications play a role not just in cancer, which is being thoroughly researched, but also in the progression of chronic non communicable metabolic condition for example cardiovascular disease, diabetes, obesity, neurodegeneration, and cardiovascular illnesses. Since epigenetic modification can be influenced and reversed by both internal and external environmental factors, epigenetics is currently seen as a foundation for clinical intervention. Moreover, bioactive food components and nutrients can alter the expression of genes related to physiological and pathological processes by changing their epigenetic patterns. Various epigenetic alterations have been recognized and documented thus far: sumoylation and acetylation of lysine, posttranslational changes of histones encompassing methylation, ubiquitination, DNA methylation of cytosine at cytosine-phosphate-guanine (CpG) dinucleotides, phosphorylation of serine and threonine, arginine methylation, as well as a range of noncoding RNAs (ncRNAs), such as miRNAs, that modulate expression of genes at

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several levels [3]**.** Numerous phytochemicals found in plant- foods, particularly flavonoids, are thought to have the ability to alter epigenetic cellular mechanisms [4]. Flavonoids are important phenolic compounds that form a major group of secondary metabolites with significant biological impacts and the ability to affect epigenetic processes. Flavonoids are associated with various health advantages owing to their antiviral/bacterial, anti-mutagenic, anti-inflammatory, anti-carcinogenic, anti-mutagenic, antioxidant, cardioprotective, antiviral/bacterial, anti-aging properties, and their ability to affect enzyme activity. The structure of flavonoids comprises two benzene rings linked by a heterocyclic pyran ring (C ring) comprising oxygen. Flavones contain a double bond at C2C3 and have a C4-oxo group. Flavonols are similar compounds to flavones that have a 3-hydroxy group [5]. Rich sources of flavanols are e.g. apple, grapes, cocoa, tea or wine [6]. Furthermore, quercetin is the main derivative of flavanones, characterized by the hydroxyl group constantly linked to the third position of ring C. Anthocyanins have a simple chemical structure comprising a flavylium cation that connects to the methoxyl and hydroxyl group situated at R positions such as R_1, R_2, or R_3 [5]. Flavanols or catechins are derivatives of 3-hydroxy. The bioavailability of different flavonoids differs among flavonols, and there is no correlation among the administered dosage and the levels found in the human body [7]. In pharmacokinetics research, it's crucial to account for each step and all enzymes included in absorption, alteration and transport to improve understanding of the beneficial effects of flavonoids [8]. Further research on flavonoids showed that wine serves as a nutritive source of phytochemicals. Since then, numerous epidemiological studies have shown a positive connection between health of human and the consumption of red wine. Grasping the precise epigenetic alterations influenced by flavonoids is crucial for developing epigenetic therapies and integrated treatment approaches for cancer. This review aims to comprehensively examine the epigenetic alterations caused by flavonoids and their therapeutic effects in various chronic conditions, including obesity, cancer, diabetes, cardiovascular diseases, neurodegeneration and diabetes [9].

2. Epigenetic Mechanisms Influenced by Flavonoids

Epigenetics is the examination of processes that change expression of gene while leaving the original sequence of DNA unaltered. Epigenetic processes are reversible and inheritable, encompassing alterations in and small noncoding microRNAs , modifications of histones and DNA methylation. Interference with epigenetic mechanisms can result in changed gene activity and cancerous cell formation [10].

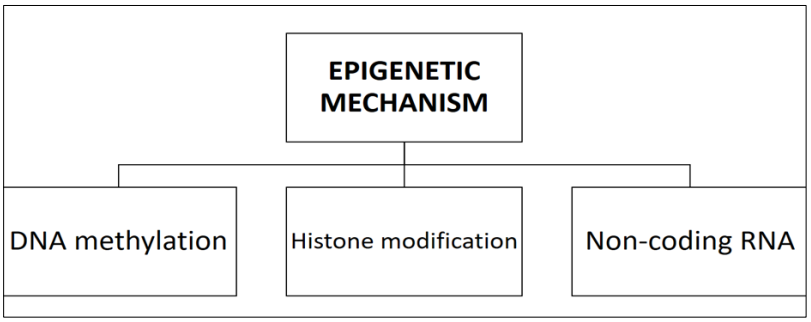

Figure 1 Epigenetic mechanism

2.1. DNA methylation

DNA hydroxymethylation or methylation or serves as a crucial mechanism of epigenesis for regulation genes within the cells [11] and patterns of DNA methylation play a role in forming memory of epigentics [12]. DNA methylation is typically inversely related to gene expression; however, its effect also relies on the positioning of the bases that are methylated and is concerned with the regions for the coding of the controlled genes [13]. Methylation of cytosine primarily takes place at CG islands that are extensively spread throughout the gene pool [9]. CG methylation-mediated TGS also limits the tissue-specific genes expression during differentiation and development by suppressing them in non-expressing cells [14]. Throughout development, the design of CG methylation alters in a consistent way. During early embryonic development, methylation is removed across the entire genetic code and subsequently reinstated in all regions except islands of CG. Islands of CG stay undermethylated until later stages of development, at which point a few of them get methylated. Later cytosines' methylation within islands of CG and at various dinucleotides is linked to repression of transcription [15]. In some pathological conditions, such as human cancers, two epigenetic events have been observed In certain health problems, like cancer in human, two epigenetic occurrences have been noted [16]: Worldwide hypomethylation of CG sites that are not part of the island of CG is associated with instability of gene sequence, manifesting as either the activation of mitotic recombination or the activation of transposons [17]; and

promoter region' hypermethylation , particularly CG sites, linked to the resulting silencing of tumor suppressor genes. Micro RNA genes are often identified within the cancer-related genomic areas [18].

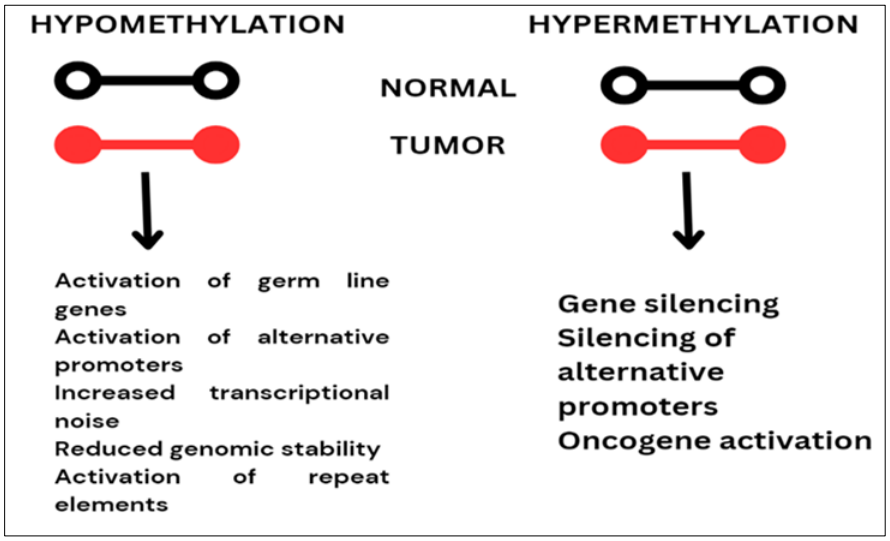

Figure 2 DNA hypomethylation and DNA hypermethylation in cancer

Heparanase (HPSE), a type of endo-β-D-glucuronidase, is capable of cutting the sulfate heparan chain found in heparan sulfate proteoglycans and have a significant role in the degradation of the extracellular matrix. Heparanase activity can be identified in activated T lymphocytes, neutrophils, platelets, and numerous cancers, such as Prostate Cancer. HPSE gene hypomethylation has been observed in eight to thirty% of instances of PC [19].

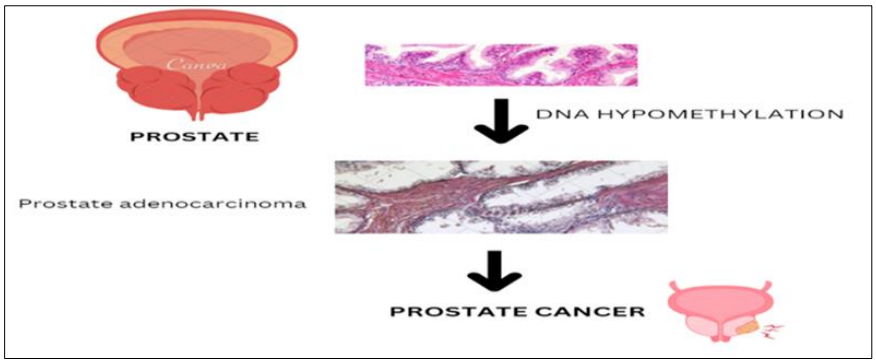

Figure 3 Hypomethylation of HPSE gene leads to adenocarcinoma

Polyphenols, especially flavonoids, represent the most intriguing element of leaves of green tea. the primary flavonoids found in green tea is catechins. The four primary catechins are epigallocatechin-3-gallate, 3-gallate epicatechin, epigallocatechin and epicatechin [20]. In the past 20 years, research has concentrated on the possible chemopreventive and therapeutic effects of polyphenols. Recent studies indicate significant chemopreventive and potentially cancer chemotherapeutic effects of EGCG and green tea polyphenols on skin (both chemically induced and UV radiation), lung, liver, stomach, colon, breast and prostate cancers [21]. While the specific molecular mechanisms behind the antiproliferative effects of catechins remain unclear, these catechins appear to act as multitarget agents, influencing various signaling pathways [22]. Moreover, it has been noted that catechins in green tea can influence epigenetic mechanisms. Unusual epigenetic changes in the genome, including chromatin and DNA methylation remodeling, are crucial in the onset of cancer. Given that epigenetic modifications are seen as more readily reversible than genetic alterations, epigenetic therapy may prove highly beneficial in correcting few of these issues. Certainly, epigenetic mechanisms have been identified as a novel focus for anticancer medication development [23]. In genes associated with Parkinson's Disease, lowering the level of methylation leads to a buildup of degeneration and α-synuclein of DA neurons [24] . In Parkinson diasease altered DNAm has been identified in the brain and blood of individuals that have been diagnosed. In Parkinson's Disease, reduced DNAm and the decreased expression of DNA Methyl Transferase 1 in the brain have been linked to an increase of DNA Methyl Transferase 1 outside the cell nucleus. Genes like TNF-α (tumor

necrosis factor-alpha) and SNCA influence the development of PD by contributing to the dysregulation of DNAm [25]. In patients with Parkinson Disease, the promoter regions of the TNF-α genes and SNCA showed significant hypomethylation. This process is supposed to have a significant role in the atypical neuro-inflammation observed in the development of Parkinson Disease [26].

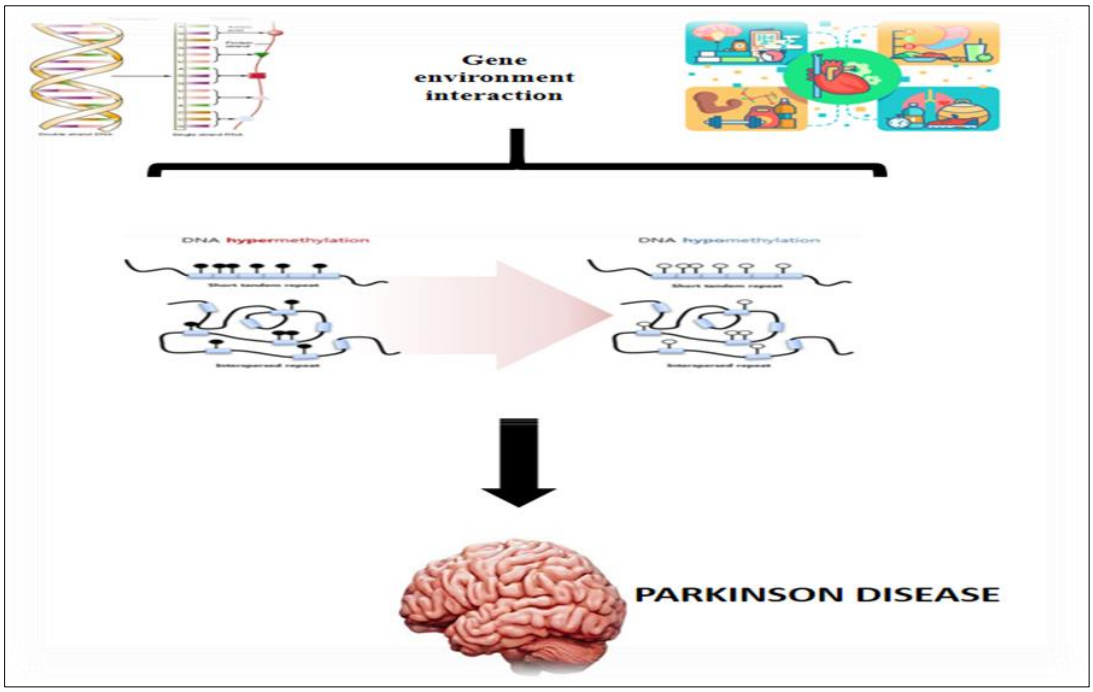

Figure 4 DNA methylation in Parkinson disease

Irregular methylation of DNA is intensely linked to the onset of various cardiovascular diseases, such as heart failure, atherosclerosis, hypertension and coronary artery disease [27]. For instance, a hyperglycemic setting causes permanent alterations in the function of DNMTs. Meanwhile, hypermethylation of the promoter for PGC-1α gene in pancreatic cells can reduce the transcription the peroxisome proliferator-activated receptor gamma coactivator-1 and hinder insulin secretion [28]. Redox imbalance is linked to increased resistance of insulin in cardiac cells. The activation of the TNF-α (pro-inflammatory cytokine TNF-α) can elevate the level of DNA methylation, which results in the methylation of the SERCA2a promoter region, reducing sarcoplasmic reticulum Ca2+-ATPase levels and resulting in Ca2+ overload, ultimately dysfunction of cardiac muscles and, in severe instances, heart failure [29]. During insulin resistance and hyperglycemia, RAAS system gets activated, causing AT1b promoter to undergo methylation, which increases angiotensin type II-1b expression and contributes to myocardial hypertrophy[30]. Insulin resistance and elevated blood sugar are intimately linked to DNA methylation. DNA methylation regulates the gene expression linked to DCM development, resulting in reduced contractile cardiac function, heightened oxidative stress, which in turn leads to remodeling of cardiac muscles ,cardiomyocyte apoptosis, and the progression and onset of DCM [31].

2.2. Histone modification

Histones are basically proteins with a positive charge that contribute to the condensation and packaging of DNA into chromatin within the nucleus. Configuration in open chromatin (euchromatin) is linked to transcriptional activation, while closed chromatin configuration (heterochromatin) is linked to the transcriptional repression [9]. Histone modifications are post-translational changes that primarily take place on the N-terminal tails of core histones, which include, sumoylation, ubiquitination, phosphorylation, methylation and acetylation [32]. For instance, it has been reported that chromosomal condensation is rectified by histone H1 phosphorylation levels [33]. Histone H2B and H2A ubiquitination plays a significant role in controlling transcription silencing initiation, and elongation [34]. For sumoylation, it has been reported that histone H4 is altered by small ubiquitin-like modifier proteins to suppress transcription of euchromatic [35]. As a result, histone modifications can influence expression of gene by modulating chromatin dynamics, leading to issues with modification of chromatin structure[36]. Methylation of proteins primarily takes place on Lys and Arg side chains; however, in mammals, methylation can also happen on other residues [37]. Lysine residues can undergo monomethylation, dimethylation, or trimethylation (me1, me2, and me3), while residues of arginine can be monomethylated or undergo symmetrical or asymmetrical dimethylation (me1, me2s, or me2as).

Methylation of Histone primarily operates by directly attracting or blocking the attachment of HBP. For instance, H3K4me3 selectively attracts activating proteins, such as transcription factors to gene promoters, while preventing the binding of transcription repressors like the nucleosome remodeling and deacetylase complex [38]. In contrast to phosphorylation and acetylation, methylation of histone does not change the protein's charge [39]. Acetylation typically takes place at lysine residues, counteracting their cation and resulting in histones separating from DNA, which possesses a negative charge. The disclosed structure enhances accessibility to transcriptional components like RNA polymerase II and transcription factors[40]. Consequently, acetylation promotes and increases gene expression overall. Deacetylation and acetylation of Histone is facilitated by histone deacetylases (HDACs) and histone acetyltransferases (HATs), respectively. HATs are divided into two categories: type A and type B. Type A HATs are primarily found in the nucleus and consist of MYST (Ybf2, MOZ, Tip60, Sas2), Gcn5-related N-acetyltransferases as well as the CBP or p300 families. This add an acetyl group to nucleus of histones by relocating it from Acetyl-CoA. In the meantime, type B HATs are found in the cytosol and acetylate unbound histones or non-histone proteins [41].

Curcumin has been documented to influence acetylation of histone and the release of pro-inflammatory cytokines in high-glucose environments. The findings indicated that using curcumin as a therapeutic agent not only significantly decrease activity of HAT and the amount of p300 (a co-activator of NF-κB), but also stimulate the expression of HDAC2. The findings suggest that curcumin reduces cytokine production in monocytes triggered by high glucose through epigenetic modifications related to NF-κB [42]. Kiss and colleagues demonstrated that ellagic acid reduced activity of HAT in TNF-α-stimulated human monocytic (THP-1) cells, and that ellagic acid additionally heightened HDAC activity. This resulted in the reduction of inflammatory cascade and enhanced cell survival [43].

Table 1 Epigenetic target and drugs in coronary heart disease[1]

Histone modification		
Disease	Epigenetic modification	Epigenetic drug
Atherosclerosis	SIRT1 HDAC1, HDAC2 ICAM1	Resveratol Statins Trichostatin A
Hypertension	HDAC6	Tubastatin A
Myocardial infarction	FOXO3-a AKT-1, TNF-A HDAC6	Etinostat Trichostatin A VPA
Heart Failure	TNF A Mitochondria genes SIRT1, IL6	5-azacytidine Chaetocin Reveratrol

2.3. Non-coding RNA

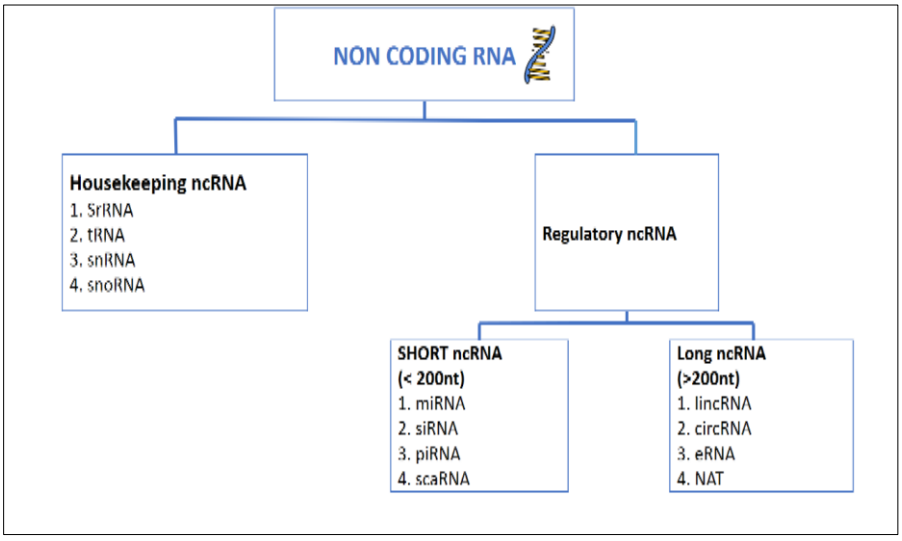

Figure 5 Classification of Non-coding RNA

miRNAs (MicroRNAs) are an abundant category of small non-coding RNAs that act as negative regulators of genes. They oversee various biological functions, and bioinformatic information suggests that every microRNA can regulate many gene targets, highlighting the significant impact of microRNAs on nearly every signaling pathway. Mutations or incorrect expression of miRNAs are linked to multiple human cancers, suggesting that miRNAs may function as tumor and oncogenes suppressors. Additionally, multiple miRNAs can influence the expression of a particular mRNA. The frequently associated cancer microRNAs (onco-miRNAs) that show potential for cancer therapy include miR-16, let-7 and miR-15 [44]. Insulin released by b-cells has various effects on perilesional tissues that help regulate glucose balance while food is being absorbed. Insulin enhances glucose transport in skeletal muscle, allowing glucose to enter and promoting synthesis of glycogen. Insulin stimulates the formation of glycogen in the in the liver and prevents endogenous glucose production. Insulin inhibits lipolysis and encourages lipogenesis in adipose tissues [45]. Insulin resistance signifies that perilesional tissues do not adequately respond to typical insulin levels, resulting in increased glucose levels along with reduced insulin-driven uptake of glucose in skeletal muscle and fat tissue, and also as a hindered repression of glucose release in the liver [46]. Herrera et al analyzed a group of microRNAs in insulin-responsive tissues of Goto-Kakizaki (GK) rats, a natural rat model of T2D, and observed increased levels of miR-27a and miR-222 ; increased expression of miR-103, miR-125a and miR-195 in the liver; and decreased levels of miR-10b in muscle [47]. Long noncoding RNAs (lncRNAs) are generally defined as transcripts exceeding 200 nucleotides in length. The biology mediated by lncRNAs has been associated with numerous cellular functions and comorbities [48]. The genome of mammal is transcribed intricately, resulting in the generation of numerous lncRNAs. lncRNAs are characterized as transcripts exceeding 200 nucleotides that have a similar structure to mRNAs yet do not code for proteins. These lncRNAs are involved in various biological functions, including epigenetic regulation, chromosome imprinting, control of the cell cycle, splicing, translation, transcription, and differentiation of cells. Improper regulation of long coding RNAs is linked to increased vulnerability to various human illnesses, such as cancers, cardiovascular conditions, and neurological diseases [49]. A significant quantity of lncRNAs is associated with every indicator of cancer. Among the prominent lncRNAs linked to tumor advancement in humans, those related to the proliferation, survival, and migration of malignant cells [50]. Ginsenoside is a naturally occurring steroid glycoside with various chemical structures that exhibit multiple pharmacological actions on the nervous, cardiovascular, and immune systems, as well as in cancer [51]. These substances modify the lncRNAs expression and additional cancer-associated genes through epigenetic changes [52]. lncRNA-C3orf67 AS1 is highly expressed in breast cancer cells, and reducing it with specific siRNA in MCF-7 cells results in limited colonization and growth by triggering apoptosis. Ginsenoside (Rh2) is crucial in treating breast cancer as it can reduce C3orf67-AS1 levels by inducing hypermethylation of the C3orf67-AS1 promoter in MCF-7 cells [53].

3. Flavonoids and Disease Prevention through Epigenetics Modulation

3.1. Cancer

It is generally believed that epigenetic changes in cancer result from modifications in histones and DNA that cause the knockdown of tumor suppressor genes and the activation of oncogenes. Additional outcomes stemming from epigenetic modifications, like the improper expression or suppression of certain genes in an incorrect cellular setting, may also lead to disruptions in regulatory and physiological systems, transforming a normal cell into a tumorigenic one [54]. Therefore, this indicates that the conversion of healthy cells to cancer cells entails epigenetic changes and is usually preceded by a genetic mutation [9]. Numerous agents can serve as epigenetic modulators for the prophylaxis and treatment of cancer. Flavonoids are among those. Primarily in cancer, these photochemical agents inhibit tumor progression by targeting crucial signaling transducers, leading to the reactivation of oncosuppressor genes and the inhibition of oncogene expression. These changes and subsequent anti-tumor effects typically arise from the epigenetic modulation by flavonoids, which affects epigenetic enzymes like HATs, DNMTs, and HDACs [55]. Flavones are the most frequently utilized flavonoids as epigenetic modulators in the progression of cancer. Flavones are a category of flavonoids that feature the structure of 2-phenylchromen-4-one, possessing various pharmacological effects, and are typically present in herbs like celery and parsley, as well as in nearly all edible grain varieties luteolin, baicalein, tangeretin, rhoifolin, tangeretin, chrysin, apigenin, tricin and 6-hydroxyflavone are a few well-known flavones [56]. Apigenin suppresses class I HDACs, especially HDAC1 and HDAC3, modifies chromatin to trigger apoptosis and growth inhibition in human prostate cancer cells. Apigenin suppressed the proliferation of MDA-MB-231 breast cancer cells and tumor growth through the induction of G2/M arrest and the expression of p21 mediated by histone H3 acetylation [57]. Apigenin boosts the expression of miR-16 and miRNA215-5p to impede colon and glioma cancer development, while also rendering doxorubicin-resistant liver cancer cells more sensitive to chemotherapy by affecting the miR-520b/ATG7 pathway [58]. It was recently found that luteolin suppressed the growth and spread of androgen receptor-positive triple-negative breast cancer cells by epigenetically regulating MMP9 expression, reducing the levels of

AKT/mTOR-induced H3K27Ac and H3K56Ac. It was previously disclosed that luteolin inhibits the metastasis of triple-negative breast cancer by downregulating ß-catenin expression, thereby overturn epithelial-to-mesenchymal transition [59]. In colorectal cancer cells, Luteolin triggers apoptosis through the downregulation of calpain, UHRF1 or DNMT1 levels. This study additionally indicates that calpain could play a role in the inheritance of the epigenetic code by modulating the epigenetic integrator UHRF1 [60]. In human prostate cancer (PC-3) cells, Gefitinib and Luteolin influence cell cycle pathway genes (CDC25A, CCNE2, CDKN1B, CCNA2 or PLK-1) via a shared mechanism that involves EGFR-linked tyrosine kinase[61]. Researchers proposed that these phytochemicals probably influence the epigenetic regulation of gene expression, as demonstrated earlier by their team, indicating that luteolin engages with type II binding sites on H4 histone [62].

Another instance is Epigallocatechin gallate (EGCG), a strong polyphenolic, chemo-preventive substance extracted from green tea that is part of the catechin category of flavonoids. EGCG modifies the expression of several antioncogenes by blocking histone deacetylases and DNA methyltransferases and in human cervical cancer HeLa cells. Furthermore, exposure to EGCG over time led to the reactivation of recognized antioncogenes in these cells due to significant changes in the methylation patterns of the promoter regions of these genes [63]. A different study described the anticancer action of EGCG by coordinating transcriptional changes of multiple molecular targets through various signaling pathways in Hela cells [64]. Additionally, the combined effects of clofarabine with genistein or EGCG significantly suppressed the proliferation of breast cancer cells (MDA-MB-231 and MCF7) and triggered apoptosis, resulting in RARB hypomethylation, which led to a substantial rise in the transcript levels of PTEN, CDKN1A and RARB. This combination encourages apoptosis and reactivates DNA methylation-silenced tumor suppressor genes in human breast cancer cells with atypical invasive potential [65].

3.2. Neurodegenerative diseases

Neurodegenerative diseases (NDDs) are significant public health issues in Western nations and are commonly linked to the aging process. The worldwide financial impact of dementia surpasses USD 800 billion, with average costs ranging from USD 30,000 to USD 60,000 per individual annually [66]. The sensorium coordinates intricate functions with distinct epigenetic patterns precisely designed for particular purposes. Because of this complexity, the transcription machinery encounters a difficult obstacle in the nervous system, rendering it very sensitive to epigenetic disturbances [67]. Thus, the importance of epigenetics in the nervous system is highlighted by the emergence of severe cerebral degenerative diseases (NDDs) caused by mutations in epigenetic genes [68]. The interaction between epigenetic and genetic codes has been thoroughly studied in relation to memory or learning. Groundbreaking research has demonstrated the essential role of epigenetic modifications in processes associated with memory, learning or synaptic adaptability [69]. It is clear that disordering in epigenetic processes not only impede normal brain function but are also associated with several neurological disorders, especially Alzheimer's disease (AD) and Parkinson's disease (PD) [70]. Alzheimer’s disease (AD) is a long-term condition marked by memory loss and cognitive impairments, including apraxia, aphasia, and agnosia, among others, which disrupt daily activities and affect the person’s job performance. The frequency rate is approximately 7% for those aged 65 and older, with the chance increasing twofold every 5 years [71]. Flavonoids serve as highly effective agents in treating AD, with baicalein being capable of preventing damage to hippocampal long-term potentiation (LTP) caused by Aβ and enhancing cognitive deficits linked to AD. Researchers have investigated the anticholinesterase effects of several flavonoids [72]. As we are aware, cholinesterase activity rises in Alzheimer's disease, so flavonoids with anticholinesterase properties can help safeguard neuronal impairment in the hippocampus of patients with AD. A multitude of flavonoids has been used as AChE inhibitors, but quercetin emerged as a particularly strong inhibitor of AChE [73]. Additionally, Flavonoids have demonstrated the ability to counteract cognitive deficits and slow the advancement of Alzheimer’s disease, suggesting that they could possess therapeutic benefits [74] Diets high in flavonoids such as blueberries, cocoa or grape juice are consumed to boost memory [75]. Several studies have examined the antiamyloidogenic properties of flavonoids as a possible natural therapy for Alzheimer’s disease. Flavonoids exhibit various biochemical characteristics, yet their most significant biological function is noted to be their hydrogen-donating or antioxidant [76]. The flavonoids antioxidant property is largely attributed to the functional groups linked to their structure. Oxidative stress occurs due to the disparity between antioxidants or ROS (reactive oxygen species), representing a major event in all neurodegenerative diseases. In addition to neurodegenerative diseases, oxidative stress has been associated with several other conditions such as cancer, ischemic injury, atherosclerosis, and inflammation. Metal toxicity and oxidative stress significantly contributed to the development of AD [77]. Flavonoids are essential in shielding neurons from oxidative stress, thereby mitigating the harmful impact of ROS, reducing neuronal damage, and enhancing cognitive function [78]. Parkinson's striatal dopamine and the creation of Lewy bodies in the substantia nigra (SN). Parkinson's disease is among the most prevalent age-associated neurodegenerative conditions following Alzheimer's. The occurrence of PD rises consistently with age and reaches its highest point after 80 years old [79]. Two main alterations define PD: the gradual deterioration of dopaminergic (DA) neurons, resulting in a decrease of symptoms of Parkinson's disease such as postural instability

bradykinesia, resting tremor, difficulties in gait and rigidity [80]. Flavonoids significantly contribute to alleviating these symptoms a flavone, baicalein found in the roots of Scutellaria baicalensis, reduced the formation of α-synuclein oligomers and thus stopped their fibrillation [81]. In neurodegenerative conditions such as PD, α-synuclein, a protein found in presynaptic neurons, misfolds and creates abnormal oligomers, protofibrils, or amyloid fibrils that lead to synaptic disruption and neuronal death. Additionally, released α-synuclein can spread to adjacent cells, speeding up the aggregation process and thereby aiding in disease spread [82] Consequently, therapy aimed at α-synuclein has arisen as an encouraging method for treating PD [83]

3.3. Cardiovascular Diseases

Currently, numerous natural substances that are epigenetically active (like polyphenols and flavonoids) and synthetic agents such as HDAC inhibitors or DNMT inhibitors have been identified. Both natural and synthetic DNMT and HDAC inhibitors exhibit numerous cytoprotective effects, including anti-apoptotic, antioxidant, anti-inflammatory, anti-fibrotic, and anti-hypertrophic characteristics, which aid in the treatment of various cardiovascular diseases [84]. Growing evidence indicates that the heightened risk of cardiovascular disease due to endothelial cell dysfunction and subsequent arteriosclerosis can be reduced by a greater intake of fruits and vegetables. These foods include phytochemicals like polyphenols and carotenoids, along with dietary fiber. Polyphenol-class flavonoids are present in vegetables, stems, bark, fruits, grains, flowers, roots, wine and tea. Numerous studies have shown that flavonoids lower CVD deaths by preventing endothelial dysfunction. Flavonoids share a common carbon structure and are categorized into flavanols, flavanones, flavonols, anthocyanidins, flavones, and isoflavones [85]. Flavonols are 3-hydroxy derivatives of flavones and include several well-researched phytochemicals, such as quercetin. Quercetin is the most widely ingested flavonol and is plentiful in onions, tea, apples, and berries [86, 87]. The consumption of quercetin is negatively associated with mortality from ischemic heart disease in a dose-dependent way [88]. Moreover, quercetin has demonstrated protective effects against ischemia/reperfusion damage, cardiac injury caused by isoproterenol, remodeling of the heart due to aortic constriction, and diabetic cardiomyopathy [89-92]. Quercetin, functioning as an HDAC inhibitor, would modify the electrostatic interactions between histone proteins and DNA directly influencing gene expression and consequently affecting cellular fate [93]. Quercetin is the predominant flavonoid found in numerous flowers, fruits, and medicinal herbs, recognized for its potent free radical scavenging ability, which may exhibit anti-inflammatory, antitumor, and antioxidant properties. Recent research has also indicated its significant influence on diverse miRNA expressions in various disorders [94]. Growing evidence has shown that the regulation of miRNA expression through dietary compounds enhances their ability to alleviate the pathology of cardiovascular diseases. Dietary polyphenols influence epigenetic processes, posttranslational alterations, and miRNA expression, implying possible roles in the creation of medications for therapeutic treatment [95]. Therefore, the use of polyphenols to target miRNAs presents a favorable therapeutic approach for CVDs [96]. The anti-inflammatory effects of quercetin involve the downregulation of miR-155 and the enhancement of miR-21 expression, which is recognized as a pro-inflammatory miRNA [97]. Reducing miR-199a levels through quercetin is linked to the upregulation of SIRT1 expression by directly affecting its 3′-UTR [98]. We outlined the roles of nine distinct miRNAs, comprising three that protect the heart (miR-221/222, miR-145, and miR-126), two that promote heart disease (miR-155 and miR-34a), and four miRNAs whose exact function in cardiovascular disease pathology remains unclear (miR-15/16, miR-21, miR-199a, and miR-210) [96].

3.4. Metabolic disorders

Epigenetic abnormalities can be corrected, and research has indicated that specific natural substances derived from plants, including tea polyphenols, genistein, ellagic acid, curcumin, urolithins, citrus isoflavanoids and isothiocyanates have demonstrated the ability to prevent weight gain. These compounds possess significant antioxidant abilities and are highly intriguing due to their capacity to alter epigenetic mechanisms [99]. Flavonoids have a structure made up of two aromatic rings (known as A and B rings) linked by a 3-carbon chain, creating an oxygenated heterocyclic C ring [100]. Usually, several hydroxyl groups (–OH) are connected to the phenolic rings of flavonoids. The quantity and arrangement of these hydroxyl groups play a crucial role in defining the antioxidant and anti-inflammatory properties of flavonoids, which are significant for managing obesity [101]. More hydroxyl groups typically relate to a greater antioxidant capacity [101]. Modifications on the A- and B-rings were observed to influence their biological activities. For example, the hydroxylation occurring at the 3′- and 4′-positions of the B-ring improves the inhibitory action of flavonoids on adipogenesis [102]. A frequently targeted pathway of flavonoids is the PPAR. Flavonoids engage with and alter the activity of PPAR isotypes, including PPARα, PPARβ/δ, and PPARγ [102-104], that perform different functions in metabolism [105]. The PPAR functions as a transcription factor that converts nutritional signals into a gene expression pattern that regulates cellular bioenergetics. Consequently, these receptors function as nutritional detectors that alter systemic metabolism by controlling metabolic activities throughout different organs [106]. The gene expression regulated by PPAR encompasses genes that play a role in glucose balance, lipid metabolism, and inflammation related to obesity [105]. Apigenin has been shown to interact directly with PPARγ and inhibit its downstream regulators (NF-κB) in a model of obesity in animals. In this instance, the intraperitoneal administration of

apigenin over 21 days effectively hindered the nuclear translocation of p65, leading to the repositioning of the PPARγ/p65 complex along with macrophage polarization. Consequently, the phosphorylation of p65 is inhibited, leading to the inactivation of NF-Kb [106]. As a result, the elevated levels of inflammatory signaling pathways triggered by adipocytes in obesity are inhibited [107] . In a similar manner, apigenin prevents the differentiation of adipocytes by promoting the phosphorylation of 5′-adenosine monophosphate-activated protein kinase (AMPK) through the downregulation of the PPARγ pathway [108]. After treatment with quercetin, differentiated adipocytes showed reduced expression of C/EBPβ, an initial adipogenic factor, followed by decreases in C/EBPα, PPARγ, and FABP4, which are essential adipogenic factors [109]. Research indicates that dietary genistein enhances glucose and lipid metabolism, regulates hypothalamic circadian rhythms, and reduces body weight providing protection against metabolic disorders [110]. Key transcription factors like PPARg and C/EBPa control adipogenesis. Genistein has been shown to inhibit the formation of adipocytes, even in small amounts in mature adipocytes, by modifying the expression of PPARg1, PPARg2, mRNAs for C/EBPa, and GLUT4 [111]. Citrus flavonoids have been shown to reduce adipocyte counts, increase energy expenditure, stimulate fatty acid oxidation, and inhibit obesity in experimental animal studies. Naringenin enhances the expression of genes related to fatty acid oxidation, like UCP2 and CPT-1, which are both recognized to be controlled by PPAR. Consequently, naringenin was given to rats, resulting in a decrease in triglyceride levels and adiposity in parametrial adipose tissue [112]. Nevertheless, only a limited number of studies explore the impact of citrus flavonoids on the epigenetic regulation of genes linked to obesity [113]. Research conducted by de la Garza et al. discovered that extracts from grapefruit and helichrysum decreased the expression of numerous pro-inflammatory genes and enhanced DNA methylation at the TNF-α gene promoter in the epididymal adipose tissue and liver. Furthermore, it has been confirmed that naringenin demonstrates its antioxidant properties through epigenetic regulation affected by miR-173P and miR-255P [114]. Dietary flavonoids act as natural epigenetic regulators for identifying biomarkers that aid in diabetes prevention and for creating alternative treatment options [115]. Flavonoids promote the phosphorylation of the insulin receptor and IRS, activate the PI3K/Akt pathway and AMPK, and enhance GLUT4 translocation. The flavonoids-activated PI3K/Akt pathway reduces PEPCK and G6P expression, inhibiting gluconeogenesis and encouraging glycogen synthesis. Flavonoids decrease the amounts of FFAs and inflammation factors, diminishing the adverse impact on insulin signal transduction by JNK, NF-κB, and PKC [116]. Quercetin consumption is negatively correlated with the occurrence of T2DM in the Chinese demographic, indicating its protective effects against T2DM [117, 118]. The antidiabetic effect of quercetin entails decreasing lipid peroxidation, glucose uptake via PI, and blocking insulin-induced activation of phosphoinositide 3-kinases (PI3K) [119, 120]. Moreover, quercetin and its derivatives promote glucose absorption in muscle cells and activate AMPK [121]. The influence of quercetin on the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) additionally aids in enhancing glucose-induced insulin secretion [122]. Kaempferol exhibits multiple antidiabetic properties, such as enhancing AMP activated protein expression and function, lowering cellular apoptosis by inhibiting caspase 3 activities, and boosting insulin production and secretion from β-cells [123]. 3,7,3′,4′-Tetrahydroxyflavone (fisetin) is prevalent in fruits and vegetables such as apples, grapes, persimmons, cucumbers, strawberries and onions [124, 125]. Fisetin exhibits anti-inflammatory, anti-diabetic, and neurotrophic properties [126]. In an in vivo experiment, the findings indicated that fisetin treatment markedly decreased the levels of Hemoglobin A1C (HbA1c), NF-κB p65, serum nitric oxide (NO), and blood glucose [127]. Fisetin likewise suppresses cytokine production in monocytes caused by high glucose, potentially blocking diabetes [128]. Many studies highlight the potential role of flavonoids in managing diabetes and reveal their hypoglycemic effects across different experimental models and treatments [129-133]. Epigallocatechin gallate, administered intraperitoneally to rats, causes a decrease in blood glucose and insulin levels [134-136]. The findings indicate that during oral glucose tolerance assessments, glucose metabolism in healthy individuals is enhanced by green tea and an anti-hyperglycaemic effect is produced without impacting insulin secretion in diabetic mice induced by streptozotocin [130]. Genistein also lowers blood glucose levels in diabetic rats when compared to the control group during glucose tolerance tests. Comparable results have been achieved with long-term treatments using genistein and daidzein in db/db mice and rats induced with streptozotocin [134-136]. Flavonoids might affect the production and secretion of insulin from β-cells. In rats with streptozotocin-induced diabetes, the oral intake of genistein has demonstrated an increase in insulin release from mouse pancreatic islets when glucose is present [137]. The process behind this biological effect might include elevated intracellular cAMP due to enhanced adenylate cyclase activity and the stimulation of protein kinase A (PKA), indicating that genistein modulates the insulinotropic response via activation of the cAMP/PKA signaling pathway [138]. Furthermore, green tea catechins demonstrate hypoglycemic effects both in vitro and in vivo. In reality, prolonged use of a green tea-derived supplement leads to an enhancement of both the baseline and insulin-induced glucose absorption in fat cells [139, 140]. Cyanidin-3-glucoside (C3G) and cyanidin-3-rutinoside (C3R) stimulate insulin secretion in MIN 6 cells by enhancing glucokinase expression and activating the GLP-1 receptor, leading to increased intracellular ATP levels and promoting the survival of β-cells via elevated levels of duodenal homeobox factor-1 (PDX-1) [141]. Formononetin demonstrates antidiabetic properties via multiple mechanisms, such as preventing apoptosis in islet B cells and promoting their regeneration by decreasing levels of Fas and Caspase-3 mRNA and protein while increasing PDX-1 and insulin receptor substrate 2 (IRS2) mRNA levels.

Moreover, it stimulates insulin release and enhances the mRNA and protein levels of GK and GLUT2 in pancreatic tissue from mice with alloxan-induced type 1 diabetes [142].

4. Challenges and future perspectives

The majority of flavonoids usually demonstrate restricted oral bioavailability, likely due to their low solubility, poor permeability, and inadequate stability, which significantly diminishes their efficacy as therapeutic agents. For instance, the double bond found between positions 2 and 3 of flavones and flavonols allows for the creation of planar structures, leading to a compact molecular arrangement, which makes it hard for solvent molecules to infiltrate their molecular structures [143, 144]. This led to their limited aqueous solubility and inadequate oral bioavailability; for instance, myricetin, a standard flavonol with a planar configuration, has an oral bioavailability of merely 9.62% in rats, likely due to its low aqueous solubility of 16.60 μg/mL [145, 146]. Flavonoids break down and combine with the primary enzymes in the colon, liver, and intestine. In the intestine, the hydrolyzed and bound enzymes transform monomeric units of flavonoids into sulfate esters, O-glucuronides, and O-methyl esters [147]. The conjugation of flavonoids takes place in two stages: first in the small intestine (phase I), followed by the liver, where the end of phase one coincides with the start of phase II. In the liver, the conjugated metabolites are further processed to generate glucuronide and sulfate derivatives, which are then facilitated and excreted via bile and urine [148]. Furthermore, the colon significantly influences the bioavailability of dietary flavonoids, as a considerable portion of these natural compounds is not absorbed in the small intestine. The unabsorbed flavonoids travel unchanged to the large intestine, where the microbiota thoroughly metabolizes them into several small aromatic compounds and phenolic acids that are readily absorbed in the colon [149]. Surprisingly, these metabolites from the colon (primarily phenylpropionic, phenylacetic, and benzoic acid derivatives) are present in plasma at greater concentrations (μM levels) than real flavonoids and their conjugated forms. As a result, parent compounds and their metabolites, along with the colonic metabolites produced by the gut microbiota, and are seen as the key contributors to the biological functions of flavonoids [149]. Despite having multiple pharmacological uses, flavonoid compounds typically demonstrate low oral bioavailability because of their limited solubility in water. To tackle this issue, various effective strategies, including the use of an absorption booster, structural modifications (e.g., glycosylation, prodrugs), and pharmaceutical advancements (e.g., crystals, carrier complexes, nanotechnology,), have been devised and utilized to deliver flavonoids with low water solubility. These formulation strategies can significantly enhance the oral bioavailability of flavonoids by increasing their solubility, dissolution rate, and permeability; protecting them from degradation or metabolism in the gastrointestinal system; and/or transporting them straight to their biological targets [150]. During the design phase of formulation, options for enhancing the dissolution properties of poorly water-soluble drugs include reduction in particle size (such as micronization, forming nanosuspensions, and creating solid lipid nanoparticles), complexation/solubilization (involving cyclodextrins and surfactants), drug dispersion in carriers (like phospholipid complexes and solid dispersions), as well as mesoporous silica templates [151, 152]. Moreover, for an ionizable drug, improving its dissolution rate or solubility via pH modification is considered a key approach [153]. In the latest years, the method of complexing herbal drug molecules with various carriers has emerged as a promising drug delivery system to enhance the bioavailability and therapeutic effectiveness of plant extracts/active compounds that have low absorption, since this approach can transport the drug molecules to the intended physiological target while preserving their integrity or bioactivity [154, 155].

Flavonoids have garnered growing interest because of their various health-benefiting properties. Particularly, the potential chemopreventive and antitumor properties of flavonoids and various natural substances are significant because cancer rates and deaths remain remarkably elevated worldwide [156]. Paclitaxel is an FDA-approved chemotherapeutic medication employed in curing various cancers, including breast, lung, ovarian, cervical, and pancreatic cancers. Prolonged use of paclitaxel results in the emergence of drug resistance and tumor advancement. To address these issues, a mixture of polyphenols like apigenin may be utilized. A study showed the combined effect of paclitaxel and apigenin in ovarian cancer treatment. Hep3B, A549, HeLa, and HEK293A cells received treatment with apigenin alongside paclitaxel. Consequently, both paclitaxel and apigenin triggered apoptosis by ultimately reducing the count of viable cells [157]. Integrating plant-based compounds with conventional chemotherapy and/or radiotherapy could result in improved outcomes and/or decrease in side effects. It is essential to further explore the global trends of epigenetic changes caused by phytochemicals to identify new targets and appealing agents in the battle against cancer [158].

Nonetheless, despite promising results from clinical analysis on flavonoids, the current proof for their clinical use remains inadequate. Moreover, the clinical trials conducted face various constraints, including a limited number of participators. Consequently, more clinical research might be required to better validate the capability of functional foods in cancer therapy and to create novel strategies (such as Nano-drug carriers and combined administration) to address bioavailability issues [158]. Additionally, numerous clinicians are often skeptical of phytochemicals for treating

life-threatening illnesses, and suitable animal and clinical research involving flavonoids remains quite scarce. Regarding cancer therapy, oncologists hold reservations about the antioxidant properties of flavonoids, particularly when used alongside traditional cytostatic medications. The role of antioxidant properties during chemotherapy remains uncertain. Typically, the application of flavonoids, particularly at very high doses as observed in various in vitro studies, needs to be scrutinized for them in vivo context. Additionally, the majority of flavonoids and other polyphenols exhibiting epigenetic effects in vitro have not been evaluated in animal models, and when they are, only a limited number of epigenetic markers have been thoroughly examined. Moreover, the total functional significance of epigenetic changes induced by flavonoids and other natural substances in chemotherapy and chemoprevention needs to be further clarified [159]. Undoubtedly, pharmacological medications are essential for cancer treatment, yet it appears that flavonoids and other natural substances may play a role in future therapeutic approaches [4]. Additional thorough research and anticipated mechanistic studies are needed to explore the advantageous effects of various flavonoids in detail. According to this data, minor adjustments in food and diet consumption may aid in the prevention and management of human illnesses, including cancer [160].

5. Conclusion

Flavonoids, a ubiquitous class of polyphenolic compounds abundant in fruits, vegetables, and medicinal plants, have emerged as pivotal epigenetic modulators with transformative potential in modern medicine. Their ability to interact with epigenetic machinery— histone modifications, DNA methylation and non-coding RNA regulation—positions them as natural agents capable of reversing pathogenic epigenetic alterations. This review underscores their therapeutic versatility, spanning cancer, neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes, while also highlighting the challenges and future directions for harnessing their full potential. Flavonoids exert their effects through precise epigenetic interventions. For instance, DNA methylation, a key mechanism in gene silencing, is modulated by flavonoids like genistein (soy isoflavones) and epigallocatechin gallate (EGCG) from green tea. These compounds inhibit DNA methyltransferases (DNMTs), reactivating tumor suppressor genes in cancers such as breast and prostate malignancies. Similarly, histone modifications, including acetylation and deacetylation, are influenced by curcumin (a turmeric derivative), which acts as a histone deacetylase (HDAC) inhibitor, restoring chromatin plasticity in neurodegenerative models of Alzheimer's disease. Non-coding RNAs, particularly miRNAs, are regulated by resveratrol (found in grapes), which downregulates oncogenic miR-21 while upregulating tumor-suppressive miR-34a, offering dual anticancer benefits. These examples illustrate the mechanistic diversity of flavonoids, enabling multitarget approaches to disease management.

In cancer, flavonoids like apigenin (celery, parsley) and luteolin (citrus fruits) not only suppress tumor growth but also enhance chemosensitivity by reversing hypermethylation of pro-apoptotic genes. For neurodegenerative diseases, fisetin (strawberries) enhances memory via histone acetylation-mediated synaptic plasticity, while quercetin (onions, apples) mitigates neuroinflammation by modulating miRNA-155. Cardiovascular benefits are evident in quercetin's regulation of endothelial function through miRNA-126, improving vascular integrity in hypertension models. In metabolic disorders, naringenin (citrus fruits) rectifies insulin resistance by altering DNA methylation patterns in gluconeogenic genes, offering a dietary strategy for diabetes management. Despite these preclinical successes, human trials remain sparse, underscoring the need for robust clinical validation to translate cellular findings into therapeutic outcomes.

A significant barrier to flavonoid efficacy is their poor bioavailability, driven by rapid metabolism, limited intestinal absorption, and enzymatic degradation. Innovative delivery systems, such as nanoparticle encapsulation (e.g., liposomal EGCG) and structural modifications (e.g., methylated or acetylated derivatives), are being explored to enhance stability and tissue targeting. Additionally, synergistic combinations with conventional drugs—such as curcumin with paclitaxel in breast cancer—could lower therapeutic doses and reduce side effects. Translational gaps further complicate progress; while murine models show promise, interspecies metabolic differences and divergent dosing regimens often obscure human applicability. Advanced models like 3D organoids and humanized mice could bridge this gap, providing more predictive platforms for preclinical testing. The integration of multi-omics technologies (epigenomics, metabolomics) will be crucial for unraveling flavonoid interactions at the molecular level. Artificial intelligence (AI) could accelerate drug discovery by predicting flavonoid-epigenome interactions or optimizing nanoformulations. Personalized medicine approaches, informed by genetic and epigenetic profiling, may tailor flavonoid regimens to individual patient needs, maximizing efficacy. For instance, polymorphisms in DNMT or HDAC genes could influence responsiveness to flavonoid therapy, necessitating biomarker-driven trials. Beyond therapy, flavonoids offer preventive potential. Public health initiatives promoting flavonoid-rich diets—akin to the Mediterranean diet—could mitigate disease incidence on a population scale. Policy measures, such as subsidies for organic produce or flavonoid-fortified foods, may enhance accessibility. Economically, flavonoid-based therapies could reduce healthcare burdens by offering low-cost alternatives to synthetic drugs, particularly in low-resource settings. Realizing the promise of flavonoids

demands concerted efforts from academia, industry, and policymakers. Increased funding for clinical trials, interdisciplinary collaborations (e.g., pharmacologists, nutritionists, and data scientists), and educational campaigns for healthcare providers are essential. By addressing current limitations and prioritizing translational research, flavonoids could redefine epigenetic therapy, offering safer, holistic, and cost-effective solutions for global health challenges.

Compliance with ethical standards

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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