Review Article

Targeting the NF-κB–Epigenetic axis using nutraceutical in chronic inflammatory disease management

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Abstract

Chronic inflammatory diseases, including cardiovascular disorders, metabolic syndrome, autoimmune diseases, cancer, and neurodegenerative conditions, are driven largely by continuous activation of nuclear factor kappa-B (NF-κB) signalling. While NF-κB is recognized as a transcription factor regulating immune and inflammatory gene expression, emerging evidence demonstrates that NF-κB activity is tightly controlled through epigenetic mechanisms such as DNA methylation, histone modifications, chromatin remodelling, and non-coding RNA regulation. Dietary polyphenols have gained increasing attention as epigenetic modulators of this NF-κB signalling pathway. This review focuses on current advances in understanding how dietary polyphenols including resveratrol, curcumin, epigallocatechin gallate (EGCG), quercetin, genistein, fisetin, luteolin, and epicatechin regulate inflammatory signalling through epigenetic reprogramming. These compounds influence DNA methyltransferases, histone acetyltransferases, histone deacetylases, Silent Information Regulator T1(SIRT1) activation, and microRNA networks, ultimately reducing NF-κB p65 acetylation, suppressing transcriptional activation of pro-inflammatory genes, and restoring immune homeostasis. Evidence from experimental studies reveal the potential of these polyphenols in managing chronic inflammatory disorders like atherosclerosis, type 2 diabetes, rheumatoid arthritis, cancer, and neuroinflammatory disorders. Despite promising insights, translational challenges remain, including limited bioavailability, variability in metabolism, optimal dosing strategies, and potential epigenome-wide effects. Future studies integrating nutrigenomics, epigenomics, systems biology, and clinical trials are required to validate polyphenol-based interventions. Targeting the NF-κB–epigenetic axis is an innovative strategy for precision therapeutics and management of chronic inflammatory diseases through dietary and nutraceutical approaches.

Keywords: NF-κB; Epigenetic regulation; Nutraceutical polyphenols; Chronic inflammation; DNA methylation; Histone modification.

Introduction

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation,[1] and acts by removing injurious stimuli and initiating the healing process.[2] Inflammation is therefore a vital defence mechanism for health. Acute

inflammation has a rapid onset, typically resolves within a few days, exhibits typical signs and symptoms, and is characterised by a cellular infiltrate primarily consisting of neutrophils.[3] The erythema observed in acute inflammation results from increased blood flow triggered by various mediators, like histamine acting on vascular smooth muscle cells. This process initially affects the arterioles and opens new capillary beds in the affected area.[4] Lymphatic vessels are active in acute inflammation. During inflammation, lymph flow increases, facilitating the drainage of oedema fluid that accumulates as a result of increased vascular permeability.

Along with fluid, leukocytes, cell debris, and microbes may also enter the lymph.[5] Similar to blood vessels, lymphatic vessels proliferate during inflammatory reactions to handle the increased load[6]. Thus, the acute inflammation is a protective mechanism that removes the injurious stimuli and initiates a healing process, restoring the homeostasis of the organism.[2. Uncontrolled acute inflammation, however, can become chronic, and may provide the basis of a variety of serious, chronic diseases.[4–6]

Chronic inflammatory diseases constitute a major global health challenge, contributing significantly to morbidity and mortality worldwide. It is estimated that approximately 43 million individuals were affected by these diseases in 2021, accounting for more than 75% of non-pandemic deaths globally. In the same year, 18 million deaths occurred before the age of 70, of which 82% were reported in low- and middle-income countries. Cardiovascular diseases were the leading cause of mortality among non-communicable diseases (NCDs) causing 19 million deaths, followed by cancers (10 million), chronic respiratory diseases (4 million), and diabetes (over 2 million including kidney disease deaths caused by diabetes). Together, these four groups of diseases accounted for 80% of all premature NCD deaths.[7]

Despite advances in pharmacological therapy, existing treatments mainly focus on slowing disease progression, managing complications, and controlling risk factors rather than reversing by addressing upstream molecular regulators of inflammation.[8] Persistent activation of inflammatory signalling pathways results in cytokine imbalance, oxidative stress, endothelial dysfunction, and progressive organ damage.[9]

The transcription factor nuclear factor-κB (NF-κB) functions as a master regulator of inflammation by controlling genes involved in immune activation, cell survival, and stress responses.[10] Dysregulated NF-κB signalling has been implicated in chronic inflammatory disorders like atherosclerosis, chronic obstructive pulmonary disease, chronic kidney disease, metabolic disorders, and neurodegenerative conditions.[11]

Recent discoveries highlight that inflammatory signalling is not governed solely by genetic mechanisms but is profoundly influenced by epigenetic regulation. DNA methylation patterns, histone modifications, and microRNA networks determine chromatin accessibility and transcriptional activation of inflammatory genes. Importantly, epigenetic modifications are dynamic and responsive to environmental and dietary factors.[12,13]

Nutraceutical polyphenols bioactive compounds abundant in fruits, vegetables, tea, spices, and medicinal plants—have attracted considerable interest for their ability to modulate epigenetic enzymes and signalling pathways. Rather than acting merely as antioxidants, these compounds influence transcriptional programming of inflammatory pathways, particularly the NF-κB axis.[14,15]

Chronic inflammatory diseases are increasingly understood not merely as conditions of persistent immune activation but as disorders of maladaptive inflammatory memory. Repeated environmental, metabolic, and lifestyle stimuli induce stable epigenetic alterations that maintain inflammatory gene accessibility even after removal of the initial trigger.[16,17] Within this framework, NF-κB functions not only as an inducible transcription factor but as an epigenetic regulator that recruits chromatin-modifying enzymes, establishes transcriptional memory, and sustains inflammatory signalling programs.

Emerging evidence suggests that nutraceutical polyphenols do not simply suppress inflammation transiently; rather, they may reprogram inflammatory chromatin states, restoring regulatory balance through coordinated modulation of DNA methylation, histone acetylation, and non-coding RNA networks.[14,18]

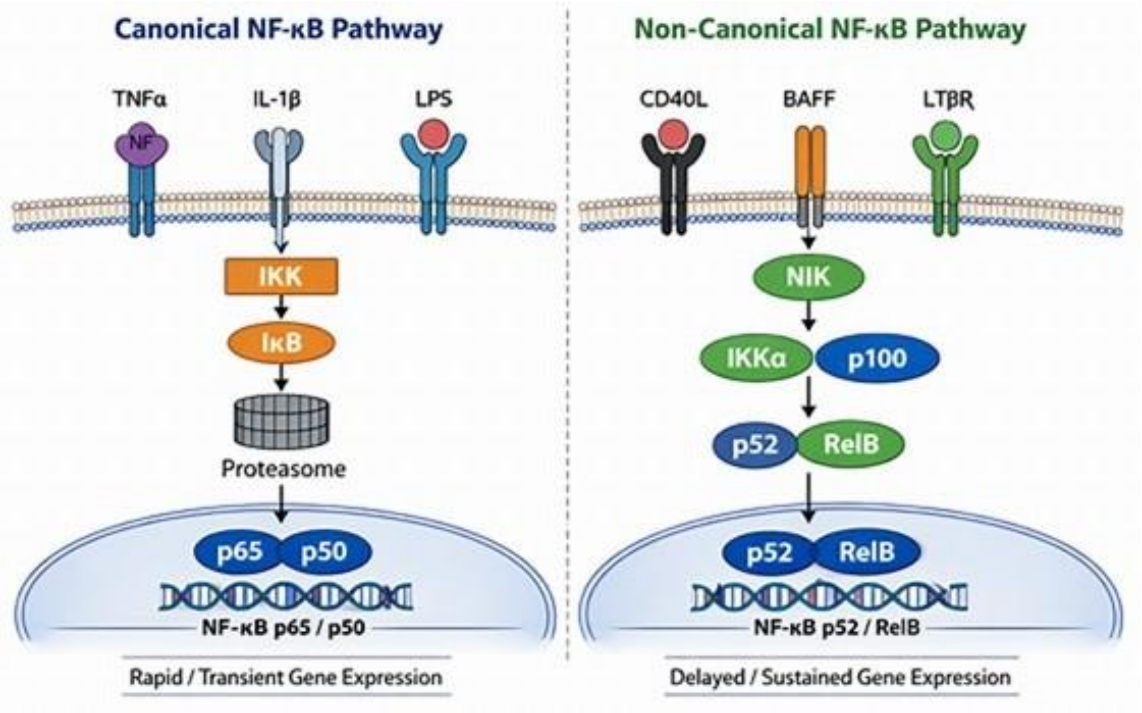
This review therefore examines chronic inflammatory diseases through the lens of the NF-κB–epigenetic switch, positioning dietary polyphenols as potential agents in nutraceutical therapy capable of reversing pathological inflammatory memory.

Nf-κb signalling in inflammation

Nuclear factor κB (NF-κB) was first identified in B cells in 1986, where it bound to the enhancer element of the κ-IgG chain gene.[19] Since then, NF-κB has been recognized as a family of inducible transcription factors expressed in nearly all cell types, regulating apoptosis, cell cycle progression, immune responses, and inflammation.[20,21] The NF-κB family consists of five members—NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel—which form homo- or heterodimers that bind to κB enhancer DNA elements to regulate transcription.[22,23] In resting cells, NF-κB dimers are sequestered in the cytoplasm by inhibitory proteins of the IκB family, of which IκBα being the most studied. Precursor proteins p105 and p100 also act as IκB-like inhibitors due to their C-terminal ankyrin repeat domains.[24–26]

NF-κB is activated in response to inflammatory stimuli such as cytokines, oxidative stress, microbial products, and metabolic imbalance. Activation commonly occurs through Toll-like receptor signalling and cytokine receptor engagement, leading to phosphorylation and degradation of inhibitory IκB proteins. This process allows NF-κB dimers to translocate into the nucleus and initiate transcription of pro-inflammatory genes.[27,28] Key NF-κB-regulated mediators include Tumour necrosis factor-α (TNF-α), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), Cyclooxygenase-2 (COX-2), and Inducible nitric oxide synthase (iNOS).[29]

Sustained NF-κB activation promotes chronic inflammation, oxidative damage, fibrosis, and metabolic dysfunction; therefore, modulation of NF-κB signalling represents a critical therapeutic target.[30] The NF-κB pathways that cells use to transmit signals to the nucleus include two primary mechanisms, known as the canonical and non-canonical NF-κB pathways, which, are schematically outlined in Figure 1. These two pathways rely on completely different receptor systems, proteins, and timelines to control gene expression. In the *canonical pathway*, ligands (such as TNF-α, IL-1β, and LPS) bind to their respective receptors, activating the IKK kinase complex. This complex phosphorylates IκB, triggering its degradation by the proteasome and releasing the p65/p50 dimer. The dimer then rapidly translocate to the nucleus to activate pro-inflammatory genes. This response is eventually terminated by the resynthesis of



IκB=Inhibitor of nuclear factor kappa B; IKK=IκB kinase complex; IKKα=IκB kinase alpha subunit; NIK=NF-κB-inducing kinase; TNFα, IL-1β, LPS, CD40L, BAFF, and Ltβ are ligands.

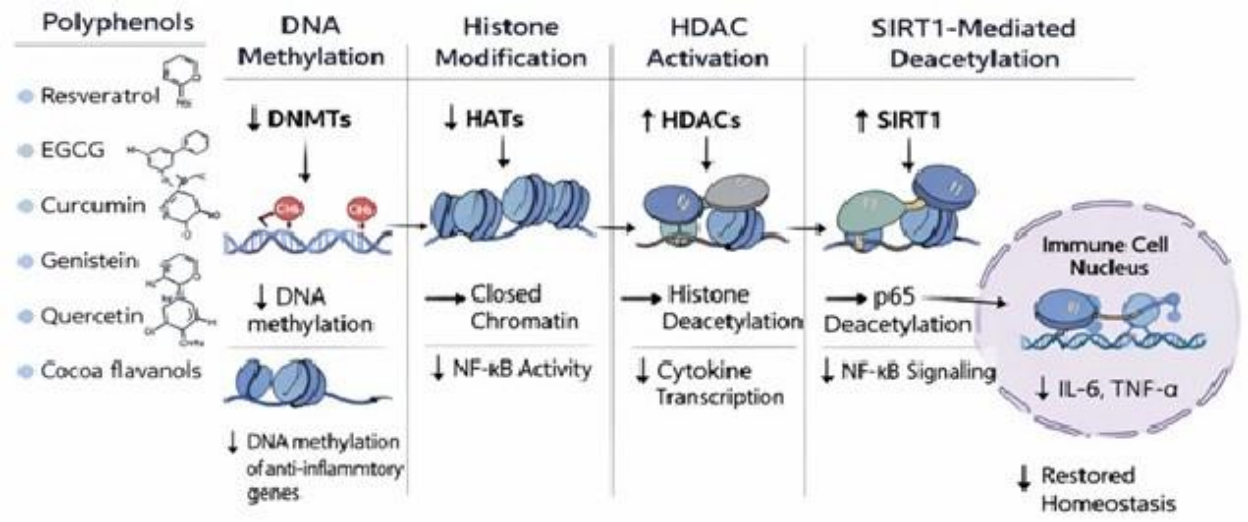
Figure 1. Schematic illustration of the canonical (left) and non-canonical (right) NF-κB pathways. Ligand binding to their respective receptors activates upstream kinases, leading to the degradation or processing of cytoplasmic inhibitors, followed by the release of the active nuclear factor dimers. The dimers then translocate to the nucleus and bind to specific DNA enhancer elements to regulate target gene transcription.

IκB and its subsequent rebinding to nuclear factors, p65 and p50. In contrast, in the *non-canonical pathway*, ligands (such as CD40L, BAFF, and LTβ) activate a distinct cascade mediated by NF-κB-inducing kinase (NIK) and its subunit, IKKα. This induces partial proteasomal processing of the precursor p100 into p52, generating the active p52/RelB dimer to drive a delayed, sustained transcriptional response.

Epigenetic regulation of nf-κb activity

Epigenetic mechanisms determine the magnitude and duration of NF-κB-mediated transcription. Immune tolerance is a highly regulated state and involves diverse mechanisms. Central to the induction of tolerance is the targeted modulation of T-cell activities of both effector and regulatory T-cell activities, in which transcription factors play a significant role. Members of the NF-κB family of transcription factors are critically involved in diverse T-cell responses and are regulated by multiple mechanisms that maintain immune tolerance and T-cell homeostasis.[30,31]

NF-κB, as a transcription factor, has been extensively studied in recent decades, and the molecular mechanisms that regulate NF-κB activities have been well documented. However, recent studies have revealed exciting new roles for NF-κB; in addition to its transcriptional activity, NF-κB can also activate diverse epigenetic mechanisms that mediate extensive chromatin remodelling of target genes to regulate T-cell activities.[32,33]



DNMT=DNA methyl transferase; EGCG=Epigallocatechin-3-gallate; HAT=Histone acetyltransferase; HDAC=Histone deacelylase; SIRT1=Sirtuin 1 (or Silent Information Regulator 1)

Figure 2: Modulation of DNMTs, HATs, and HDACs by polyphenols in immune regulation**.** Polyphenols suppress inflammation and help restore immune homeostasis through multiple epigenetic mechanisms by inhibiting DNMTs, thereby promoting the production of anti-inflammatory mediators through hypomethylation of genes involved; by inhibiting HATs, thereby influencing inflammatory signalling pathways through modulating chromatin structure; and by activating HDACs and SIRT1, thereby reducing the production of pro-inflammatory mediators through silencing specific genes.

Recent discoveries have expanded our understanding of NFkB factor. Beyond its classical role in gene transcription, NF-κB has now been shown to influence epigenetic processes (Figure 2). Through these mechanisms, NF-κB exerts broad control over T-cell function, revealing new dimensions of its role in immune regulation.[33,34]

DNA methylation

DNA methyltransferases (DNMTs) regulate the methylation of promoter regions of inflammatory genes. Hypomethylation enhances transcription of cytokine genes, whereas hypermethylation suppresses anti-inflammatory mediators.[35]

DNA methylation involves the covalent addition of a methyl group to the 5’ carbon of cytosine residues within CpG dinucleotides, catalysed by a family of DNA methyltransferases (DNMT1, DNMT3A, DNMT3B). This modification typically acts as a transcriptional repressor, silencing gene expression by hindering transcription factor binding and recruiting methyl-CpG binding proteins.[36,37] In chronic inflammatory diseases, promoter hypomethylation enhances transcription of cytokine genes (e.g., TNF, IL6, CXCL8), whereas hypermethylation suppresses anti-inflammatory mediators such as suppressors of cytokine signalling (SOCS) and PPAR-γ. Aberrant DNA methylation patterns have been identified as biomarkers and functional contributors in atherosclerosis, type 2 diabetes, chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis.[38,39]

Resveratrol has been shown to increase CpG methylation at the promoters of pro-inflammatory cytokine genes (IL-1, IL-6, TNF-α, IFN-γ) while decreasing methylation at the IL-10 gene promoter in the arterial intima of diabetic rats, correlating with reduced systemic inflammation and

endothelial protection.[40–42] Epigallocatechin gallate, (EGCG) a natural antioxidant compound found mainly in green tea inhibits DNMT activity and has been shown to reactivate methylation-silenced genes in cancer cell lines, some of which are negative regulators of NF-κB.[43,44] Curcumin modulates DNMT function in models of diabetic retinopathy and colon cancer, contributing to epigenetic reprogramming of inflammatory and tumour suppressor gene networks. Consumption of cocoa flavanols has been shown to reduce global DNA methylation in peripheral leukocytes in a randomized trial, with implications for cardiovascular inflammatory risk.[45–47]

Histone modifications

Histone acetylation promotes chromatin relaxation and transcriptional activation. Histone acetyltransferases enhance NF-κB activity, whereas histone deacetylases (HDACs) suppress inflammatory gene expression.[48]

HAT inhibition is the most widely reported epigenetic mechanism through which dietary polyphenols suppress NF-κB. The HATs p300 and CBP function as transcriptional co-activators for the p65 subunit: when recruited to NF-κB target gene promoters, they acetylate both histone H3/H4 tails and the p65 subunit itself at K310, amplifying transcriptional output. Several polyphenols directly inhibit p300/CBP acetyltransferase activity, thereby reducing p65 acetylation and chromatin remodelling at inflammatory gene promoters.[14,49,50]

Curcumin is among the most potent dietary HAT inhibitors described to date. It inhibits p300 acetyltransferase activity *in vitro* with an IC50 (half maximal inhibitory concentration) in the micromolar range and has been shown to reduce p65 acetylation and NF-κB transcriptional activity in multiple cell models, including human monocytes and synovial fibroblasts. In THP-1 monocytes under high-glucose conditions, curcumin significantly reduces HAT activity and p300 protein levels while simultaneously inducing HDAC2 expression, resulting in decreased production of IL-6 and TNF-α.[51,52]

EGCG, the predominant catechin in green tea, likewise potently inhibits p300/CBP HAT activity. Choi and colleagues demonstrated that EGCG-mediated HAT inhibition led to p65 hypoacetylation and suppressed TNF-α-induced expression of IL-6, COX-2, and iNOS in multiple cell types. Similarly, quercetin has been shown to suppress p300 activity in breast cancer and endothelial cells, reducing p300-mediated acetylation of the p65 subunit and downstream angiogenic and inflammatory gene expression.[53,54]

HDAC activation and SIRT1-mediated deacetylation

In parallel with HAT inhibition, many polyphenols promote the deacetylation of p65 and inflammatory gene histones by activating HDACs, particularly the NAD+-dependent deacetylase SIRT1. SIRT1 occupies a privileged position in NF-κB regulation: it directly deacetylates p65 at K310, the key activating acetylation site, and has been shown to inhibit NF-κB-mediated transcription and reduce inflammatory cytokine production in macrophages and other immune cells.[55,56]

Resveratrol is the archetypal SIRT1-activating polyphenol. It directly activates SIRT1 through an allosteric mechanism, enhancing its catalytic activity towards p65 and other substrates. Pan and colleagues demonstrated that resveratrol-induced SIRT1 activation suppressed TNF-α-induced NF-κB and p38 MAPK signalling in human umbilical vein endothelial cells (HUVECs), protecting against endothelial inflammation.[57] In a randomized controlled trial in type 2 diabetes patients, resveratrol supplementation over six

months significantly increased SIRT1 expression in peripheral blood mononuclear cells, correlated with reduced H3K56 acetylation and decreased NF-κB-dependent inflammatory gene expression.[58–62]

Genistein, the soy isoflavone, similarly increases SIRT1 expression, leading to downstream inhibition of NF-κB p65 and reduction of IL-1β levels in experimental models of diabetes.[63,64] Combined treatment with luteolin and fisetin has been shown to synergistically activate SIRT1 while suppressing HAT activity, providing additive anti-inflammatory effects in THP-1 monocytes. The convergence of HAT inhibition and HDAC/SIRT1 activation by polyphenols—operating in concert to reduce p65 acetylation and NF-κB activity—represents a robust and potentially synergistic therapeutic strategy.[65,66]

Non-coding RNA regulation

MicroRNAs such as miR-146a and miR-155 modulate NF-κB signalling by targeting pathway components, thus providing an additional regulatory layer. Non-coding microRNAs (miRNAs) regulate NF-κB signalling at multiple levels, by targeting upstream regulators (e.g., IκBα, IKK subunits), the p65 subunit itself, and downstream effectors (Table 1). Several oncomiRs and inflammation-associated miRNAs are themselves NF-κB transcriptional targets, creating regulatory feedback loops. Dietary polyphenols are emerging as significant modulators of these miRNA networks.[67]

Genistein regulates miRNA-155, a key pro-inflammatory miRNA that normally suppresses Suppressor of Cytokine Signalling 1 (SOCS1), a negative regulator of the NF-κB pathway. By upregulating SOCS1 through miRNA-155 suppression, genistein inhibits NF-κB-mediated inflammation in endothelial cells exposed to oxidized LDL.[68,69] Curcumin has been shown to alter miRNA expression profiles in pancreatic cancer cells, affecting pathways that regulate NF-κB activity. Resveratrol and its analogue pterostilbene modulate miRNA-mediated regulation of SIRT1 and DNMT expression in prostate cancer models, with anti-inflammatory consequences.[70,71]

Disease-specific implications

Cardiovascular disease and atherosclerosis

NF-κB-driven endothelial inflammation is a central event in atherogenesis, promoting expression of adhesion molecules, monocyte recruitment, and smooth muscle cell proliferation. Resveratrol, through SIRT1-mediated p65 deacetylation, has been shown to suppress TNF-α-induced NF-κB activation in HUVECs, with protective effects on endothelial function.[72–75] Genistein modulates the miRNA-155/SOCS1/NF-κB axis to reduce oxidized LDL-induced endothelial inflammation.[76,77] Cocoa epicatechin consumption reduces DNA methylation in leukocytes of individuals with cardiovascular risk factors in a clinical RCT. These findings collectively support a role for dietary polyphenols as epigenetic cardioprotective agents operating through NF-κB inhibition.[78,79]

Type 2 diabetes and metabolic syndrome

Chronic low-grade NF-κB-driven inflammation in adipose tissue, liver, and immune cells contributes fundamentally to insulin resistance and the progression of type 2 diabetes. Curcumin, EGCG, fisetin, and luteolin have each been shown to suppress NF-κB-dependent cytokine production in monocytes under high-glucose conditions by inhibiting HAT activity and activating HDACs. In a clinical randomized controlled trial resveratrol supplementation in type 2

Table 1. Dietary polyphenols: Epigenetic targets and effects on NF-κB signaling

Polyphenol	Dietary source	Epigenetic mechanism	Effect on NF-κB signalling
Resveratrol	Grapes, red wine	SIRT1 activation, DNMT modulation	Deacetylates p65; inhibits NF-κB-mediated transcription; reduces IL-6, TNF-α
Curcumin	Turmeric	HAT inhibition, HDAC/DNMT modulation, miRNA regulation	Reduces p65 acetylation; inhibits IκBα phosphorylation; downregulates COX-2, iNOS, TNF-α, IL-6
EGCG	Green tea	HAT inhibition, DNMT inhibition, HDAC activation	Hypoacetylates p65; suppresses NF-κB-mediated IL-6, COX-2, iNOS
Quercetin	Onions, broccoli, blueberries	HAT inhibition (p300/CBP)	Suppresses p300-mediated NF-κB acetylation; blocks NF-κB binding to pro-inflammatory gene promoters
Genistein	Soy, legumes	DNMT inhibition, HAT activation, SIRT1 activation, miRNA	Increases SIRT1; reduces NF-κB and IL-1β; modulates miRNA-155/SOCS1
Fisetin	Vegetables, strawberries	HDAC activation, HAT inhibition	Deacetylates p65; suppresses cytokine release via NF-κB pathway
Luteolin	Parsley, celery	HDAC activation, HAT/p300 inhibition	Deacetylates p65; decreases IL-6 and TNF-α; activates SIRT1 (combined with fisetin)
Epicatechin	Cocoa, red wine	HDAC modulation, HAT inhibition	Prevents H3K9 acetylation and H3K4 dimethylation; reduces NF-κB expression and TNF-α
Gallic acid	Tea, berries, olive oil	HAT inhibition, HDAC activation	Decreases HAT activity in TNF-α-activated monocytes; attenuates inflammatory response
Ellagic acid	Berries, pomegranates	HAT inhibition, HDAC activation	Reduces HAT and increases HDAC activity in monocytic cells

diabetes patients increased SIRT1 expression and reduced NF-κB-associated histone acetylation marks over six months, suggesting clinically relevant epigenetic anti-inflammatory effects. Genistein similarly increases SIRT1 and reduces NF-κB activity in diabetic animal models.[80,81]

Rheumatoid arthritis and inflammatory joint disease

Synovial NF-κB hyperactivation drives the production of IL-6, TNF-α, matrix metalloproteinases, and RANKL, mediating cartilage and bone destruction in rheumatoid arthritis (RA). Curcumin has been shown to reduce histone H3 acetylation at the IL-6 promoter in RA synovial fibroblasts by inhibiting HAT activity, thereby decreasing IL-6 expression. SIRT1 has been identified as a key epigenetic suppressor of NF-κB in RA, and resveratrol's activation of SIRT1-mediated inhibition of the RANKL pathway represents a potential therapeutic approach. EGCG has shown similar epigenetic anti-NF-κB effects in relevant cell models.[82,83]

Cancer

Constitutive NF-κB activation in tumour cells and the tumour microenvironment promotes survival, proliferation, invasion, and immune evasion. The epigenetic anti-NF-κB activities of polyphenols are relevant to oncology in several ways. EGCG inhibits DNMT activity, potentially reactivating epigenetically silenced tumour suppressor genes that act as negative regulators of NF-κB. Curcumin and resveratrol modulate HDAC and SIRT1 activity in cancer cell models, suppressing NF-κB-driven survival signals. Genistein reverses hypermethylation of tumour suppressor genes and modulates miRNA networks that regulate NF-κB in prostate and other cancers.[84–86]

Neurodegenerative Diseases

Neuroinflammation driven by microglial NF-κB activation is a key pathological feature of Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions. Curcumin, resveratrol, quercetin, and luteolin have all demonstrated anti-neuroinflammatory properties in cellular and animal models, at least in part through epigenetic suppression of NF-κB. Curcumin modulates Nrf-2 signalling and antioxidant gene expression through epigenetic mechanisms, indirectly reducing oxidative-stress-driven NF-κB activation in neural tissues.[87–89]

Translational challenges as therapeutics

Bioavailability and metabolism

A fundamental challenge in translating the epigenetic NF-κB- modulating effects of polyphenols into clinical benefit arises from their generally poor bioavailability. Most polyphenols undergo extensive metabolism, rapid conjugation (glucuronidation, sulfation, methylation), and microbial transformation in the gut, resulting in low systemic bioavailability of the parent compound. The bioactive metabolites that reach target tissues may differ substantially in potency and mechanism from the parent polyphenol. For example, resveratrol undergoes rapid metabolism to piceid and other conjugates *in vivo*, which may retain some SIRT1-activating activity but at generally lower potency.[90–94]

Strategies to enhance polyphenol bioavailability under investigation include nanoparticle encapsulation, liposomal formulations, co-administration with bioavailability enhancers (e.g., piperine with curcumin), and structural modifications to produce more bioavailable analogues (e.g., pterostilbene as a resveratrol analogue with greater lipophilicity and metabolic stability).

Dosing and clinical evidence

The concentrations of polyphenols required to produce epigenetic effects in cell culture models frequently exceed those achievable through dietary intake alone, raising questions about the clinical relevance of observed *in vitro* effects. Randomized controlled trials are limited in number and often confounded by issues of standardization, compliance, and variability in polyphenol metabolism between individuals. The two human trials reviewed here (resveratrol in type 2 diabetes and cocoa flavanols in cardiovascular risk) demonstrate proof-of-concept for clinically measurable epigenetic effects, but larger, more rigorously designed trials are needed.[95,96]

Polyphenol interactions and dietary context

The human diet contains combinations of hundreds to thousands of polyphenols; however, the synergistic or antagonistic interactions between them remain poorly understood. The observed additive anti-inflammatory effects of fisetin-luteolin combination and the complementary mechanisms of resveratrol (SIRT1 activation)

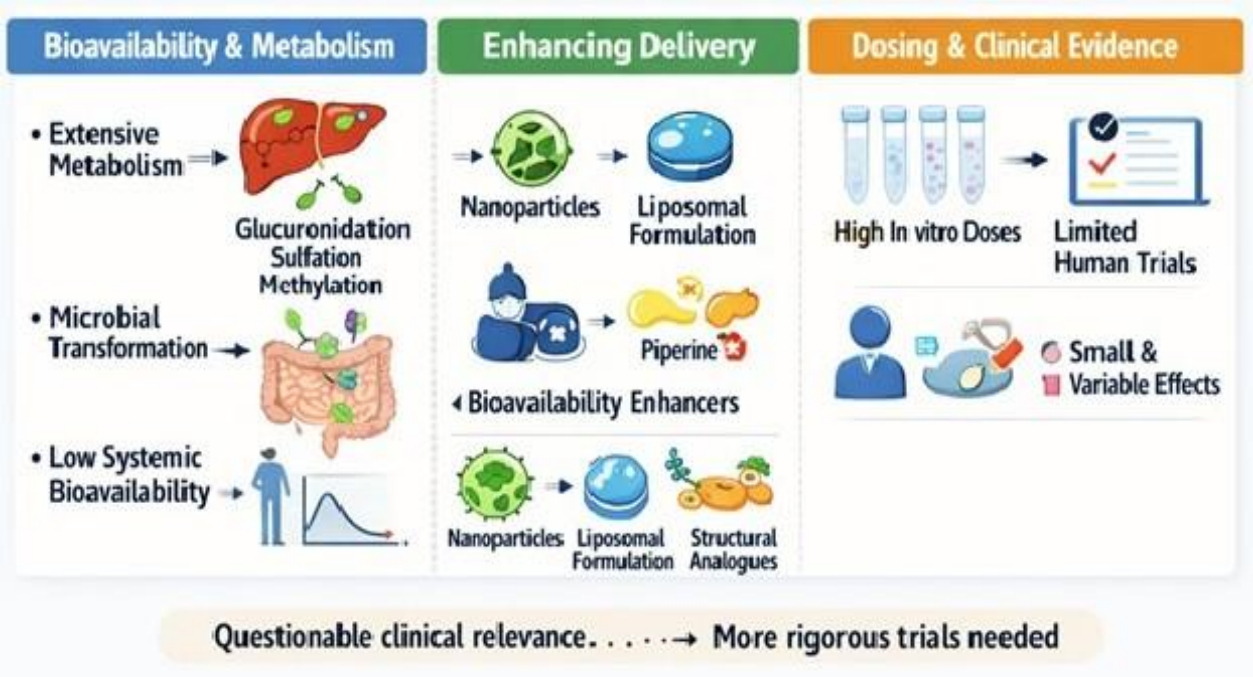


Figure 3. Clinical challenges of polyphenols**.** Polyphenols show limited clinical translation due to poor bioavailability, metabolic transformation, and rapid clearance. Delivery strategies (nanoparticles, liposomes, piperine) improve uptake, but high *in vitro* doses, few human trials, and variable effects highlight the need for more rigorous evidence.

and EGCG (HAT inhibition) suggest that co-administration or dietary patterns rich in diverse polyphenols may produce greater epigenetic NF-κB inhibition than individual compounds alone (Figure 3). Future research should examine polyphenol combinations and dietary pattern effects on NF-κB epigenetics.[69,97]

Epigenome-wide effects and off-target risks

Epigenetic modifications are, by nature, pleiotropic: interventions that modulate HAT, HDAC, DNMT, or miRNA activity will affect the expression of thousands of genes, beyond those regulated by NF-κB. The long-term consequences of dietary epigenetic modulation by polyphenols, including potential effects on immune tolerance, cell differentiation, and genomic stability, are not well characterized. High-dose polyphenol supplementation has been associated with pro-oxidative effects and, in the case of isoflavones, potential hormonal effects, underscoring the need for careful dose-response characterization and long-term safety monitoring in clinical trials.[98,99]

Conclusion

Dietary polyphenols have been shown to exert anti-inflammatory effects through the epigenetic regulation of NF-κB activity. This review discusses how polyphenols such as resveratrol, curcumin, EGCG, quercetin, genistein, fisetin, luteolin, and epicatechin engage multiple epigenetic targets through HAT inhibition, HDAC/SIRT1 activation, DNA methylation modulation, and miRNA regulation, to reduce p65 acetylation, suppress NF-κB transcriptional activity, and decrease production of pro-inflammatory cytokines and mediators.

The interplay of HAT inhibition and SIRT1-mediated p65 deacetylation emerges as an epigenetic axis through which polyphenols modulate NF-κB. Different classes of

polyphenols can work together, suggesting that a variety of dietary sources may collectively provide epigenetic anti-inflammatory protection, supporting the use of diverse diets and polyphenol combinations in therapeutic strategies.

Despite promising preclinical evidence and emerging clinical data, significant challenges remain in translating polyphenol epigenetics into clinical practice. The issues of bioavailability, effective dosing, the complexity of polyphenol metabolism, interindividual variability, and the potential for off-target epigenomic effects must be addressed through rigorous clinical trial design and mechanistic research. However, the epigenetic modulation of NF-κB by dietary polyphenols is an emerging and rapidly advancing area of research that holds significant promise for the prevention and management of chronic inflammatory diseases.

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Conflict of interest
There are no conflicts of interest.

References

1. Medzhitov R. Inflammation 2010: New Adventures of an Old Flame Cell 2010;140(6):771–6.
2. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clin Exp Immunol 2007;147(2):227–35.
3. Hannoodee S, Nasuruddin DN. Acute Inflammatory Response 2026. PubMed PMID: 32310543.
4. Abdulkhaleq LA, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MNM. The crucial roles of inflammatory mediators in inflammation: A review Vet World 2018;11(5):627–35.
5. Schwager S, Detmar M. Inflammation and Lymphatic Function. Front Immunol 2019;10.
6. Zgraggen S, Ochsenbein AM, Detmar M. An Important Role of Blood and Lymphatic Vessels in Inflammation and Allergy. J Allergy (Cairo). 2013;2013:1–9.
7. Noncommunicable diseases W (2025). WHO. 2025. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
8. Sharma P, Kishore A, De I, Negi S, Kumar G, Bhardwaj S, et al. Mitigating neuroinflammation in Parkinson's disease: Exploring the role of proinflammatory cytokines and the potential of phytochemicals as natural therapeutics. Neurochem Int 2023;170:105604.
9. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol. 2008;103(5):398–406.
10. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther 2017;2(1):17023.
11. Mao H, Zhao X, Sun S cong. NF-κB in inflammation and cancer. Cell Mol Immunol 2025;22(8):811–39.
12. Makridou A, Elemes DI, Liakou ME, Theotokis P, Gargani S, Vakirlis E, et al. Epigenetic Therapies for Inflammatory and Immune-Mediated Skin Diseases Biomedicines. 2026;14(2):373.
13. Vezzani B, Carinci M, Previati M, Giacovazzi S, Della Sala M, Gafà R, et al. Epigenetic Regulation: A Link between Inflammation and Carcinogenesis. Cancers (Basel) 2022;14(5):1221.
14. Číž M, Dvořáková A, Skočková V, Kubala L. The Role of Dietary Phenolic Compounds in Epigenetic Modulation Involved in Inflammatory Processes. Antioxidants (Basel) 2020;9(8):691.
15. Upadhyay S, Dixit M. Role of Polyphenols and Other Phytochemicals on Molecular Signaling. Oxid Med Cell Longev 2015;2015:1–15.
16. Kim HG, Rincon JC, Efron PA, Maile R. DAMP-driven trained immunity: metabolic and epigenetic reprogramming in critical illness and chronic inflammation. Front Immunol 2025;16:1669054.
17. Faraji J, Metz GAS. Environmental epigenetics: new horizons in redefining biological and health outcomes. Environ Int 2026;208:110072.
18. Rahman I. Dietary polyphenols mediated regulation of oxidative stress and chromatin remodeling in inflammation. Nutr Rev 2008;66:S42–5.
19. Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell 1986;46(5):705–16.
20. Pai S, Thomas R. Immune deficiency or hyperactivity-Nf-κb illuminates autoimmunity. J Autoimmun 2008;31(3):245–51.
21. Fei Chen BSP, Laurence M. Demers BSP, Xianglin Shi BSP. Upstream Signal Transduction of NF-κB Activation. Curr Drug Targets Inflamm Allergy 2002;1(2):137–49.
22. Nabel GJ, Verma IM. Proposed NF-κB/IκB family nomenclature. Genes Dev 1993;7(11):2063.
23. Hayden MS, West AP, Ghosh S. NF-κB and the immune response. Oncogene 2006;25(51):6758–80.
24. Scheidereit C, Krappmann D. NF-κB Pathway. In: Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine. Berlin, Heidelberg: Springer Berlin Heidelberg; 2005. p. 1286–92.
25. Oeckinghaus A, Ghosh S. The NF- B Family of Transcription Factors and Its Regulation. Cold Spring Harb Perspect Biol 2009;1(4):a000034.

26. Hinz M, Scheidereit C. The IκB kinase complex in <scp>NF</scp> -κB regulation and beyond. EMBO Rep 2014;15(1):46–61.
27. Anilkumar S, Wright-Jin E. NF-κB as an Inducible Regulator of Inflammation in the Central Nervous System. Cells 2024;13(6):485.
28. Luo JL. IKK/NF- B signaling: balancing life and death - a new approach to cancer therapy. J Clin Invest 2005;115(10):2625–32.
29. Sivamaruthi BS, Raghani N, Chorawala M, Bhattacharya S, Prajapati BG, Elossaily GM, et al. NF-κB Pathway and Its Inhibitors: A Promising Frontier in the Management of Alzheimer's Disease. Biomedicines 2023;11(9):2587.
30. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduct Target Ther 2024;9(1):53.
31. De Majo F, Calore M. Chromatin remodelling and epigenetic state regulation by non-coding RNAs in the diseased heart. Noncoding RNA Res 2018;3(1):20–8.
32. Hayden MS, Ghosh S. NF-κB, the first quarter-century: remarkable progress and outstanding questions. Genes Dev 2012;26(3):203–34.
33. Hoffmann A, Cheng G, Baltimore D. NF-κB: master regulator of cellular responses in health and disease. Immun Inflamm 2025;1(1):2.
34. Zhang L, Xiao X, Arnold PR, Li XC. Transcriptional and epigenetic regulation of immune tolerance: roles of the NF-κB family members. Cell Mol Immunol 2019;16(4):315–23.
35. Liaw A, Liu C, Ivanovski S, Han P. The Relevance of DNA Methylation and Histone Modification in Periodontitis: A Scoping Review. Cells 2022;11(20):3211.
36. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002;16(1):6–21.
37. Wu H, Lu Q. Epigenetics. In: Perricone C, Shoenfeld Y, editors. Mosaic of Autoimmunity. Elsevier; 2019. pp. 105–14.
38. Suzuki H, Toyota M, Kondo Y, Shinomura Y. Inflammation-Related Aberrant Patterns of DNA Methylation: Detection and Role in Epigenetic Deregulation of Cancer Cell Transcriptome. Methods Mol Biol 2009;512:55–69.
39. Zhao J, Wei K, Chang C, Xu L, Jiang P, Guo S, et al. DNA Methylation of T Lymphocytes as a Therapeutic Target: Implications for Rheumatoid Arthritis Etiology. Front Immunol 2022;13:863703.
40. S Panickar K. Anti-Inflammatory Effects Of Resveratrol And Related Polyphenols Contribute To Their Potential Beneficial Effects In Aging. Food Sci Nutr 2020;6(4):1–11.
41. Palsamy P, Sivakumar S, Subramanian S. Resveratrol attenuates hyperglycemia-mediated oxidative stress, proinflammatory cytokines and protects hepatocytes ultrastructure in streptozotocin–nicotinamide-induced experimental diabetic rats. Chem Biol Interact 2010;186(2):200–10.
42. Lou X dan, Wang H dong, Xia S jin, Skog S, Sun J. Effects of Resveratrol on the Expression and DNA Methylation of Cytokine Genes in Diabetic Rat Aortas. Arch Immunol Ther Exp (Warsz) 2014;62(4):329–40.
43. Fang MZ, Wang Y, Ai N, Hou Z, Sun Y, Lu H, et al. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res 2003;63(22):7563–70.
44. Sheng J, Shi W, Guo H, Long W, Wang Y, Qi J, et al. The Inhibitory Effect of (−)-Epigallocatechin-3-Gallate on Breast Cancer Progression via Reducing SCUBE2 Methylation and DNMT Activity. Molecules 2019;24(16):2899.
45. Link A, Balaguer F, Shen Y, Lozano JJ, Leung HCE, Boland CR, et al. Curcumin Modulates DNA Methylation in Colorectal Cancer Cells. PLoS One 2013;8(2):e57709.
46. Maugeri A, Mazzone MG, Giuliano F, Vinciguerra M, Basile G, Barchitta M, et al. Curcumin Modulates DNA Methyltransferase Functions in a Cellular Model of Diabetic Retinopathy. Oxid Med Cell Longev 2018;2018:5407482.
47. Smail SW, Bergsten P, Taha KO, Yashooa RKh, Hawezy DJ, Abbas MA, et al. Curcumin: biochemistry, pharmacology, advanced drug delivery systems, and its epigenetic role in combating cancer. Front Pharmacol 2025;16:1695200.
48. Chen HP, Zhao YT, Zhao TC. Histone Deacetylases and Mechanisms of Regulation of Gene Expression. Crit Rev Oncog 2015;20(1–2):35–47.
49. Rajendran P, Ho E, Williams DE, Dashwood RH. Dietary phytochemicals, HDAC inhibition, and DNA damage/repair defects in cancer cells. Clin Epigenetics 2011;3(1):4.
50. Ullah H, De Filippis A, Santarcangelo C, Daglia M. Epigenetic regulation by polyphenols in diabetes and related complications. Med J Nutrition Metab 2020;13(4):289–310.
51. Morimoto T, Sunagawa Y, Kawamura T, Takaya T, Wada H, Nagasawa A, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J Clin Invest 2008;118(3):868-78.
52. Hassan F ul, Rehman MS ur, Khan MS, Ali MA, Javed A, Nawaz A, et al. Curcumin as an Alternative Epigenetic Modulator: Mechanism of Action and Potential Effects. Front Genet 2019;10:514.
53. Xiao X, Shi D, Liu L, Wang J, Xie X, Kang T, et al. Quercetin Suppresses Cyclooxygenase-2 Expression and Angiogenesis through Inactivation of P300 Signaling. PLoS One. 2011;6(8):e22934.
54. Choi KC, Myung GJ, Lee YH, Joo CY, Seung HK, Kang HB, et al. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. Cancer Res 2009;69(2):583–92.
55. Yang H, Feldser HG, Zhang W, Zhong Z, Loh C, Ellis J. SIRT1 activators promote p65 deacetylation and suppress TNFa stimulated NF-kB activation. The FASEB Journal 2011;25:945.12-945.12.
56. Rahman I, Chung S. Dietary Polyphenols, Deacetylases and Chromatin Remodeling in

Inflammation. J Nutrigenet Nutrigenomics. 2010;3(4–6):220–30.
57. Pan W, Yu H, Huang S, Zhu P. Resveratrol Protects against TNF-α-Induced Injury in Human Umbilical Endothelial Cells through Promoting Sirtuin-1-Induced Repression of NF-KB and p38 MAPK. PLoS One 2016;11(1):e0147034.
58. Gerszon J, Rodacka A, Puchała M. Antioxidant Properties of Resveratrol and its Protective Effects in Neurodegenerative Diseases. Adv Cell Biol 2014;4(2):97–117.
59 . Iside C, Scafuro M, Nebbioso A, Altucci L. SIRT1 Activation by Natural Phytochemicals: An Overview. Front Pharmacol 2020;11:1225.
60. Ciccone L, Piragine E, Brogi S, Camodeca C, Fucci R, Calderone V, et al. Resveratrol-like Compounds as SIRT1 Activators. Int J Mol Sci 2022;23(23):15105.
61. Zhu X, Liu Q, Wang M, Liang M, Yang X, Xu X, et al. Activation of Sirt1 by Resveratrol Inhibits TNF-α Induced Inflammation in Fibroblasts. PLoS One 2011;6(11):e27081.
62. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules 2021;26(1):229.
63. Dafriani P, Indrawati Lipoeto N, Diana Morika H, Arman E, Sartiwi W, Annita A. Effect of Genistein on Interleukin 1β and Transforming Growth Factor β in Diabetic Rat. Journal of Food and Nutrition Research 2019;7(4):287–90.
64. Yousefi H, Alihemmati A, Karimi P, Alipour MR, Habibi P, Ahmadiasl N. Effect of genistein on expression of pancreatic SIRT1, inflammatory cytokines and histological changes in ovariectomized diabetic rat. Iran J Basic Med Sci 2017;20(4):423–9.
65. Gutiérrez-Venegas G, Contreras-Sánchez A. Luteolin and fisetin inhibit the effects of lipopolysaccharide obtained from Porphyromonas gingivalis in human gingival fibroblasts. Mol Biol Rep 2013;40(1):477–85.
66. Kim A, Yun JM. Combination Treatments with Luteolin and Fisetin Enhance Anti-Inflammatory Effects in High Glucose-Treated THP-1 Cells Through Histone Acetyltransferase/Histone Deacetylase Regulation. J Med Food 2017;20(8):782–9.
67. Lui PY, Jin DY, Stevenson NJ. MicroRNA: master controllers of intracellular signaling pathways. Cell Mol Life Sci 2015;72(18):3531–42.
68. Zhang H, Zhao Z, Pang X, Yang J, Yu H, Zhang Y, et al. Genistein Protects Against Ox-LDL-Induced Inflammation Through MicroRNA-155/SOCS1-Mediated Repression of NF-κB Signaling Pathway in HUVECs. Inflammation 2017;40(4):1450–9.
69. Javed Z, Khan K, Herrera-Bravo J, Naeem S, Iqbal MJ, Sadia H, et al. Genistein as a regulator of signaling pathways and microRNAs in different types of cancers. Cancer Cell Int 2021;21(1):388.
70. Fattahi MR, Shoja F, Mojaradi MA, Nazarinezhad P, Dehghanbanadaki H, Arefnezhad R, et al. Therapeutic potentials of curcumin in prostate cancer: a comprehensive review of pathways and clinical prospects. Prostate Int 2025. Available on: https://doi.org/10.1016/j.prnil.2025.10.001 [Last assessed on 2026 Jun 19].
71. Wang M, Jiang S, Zhou L, Yu F, Ding H, Li P, et al. Potential Mechanisms of Action of Curcumin for Cancer Prevention: Focus on Cellular Signaling Pathways and miRNAs. Int J Biol Sci 2019;15(6):1200–14.
72. D'Onofrio N, Servillo L, Balestrieri ML. SIRT1 and SIRT6 Signaling Pathways in Cardiovascular Disease Protection. Antioxid Redox Signal 2018;28(8):711–32.
73. Collins T, Cybulsky MI. NF-κB: pivotal mediator or innocent bystander in atherogenesis? J Clin Invest 2001;107(3):255–64.
74. Kitada M, Ogura Y, Koya D. The protective role of Sirt1 in vascular tissue: its relationship to vascular aging and atherosclerosis. Aging (Albany NY) 2016;8(10):2290–307.
75. Kang H. Regulation of Acetylation States by Nutrients in the Inhibition of Vascular Inflammation and Atherosclerosis. Int J Mol Sci 2023;24(11):9338.
76. Xie X, Cong L, Liu S, Xiang L, Fu X. Genistein alleviates chronic vascular inflammatory response via the miR-21/NF-κB p65 axis in lipopolysaccharide-treated mice. Mol Med Rep 2021;23(3):192.
77. Milenkovic D, Declerck K, Guttman Y, Kerem Z, Claude S, Weseler AR, et al. (−)-Epicatechin metabolites promote vascular health through epigenetic reprogramming of endothelial-immune cell signaling and reversing systemic low-grade inflammation. Biochem Pharmacol 2020;173:113699.
78. Ponnian SMP. Preventive effects of (−) epicatechin on tachycardia, cardiac hypertrophy, and nuclear factor-κB inflammatory signaling pathway in isoproterenol-induced myocardial infarcted rats. Eur J Pharmacol 2022;924:174909.
79. Galleano M, Oteiza PI, Fraga CG. Cocoa, Chocolate, and Cardiovascular Disease. Journal of Cardiovascular Pharmacology 2009;54(6):483–90.
80. Clemente-Suárez VJ, Martín-Rodríguez A, Beltrán-Velasco AI, Rubio-Zarapuz A, Martínez-Guardado I, Valcárcel-Martín R, et al. Functional and Therapeutic Roles of Plant-Derived Antioxidants in Type 2 Diabetes Mellitus: Mechanisms, Challenges, and Considerations for Special Populations. Antioxidants (Basel) 2025;14(6):725.
81. Aggarwal BB. Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals. Annu Rev Nutr 2010;30(1):173–99.
82. Huang C, Liang Y, Li Y, Wei Q, Ouyang L, Zhang J. The epigenetic landscape of rheumatoid arthritis: Pathogenesis and drug therapeutic potentials. Acta Pharm Sin B 2025;15(11):5601–31.
83. Miagkov AV, Kovalenko DV, Brown CE, Didsbury JR, Cogswell JP, Stimpson SA, et al. NF-κB activation provides the potential link between inflammation and hyperplasia in the arthritic joint. Proc Natl Acad Sci U S A 1998;95(23):13859–64.
84. Tabolacci C, De Vita D, Facchiano A, Bozzuto G, Beninati S, Failla CM, et al. Phytochemicals as Immunomodulatory Agents in Melanoma. Int J Mol Sci 2023;24(3):2657.

85. Lyubitelev A, Studitsky V. Inhibition of Cancer Development by Natural Plant Polyphenols: Molecular Mechanisms. Int J Mol Sci 2023;24(13): 10663.
86. Khan A, Zhang Y, Ma N, Shi J, Hou Y. NF-κB role on tumor proliferation, migration, invasion and immune escape. Cancer Gene Ther 2024;31(11):1599–610.
87. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Eur J Med Chem 2018;153:105–15.
88. Sharma D, Rajbongshi B, Isphak T, Basumatary S, Dutta K, Rudrapal M, et al. Plant-Based Therapies to Ameliorate Neuroinflammation in Parkinson's Disease, Alzheimer's Disease, and Epilepsy: A Narrative Review. Chem Biodivers 2025;22(9):e202500038.
89. Yu Y, Shen Q, Lai Y, Park SY, Ou X, Lin D, et al. Anti-inflammatory Effects of Curcumin in Microglial Cells. Front Pharmacol 2018;9:386.
90. Scheepens A, Tan K, Paxton JW. Improving the oral bioavailability of beneficial polyphenols through designed synergies. Genes Nutr 2010;5(1):75–87.
91. Scalbert A, Morand C, Manach C, Rémésy C. Absorption and metabolism of polyphenols in the gut and impact on health. Biomed Pharmacother 2002;56(6):276–82.
92. Teng H, Chen L. Polyphenols and bioavailability: an update. Crit Rev Food Sci Nutr 2019;59(13):2040–51.
93. Lewandowska U, Szewczyk K, Hrabec E, Janecka A, Gorlach S. Overview of Metabolism and Bioavailability Enhancement of Polyphenols. J Agric Food Chem 2013;61(50):12183–99.
94. Mahdi L, Graziani A, Baffy G, Mitten EK, Portincasa P, Khalil M. Unlocking Polyphenol Efficacy: The Role of Gut Microbiota in Modulating Bioavailability and Health Effects. Nutrients 2025;17(17):2793.
95. Arora I, Sharma M, Tollefsbol TO. Combinatorial Epigenetics Impact of Polyphenols and Phytochemicals in Cancer Prevention and Therapy. Int J Mol Sci. 2019;20(18):4567.
96. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, Galvano F, et al. Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis. Am J Epidemiol 2017;185(12):1304–16.
97. Van TTT, Chang HS, Wu HC, Lu CK, Huang HC, Korinek M, et al. The SAR analysis of dietary polyphenols and their antagonistic effects on bortezomib at physiological concentrations. Front Pharmacol 2024;15:1403424.
98. Pan MH, Lai CS, Wu JC, Ho CT. Epigenetic and Disease Targets by Polyphenols. Curr Pharm Des 2013;19(34):6156–85.
99. Cory H, Passarelli S, Szeto J, Tamez M, Mattei J. The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. Front Nutr 2018;5:87.

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