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Review Article

Mechanistic Insights of a Natural Bioactive Compound: Apigenin

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ABSTRACT

Apigenin, a natural bioactive compound belonging to the class of flavone, has emerged as a subject of intense scientific scrutiny due to its potential health benefits. This review provides mechanistic insights into the multifaceted actions of apigenin and its promising therapeutic applications. Widely distributed in various fruits, vegetables, and herbs, apigenin exhibits potent antioxidant properties, neutralizing free radicals and reactive oxygen species to combat oxidative stress and cellular damage. Its anti-inflammatory effects are attributed to the inhibition of pro-inflammatory mediators, suggesting potential in managing conditions like arthritis and inflammatory bowel disease. Notably, apigenin's ability to inhibit cancer cell proliferation, induce apoptosis, and reduce metastasis underscores its potential in cancer chemoprevention. Furthermore, apigenin's role in DNA repair and genoprotection may contribute to cancer prevention and maintenance of genomic stability. In neurodegenerative conditions, apigenin's antioxidant and anti-inflammatory actions show promise in protecting neurons and enhancing cognitive function. Additionally, its influence on cardiovascular health is evident through vasodilation, blood pressure reduction, and inhibition of platelet aggregation. While the current findings highlight the immense potential of apigenin in various health applications, further clinical research is necessary to establish its efficacy and safety in human therapeutics.

Keywords: Flavonoid, Apigenin, Natural bioactive, Health application, Mechanistic Insights, Clinical research.

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INTRODUCTION

Herbs have traditionally been used to prevent and cure a wide range of ailments because of their medicinal characteristics, multi-targeted effectiveness, and minimal toxicity. Furthermore, their potential as innovative medicinal agents has been demonstrated in recent study. Herbal remedies are regarded as one of the most significant branches of medicine worldwide. Many researches over the last few decades have demonstrated that natural substances may be widely utilised to treat a variety of ailments by controlling immunity.

Flavonoids are widely dispersed in nature and have a wide range of biological actions, including anti-viral, anti-inflammatory, anti-cancer, and antioxidant properties.[1-3] Flavonoids can be chemical additions, have been utilised to their broad biological activity.[4] Furthermore, several investigations have shown that flavonoids may have immunomodulatory effect.[5,6]

Among the nearly 6000 distinct flavonoids, the five most common plant flavonoids are quercetin, kaempferol, myricetin, apigenin, and luteolin.[7] Apigenin (4,5,7-trihydroxy-flavone) is one of the most common monomeric flavonoids present in the average diet.[1] Apigenin is classified as a flavone, a subclass of the flavonoid classes, according to the chemical nature of its backbone. Apigenin has attracted the interest of researchers because of its minimal toxicity and several positive bioactivities. Apigenin is considered a significant flavonoid due to its prevalence and quantity in a wide range of natural sources, including a no of commonly consumed. The primary goal of this review study is the systemic effects of the apigenin on numerous signalling pathways related to immunomodulation and cell growth dynamics in this study. Furthermore, the holistic impacts of natural chemicals on the pathogenesis network are discussed, covering scenarios such as inflammation, oxidative stress, cancer microenvironment, autoimmune diseases, and other immunological responses.

Apigenin

Apigenin, also known as 4', 5,7,- trihydroxyflavone, is a flavone that has been the aglycone of numerous naturally occurring glycosides with the molecular formula $C_{15}H_{10}O_5$ and the molecular weight 270.24 g/mol. Flavones and some of its synthetic derivatives have been demonstrated to possess a variety of biological actions such

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as antioxidant, anti-inflammatory, anti-cancer, anti-genotoxic, anti-allergic, neuroprotective, cardioprotective, and anti-bacterial properties. Apigenin is a yellow crystalline solid used to colour wool.

Biosynthesis of apigenin

Apigenin is a secondary metabolite that is synthesized by various kinds of plants, such as parsley, celery, onions, chamomile, maize, rice, tea, wheat sprouts, some grasses, etc., are known to synthesized apigenin and its derivatives. All flavonoids are basically synthesized in plants from a single basic pathway called shikimic acid pathway (Figure 1).[8-10]

Apigenin derivatives

Apigenin, as its chemical name suggests, is a flavonoid derivative containing three hydroxyl substituents. The elimination of the hydroxyl results in the fundamental structure of flavones.[11] Apigenin may be mono-substituted at positions 4', 5', and 7, yielding distinct molecules 4'-hydroxyflavone, 7-hydroxyflavone, and 5-hydroxyflavone. Further hydroxylation can result in the formation of three dihydroxy flavones: 4', 7-dihydroxyflavone, 4,5-dihydroxyflavone, and 5, 7-dihyroxyflavone. Apigenin has at most seven potential derivatives/analogus resulting from selective hydroxyl substitutions at positions 4', 5', and 7 of the basic flavonoid skeleton (Figure 2).

Sources of apigenin

The flavonoid apigenin is frequently found in celery, parsley, and chamomile tea. In addition, it is present in fruits and vegetables like oranges and apples as well as herbs like thyme and oregano. A variety of plants, such as feverfew and yarrow, as well as some cereals, like wheat and rice, can be used to produce apigenin (Table 1).[6,12-14]

Apigenin conjugates in plants

The study of apigenin conjugates in plants has revealed a novel aspect of this bioactive chemical in the field of phytochemistry. Apigenin, like many flavonoids, appears largely in plants as conjugates. Apigenin molecules are attached to one or more sugar molecules in these conjugates, which are frequently glycosides. Apigenin conjugation is crucial for its stability and bioavailability within the plant. The production of these conjugates varies between plant species and even within the same plant (Table 2).

The scientific community has recently investigated the most potential health advantages of apigenin[27] (Figure 3). Apigenin has the ability to induce less intrinsic cytotoxicity and to inhibit malignant cell growth when compared to other standard flavonoids.[28] Various experimental investigations have revealed that apigenin has a significant background in the protection of various illnesses.[29] Apigenin's anti-inflammatory and antioxidant properties. [30,31] cause apoptosis and proliferation at the cellular level in host species and prevent cancer-causing gene overexpression.[32,33] Apigenin promotes cell death by activating several intrinsic apoptotic pathways and caspase-3 activity, which results in the formation of Apoptotic Protease Activating Factor 1 (APAF) by freeing one of the electron transport chain components known as cytochrome C.[34] This flavonoid is hypothesised to have antioxidant properties through activating several signalling cascades and inhibiting the NF-B pathway. Apigenin stimulates antioxidant enzymes such as erythrocyte superoxide dismutase, catalase, phase II detoxification enzymes, and Glutathione Peroxidase (GSH-synthase) to increase antioxidant potential.[35,36] Apigenin not only decreased the expression of tumor-causing genes including TNF-α, IL-6, and CD40, but it also boosted the activity of the tumor-suppressing STAT1 gene via IFN- gene inhibition.[37]

The therapeutic potential of apigenin, as mentioned in the literature, emphasizes its importance. Nonetheless, a comprehensive assessment of apigenin's therapeutic utility demands many meta-analyses. It is also necessary to investigate the role of apigenin in cell signaling networks. These signaling pathways are complex networks that regulate critical cellular functions, and understanding how apigenin affects them can provide vital insights into its therapeutic applications. By connecting our understanding of apigenin's medicinal potential with its involvement in cell signaling pathways, we can gain a better understanding of its therapeutic benefits and ability to influence various biological processes, paving the way for novel medical interventions and treatments.

Role of apigenin in cell signaling pathways

NF-κB Pathway

The transcription factor NF-κB is activated by Lipopolysaccharide (LPS) and pro-inflammatory cytokines such as TNF-α and IL-1. It causes autophosphorylation of Interleukin-1 Receptor-Associated Kinase (IRAK), which interacts with tumour necrosis factor receptor-associated factor, and relay activation of Myeloid Differentiation primary response 88 (MyD88) (TRAF6). As illustrated in Figure 4A, all of these activities promote activation of Transforming growth factor-Activated Kinase 1 (TAK1), which leads to phosphorylation of IB Kinase (IKK), an upstream regulator of NF-B. The Toll-Like Receptor (TLR4)-mediated MyD88 signalling pathway is critical for relay activation of the NF-κB pathway. It has been discovered that API inhibits LPS-induced TLR4 signalling. It inhibits TLR4 expression and prevents NF-κB translocation to the nucleus in macrophages and human Peripheral Blood Mononuclear Cells (PBMCs), hence boosting anti-inflammatory responses.[4]

Several studies[38-41] found that API treatment suppresses NF-B (IkBa) Kinase (IKKß) and phosphorylation of IkBa, resulting in inhibition of NF-B activation. TNF-activation of TNFR is also necessary for TAK1 activation and, as a result, NF-B signalling.[42]

Th-1 derived cytokines such as IL-2, IFN-, and IL-12 are thought to increase cellular immunity, whereas Th-2 derived cytokines such as IL-4, IL-5, and IL-6 are thought to have a negative immunoregulatory effect on cellular immunity. In the presence of API, the immunostimulatory positive effect is achieved by producing Th-1 produced cytokine, IFN-, and suppressing Th-2 derived cytokine, IL-4, and LPS/TNFR generated TNF-α. [43-45]

MAPK pathway

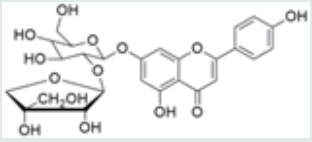
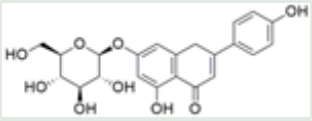
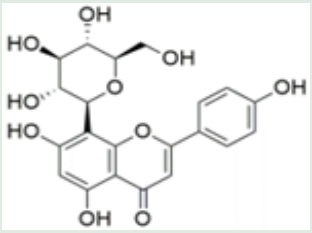
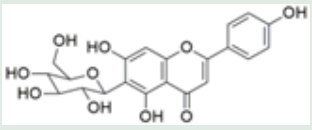
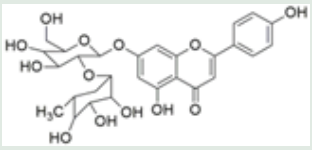
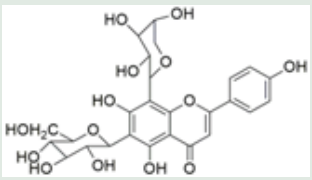
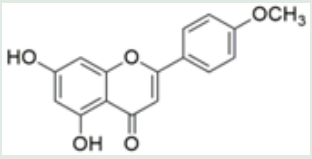
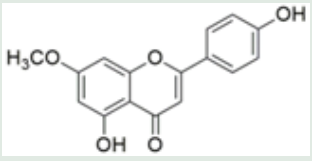
MAPKs are protein-serine/threonine kinases that include JNKs, p38s, and Extracellular signal-Regulated Kinases (ERKs). MAPKs are regulated by a variety of signals including hormones, cytokines, growth factors, and endogenous stress, and they mediate a variety of key cellular activities including proliferation, differentiation, motility, stress response, apoptosis, and survival. TAK1 activation also mediates MAPK activation in response to LPS and TNF- stimulation, as illustrated in Figure 4B. When activated, JNKs phosphorylate multiple targets, resulting in the formation of the AP-1 transcription complex. Activation of AP-1 via multiple stimulatory mechanisms, as well as activation of the JNK, p38, and ERK pathways, results in the production of inflammatory mediators such as TNF-α, interleukins (IL-6, IL-8, IL-1), Matrix Metalloproteinases (MMPs), and collagenase-1, which cause inflammation. The activation of the JNK/AP-1 axis is implicated in the development and progression of various illnesses, including cancer.[4] Activated p38 also helps to activate AP-1. QU and BA have been shown in studies to inhibit the activation of phosphorylated p38 MAP kinase.[4,41]

Table 1: Different source and quantity of apigenin.

Sl. No.	Common name	Scientific name	Parts used	Quantity (mg/100 g)
Fabaceae				
	Hyacinth bean, green	*Lablab purpureus* Linn.	Vegetables	15.3±0.6
	Holland bean	*Pisum sativum* Linn.	Vegetables	6.0±0.1
	Mung bean sprouts	*Phaseolus minimus*	Vegetables	5.2±0.4
	Black-eyed pea	*Vigna unguiculata* sinensis	Vegetables	2.9±0.2
	Kidney bean, green	*Phaseolus vulgaris* L.	Vegetables	10.8±0.3
	Pea greens	*Pisum sativum*	Vegetables	2.5±0.2
	Fava bean	*Vicia faba*	Vegetables	0.5±0.01
Solanaceae				
	Eggplant, long, pale green skin	*Solanum incanum* L.	Vegetables	8.6±0.3
	Eggplant	*Solanum incanum* L.	Vegetables	7.8±0.6
	Tomato	*Lycopersicon esculentu*m Miller	Vegetables	24.2±1.0
	Hot pepper, green	*Capsicum annuum* Linn.	Vegetables	5.0±0.0
	Tomato, cherry, yellow	*Lycopersicon esculentum* var. cerasiforme	Vegetables	19.9±0.3
	Tomato, cherry, red	*Lycopersicon esculentum* var. cerasiforme	Vegetables	20.8±0.4
Cucurbitaceae				
	Chinese wax gourd, without peel	*Benincasa hispida* (Thunb.) Cogn	Vegetables	4.0±0.3
	Cucumber	*Cucumis sativus* Linn.	Fruits	4.7±0.3
	Pumpkin	*Cucurbita moschata*	Vegetables	8.8±0.8
	Loofah	*Luffa cylindrica* Linn.	Vegetables	8.0±0.6
	Zucchini, green	*Cucurbita pepo* Linn.	Vegetables	5.3±0.1
Amaryllidaceae				
	Onion, red skin	*Allium cepa* L.	Vegetables	34.5±0.2
	Onion, white skin	*Allium cepa* L.	Vegetables	26.2±1.2
	Welsh onion	*Allium fistulosum* Linn.	Vegetables	6.8±0.8
Alliaceae				
	Garlic stalk	*Allium sativum* Linn.	Vegetables	81.7±1.5

Sl. No.	Common name	Scientific name	Parts used	Quantity (mg/100 g)
Brassicaceae				
	Cauliflower	*Brassica oleracea* Linnaeus.	Vegetables	5.1±0.1
	Potherb mustard	*Brassica juncea* Linnaeus.	Seeds	8.1±0.0
	Kale, green	*Brassica oleracea* Linnaeus.	Vegetables	2.8±0.2
	Rutabaga	*Brassica napus*	Flower	15.4±0.1
	Chinese cabbage	*Brassica rapa*	Leaf	4.5±0.1
	White radish	*Raphanus sativus* Linn.	Rhizomes	2.2±0.3
Apiaceae				
	Celery leaf	*Apium graveolens* Linn.	Leaf	139.3±5.2
	Celery stalk	*Apium graveolens* Linn.	Vegetables	8.4±0.4
	Parsley	*Apium graveolens* Linn.	Vegetables	4.4±0.1
	Fennel	*Foeniculum vulgare* Mill.	Fruits	5.2±0.3
	Parsley	*Petroselinum crispum*	Leaf	2.4±0.2
	Celery stalks	*Apium graveolens*	Leaf	10.8±1.3
	Chinese celery	*Apium graveolens*	Leaf	24.0±0.0
Dioscoreaceae				
	Yam, without peel	*Dioscorea zingiberensis*	Vegetables	8.7±0.2
Meliaceae				
	Toona leaf	*Toona sinensis*	Vegetables	8.7±0.7
Rosaceae				
	Apricot	*Armeniaca vulgaris* Lam.	Fruits	2.3±0.1
	Hawthorn	*Crataegus pinnatifid*a Bge.	Fruits	10.7±0.3
	Strawberry	*Fragaria X ananassa* Duch.	Fruits	2.4±0.1
	Grapefruit	*Citrus paradisi*	Fruits	4.9±0.3
	Kumquat	*Fortunella crassifolia*	Fruits	21.9±0.0
Rhamnaceae				
	Date	*Ziziphus jujuba* Mill.	Fruits	41.0±2.7
Ebenaceae				
	Persimmon, without peel	*Diospyros vaccinioides* Lindl.	leaf	8.1±0.4
Amaranthaceae				
	Spinach	*Spinacia oleracea*	Vegetables	1.2±0.1
Asteraceae				
	Lettuce	*Lactuca sativa*	Leaf	2.7±0.7
	Artichoke heads	*Cynara scolymus*	Flower	18.9±3.9
	Chicory leaves	*Chicorium intybus*	Leaf	68.0±0.1
Oleaceae				
	Black olives	*Olea europaea*	Oil	6.5±0.0
Poaceae				
	Millet, fonio	*Digitaria exilis*	Fruits	15.0±0.1
	Lemon-yellow sorghum	*Sorghum bicolor*	Fruits	28.7±0.1
	Red sorghum	*Sorghum bicolor*	Fruits	20.4±0.2

Table 2: **Different conjugated forms of apigenin in plants.**

Sl. No.	Common name	IUPAC name	Derived form	Structure	References
1	Apiin	Apigenin 7-O-Apioglucoside	Parsley and celery		[15]
2	Apigetrin	Apigenin 7-glucoside	*Teucrium gnaphalodes* and dandelion coffee roots.		[16]
3	Vitexin	Apigenin 8-C-glucoside	Mung bean and *Ficus deltoidea* bamboo leaves.		[17-19]
4	Isovitexin	Apigenin 6-C-glucoside	*Ficus deltoidea* mung bean.		[20]
5	Rhoifolin	Apigenin 7-O-neohesperidoside	*Rhus succedanea* and *Citrus grandis* leaves.		[21]
6	Schaftoside	Apigenin 6-C-glucoside 8-C- arabinoside	*Arisaema heterophyllum*		[22]
7	Acacetin	4'-methoxy5.7-d ihydroxyflavone	*Chrysanthemum morifolium* and *Turnera diffusa.*		[23,24]
8	Genkwanin	4',5-dihyroxy-7-met hoxyflavone	*Daphne genkwa* and *Alnus glutinosa* seeds.		[25,26]

API and QU, in combination can alter NF-B and MAPK pathways to decrease inflammatory mediators. Because the method of action differs in each individual, it is predicted to have a powerful, diverse influence on the immune system.

Nrf2 pathway

The Nrf2 signalling pathway is a typical antioxidative stress-related route that leads to the activation of antioxidant defence systems. Keap1 keeps Nrf2 in the cytoplasm in the form of Keap1-Nrf2 complexes under normal circumstances. However, oxidative stress causes the Keap1-Nrf2 complex to decouple, and the liberated Nrf2 enters the nucleus and promotes the production of antioxidant genes.

Multiple studies have established that API administration increases the Nrf2 signalling pathway, which contributes to increased HO-1 levels and inhibits inflammatory mediators such

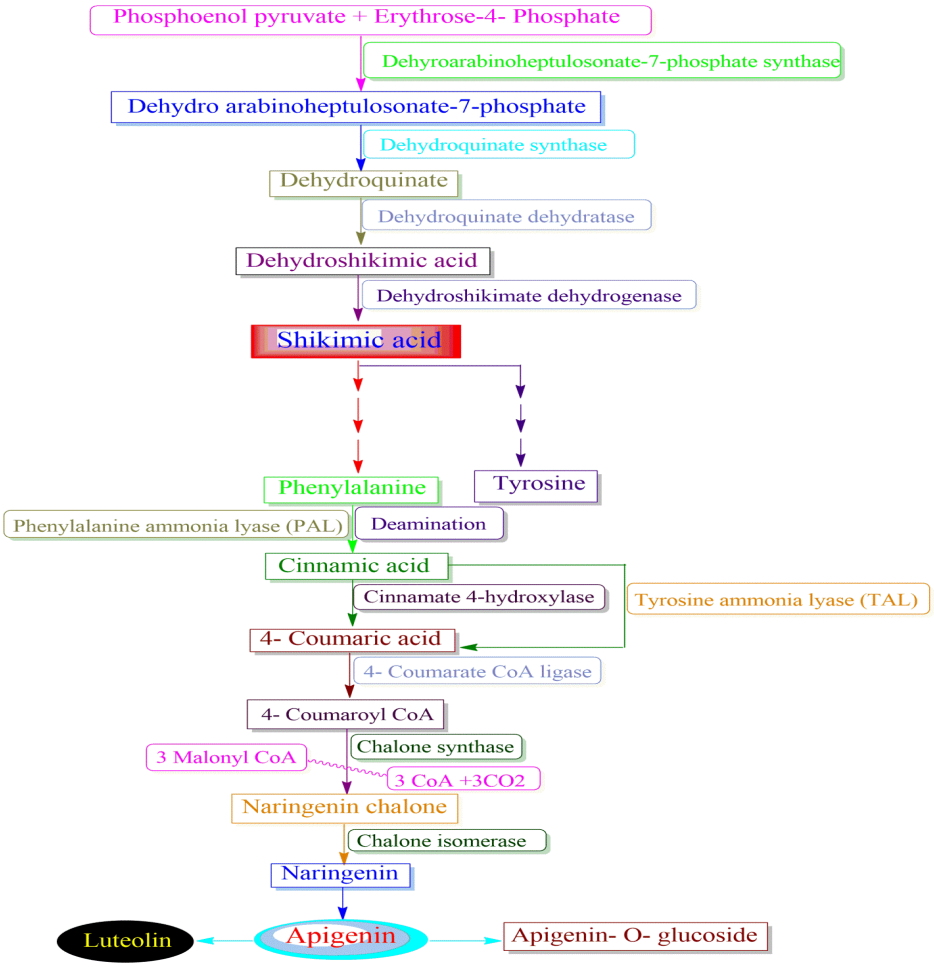


Figure 1: Biosynthesis of Apigenin.

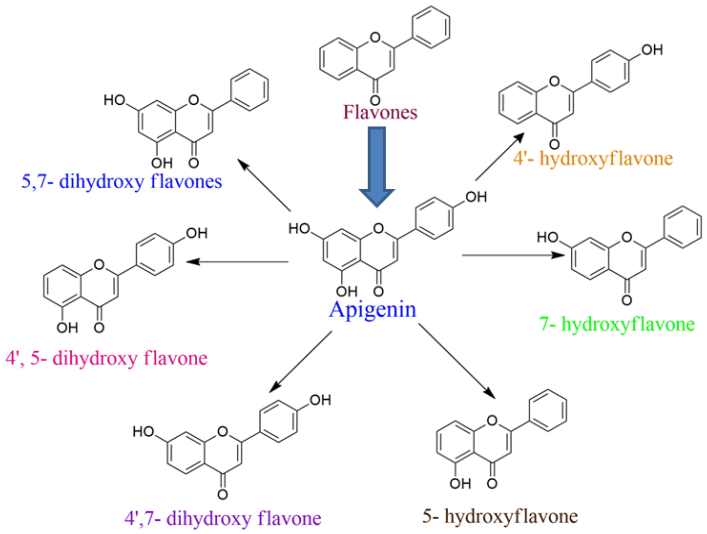


Figure 2: Different derivatives of Apigenin.

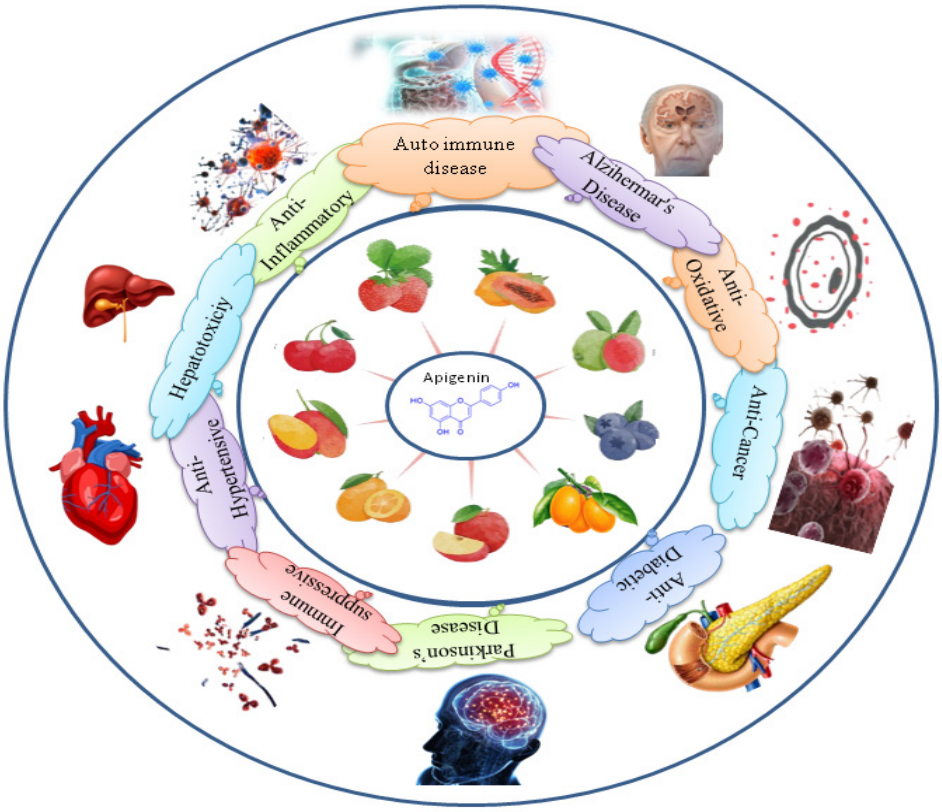


Figure 3: Different pharmacological activity of Apigenin.

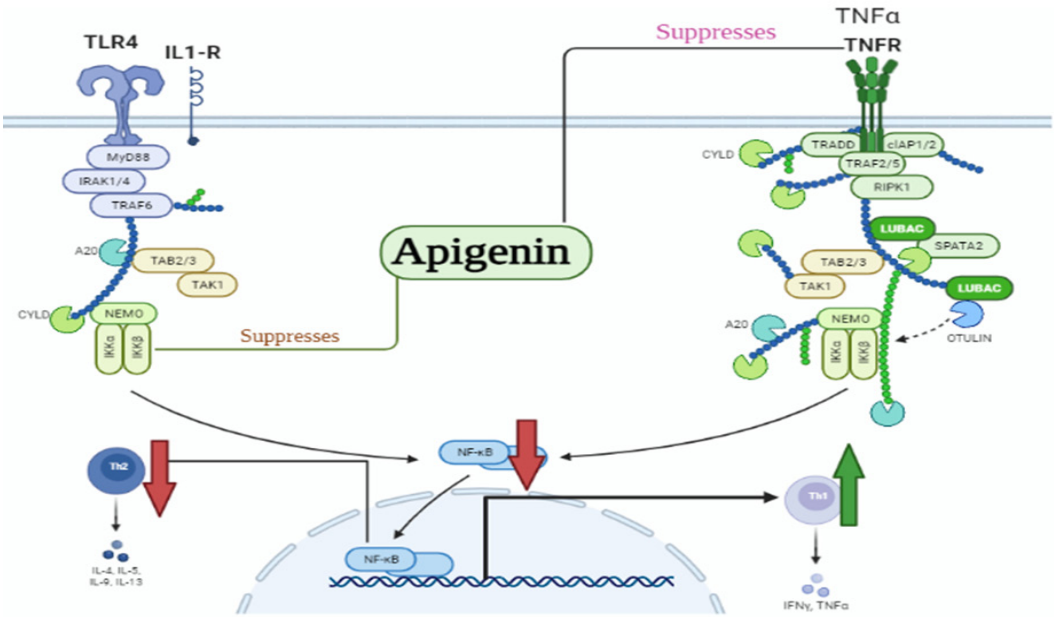


Figure 4A: Effect of apigenin on NF-κB pathway.

as iNOS, IL-6, and IL-1ß.[35,45-50] Nrf2 regulates antioxidative stress enzymes as well as Drug-Metabolizing Enzymes (DMEs) like Glutathione S-Transferase (GST) and NAD (P) H Quinone Oxidoreductase 1(NQO1). API have been shown to interact directly with Nrf2 as part of the NQO1 induction process, increasing Nrf2 protein levels.[31,50] Binding to an Antioxidant Response Element (ARE) motif in the promoter region of antioxidant enzyme-encoding genes induces Nrf2 activity.[49] API was found to regulate the Nrf2/ARE pathway in cancer patients.[42]

Furthermore, the Nrf2 pathway regulates energy metabolism, mitochondrial function, and cellular redox balance. API act as antioxidants by influencing the Nrf2 pathway, and thus a

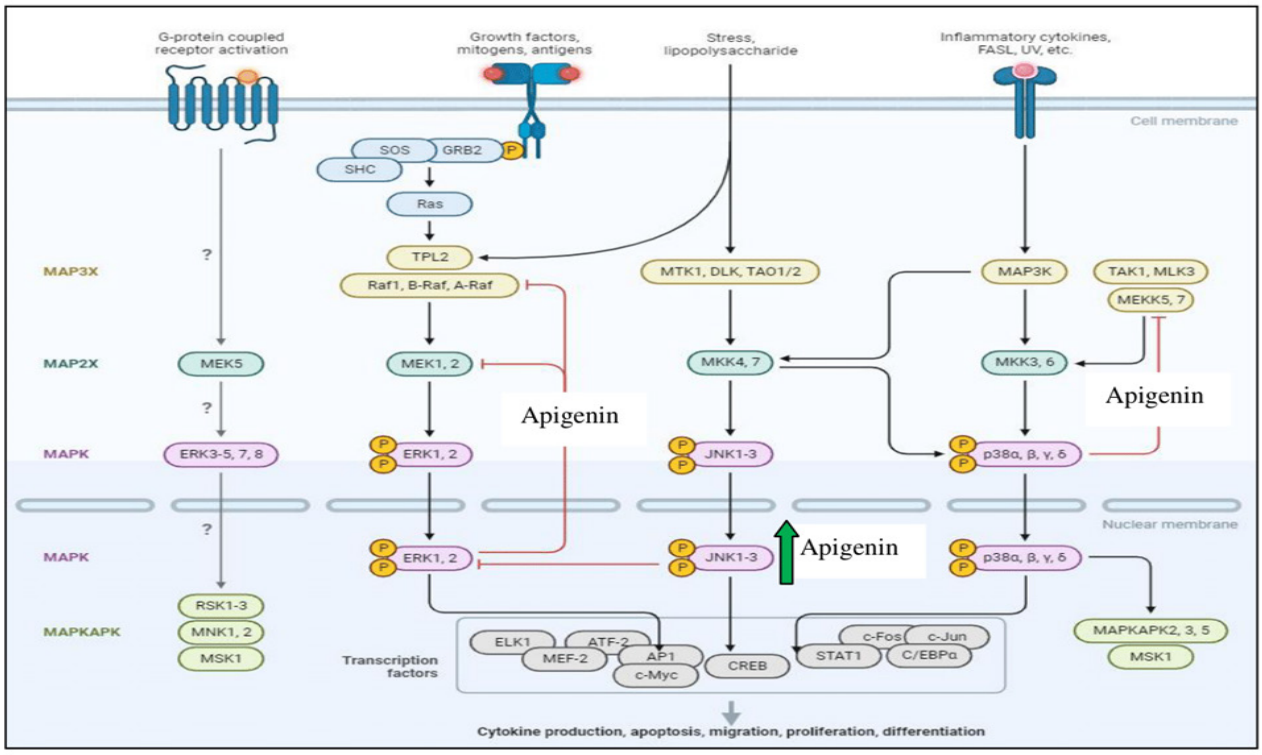


Figure 4B: Effect of apigenin in MAPK Pathway.

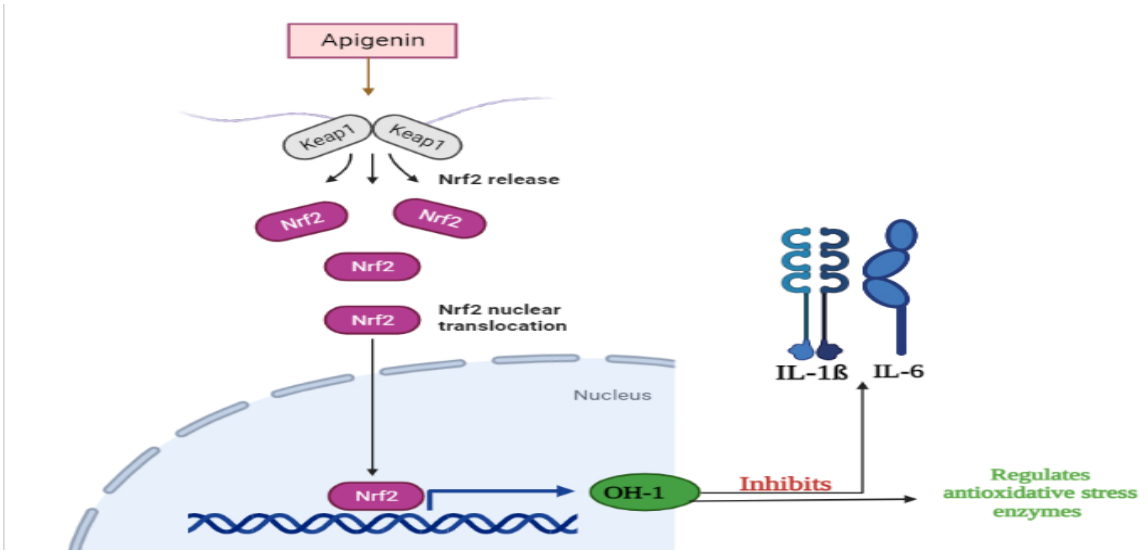


Figure 4C: Effect of apigenin in Nrf2 pathway.

combination of these phytochemicals may be beneficial in diseases where oxidative stress increases complications. Recent research has identified Nrf2 role in cancer, obesity, metabolic syndrome, diabetic nephropathy, retinopathy, and neuropathy (Figure 4C).

PI3K/PTEN/AKT/mTOR Signaling pathway

In several human cancers, the PI3K/PTEN/AKT/mTOR pathway can become abnormally activated. Its activation can boost cancer cell proliferation, tumour growth, angiogenesis, and survival, making it the most common way for bioactive components to induce apoptosis in cancer cells.[51] B and T cell receptors, receptor tyrosine kinases, cytokines, G-Protein-Coupled Receptors (GPCRs), integrins, and other stimuli such as insulin and other growth factors activate the signalling cascades. These stimuli act on their respective receptors to promote a relay of activation by recruiting IRS1 and producing Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) via Phosphoinositide 3-kinases (PI3K). Phosphatidylinositol (4,5)-bisphosphate (PIP2) is converted to PIP3 by PI3Ks, and Phosphatase and Tensin

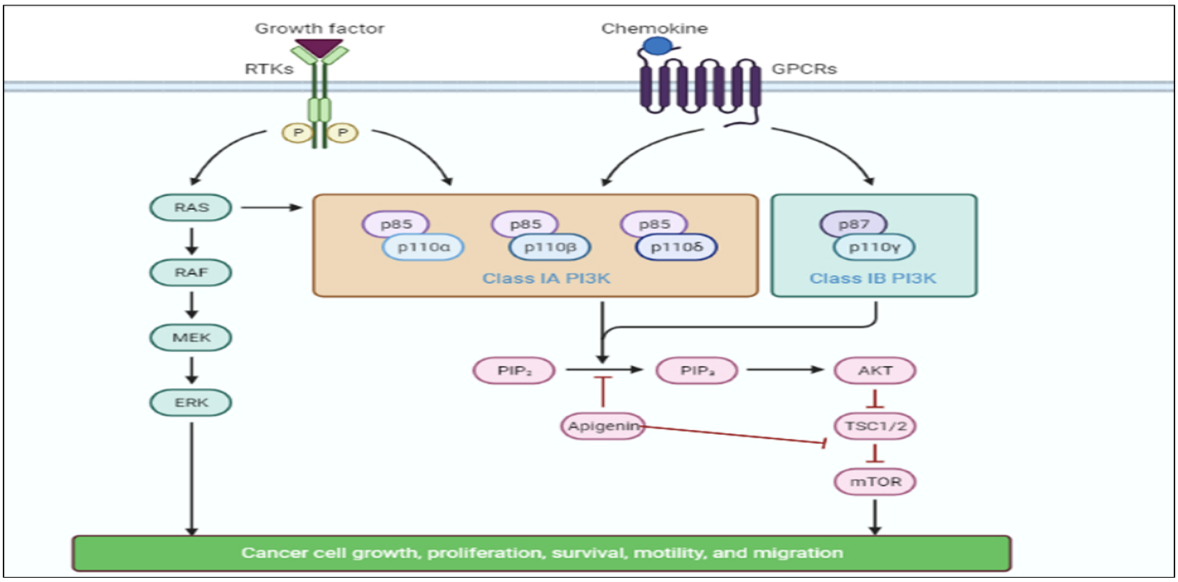


Figure 4D: Effect of apigenin in PI3K, AKT, and mTOR pathway.

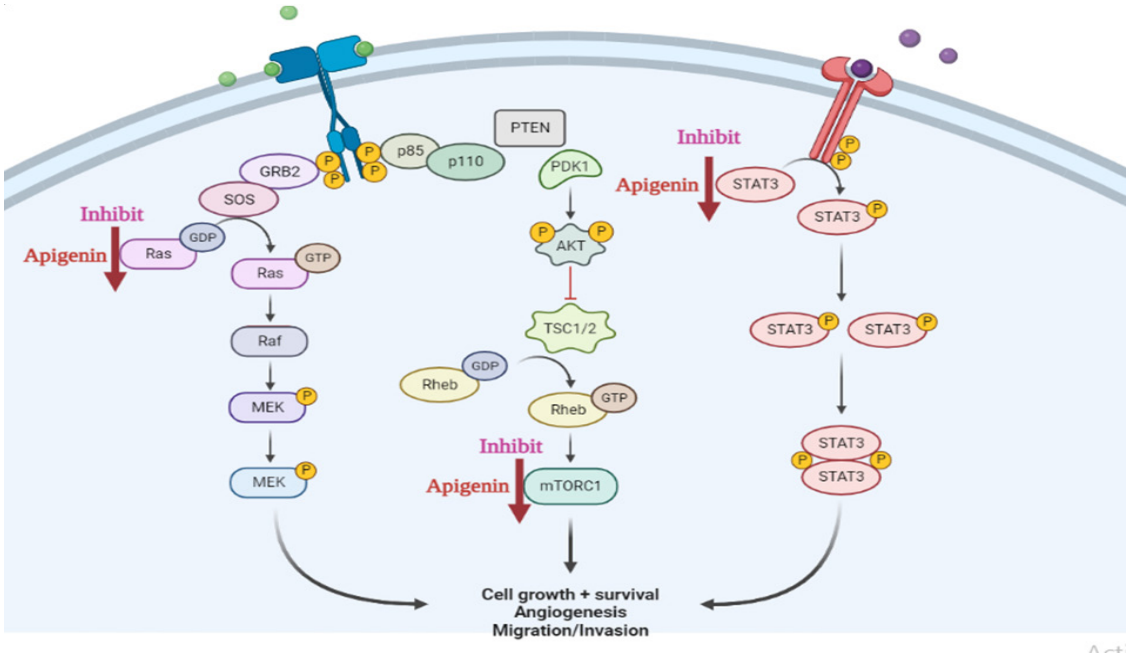


Figure 4E: Effect of apigenin in PI3K/PTEN/AKT/mTOR Signaling pathway.

homolog (PTEN) reverses the reaction. PIP2 conversion recruits and activates AKT, thereby activating mTOR. [42] Oncogenic proteins include PI3K, AKT, and mTOR (Figure 4D).

The transcriptional regulator of the adaptive response to hypoxia is Hypoxia-Inducible Factor (HIF-1). HIF-1 overexpression is linked to drug resistance and increased mortality in several cancers. HIF-1 promotes the transcription of downstream genes required for angiogenesis, such as VEGF and CREB-1, as well as the GLUT-1 glucose transporter, which is required for glycolysis. API inhibits HIF-1 in a variety of cancers, including ovarian, prostate, and lung cancer.[52]

The PI3K/AKT pathway is altered in many cancers, resulting in increased activation of signalling cascades associated with excessive cellular growth, proliferation, and survival, acting on a diverse range of downstream effectors such as Mdm2, FOXO, and SK-3,6.[49] FOXO3a, a transcription factor and tumour suppressor, is a downstream target of the PI3K/AKT signalling pathway and is negatively regulated by AKT. FOXO3a activation has been linked to poor diagnosis in a variety of cancers. API treatment induces FOXO3a expression by reducing AKT phosphorylation and then upregulating the expression of p21 and p27, FOXO3a target genes that inhibit cancer cell proliferation.[4]

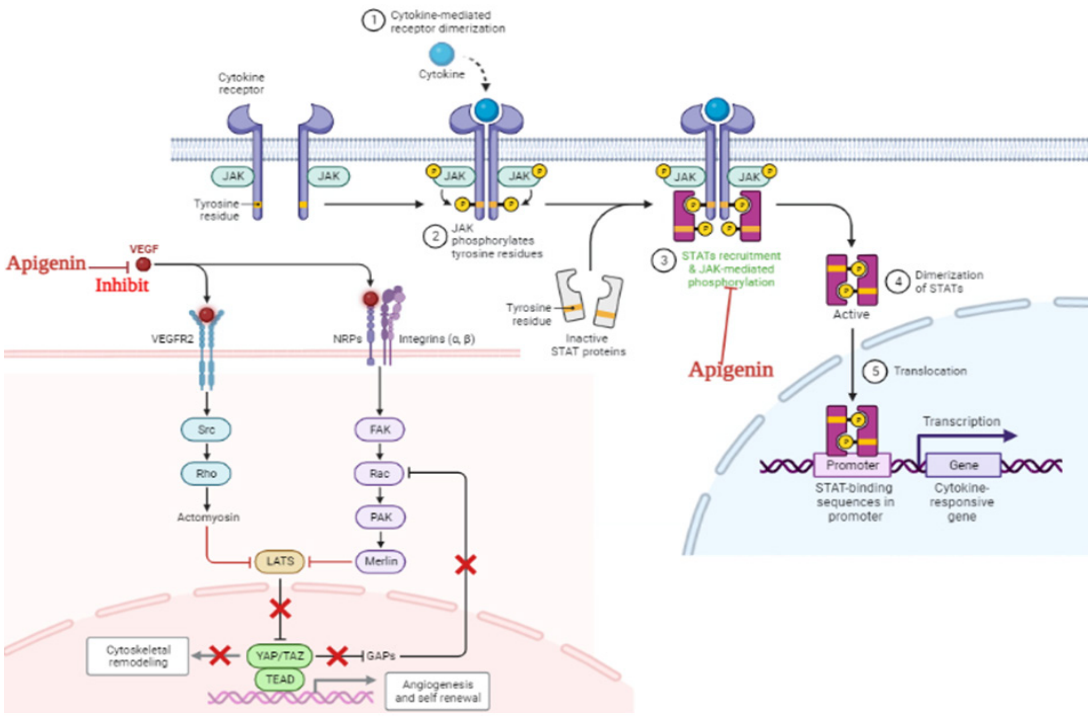


Figure 4F: Effect of apigenin in JAK- STAT pathway.

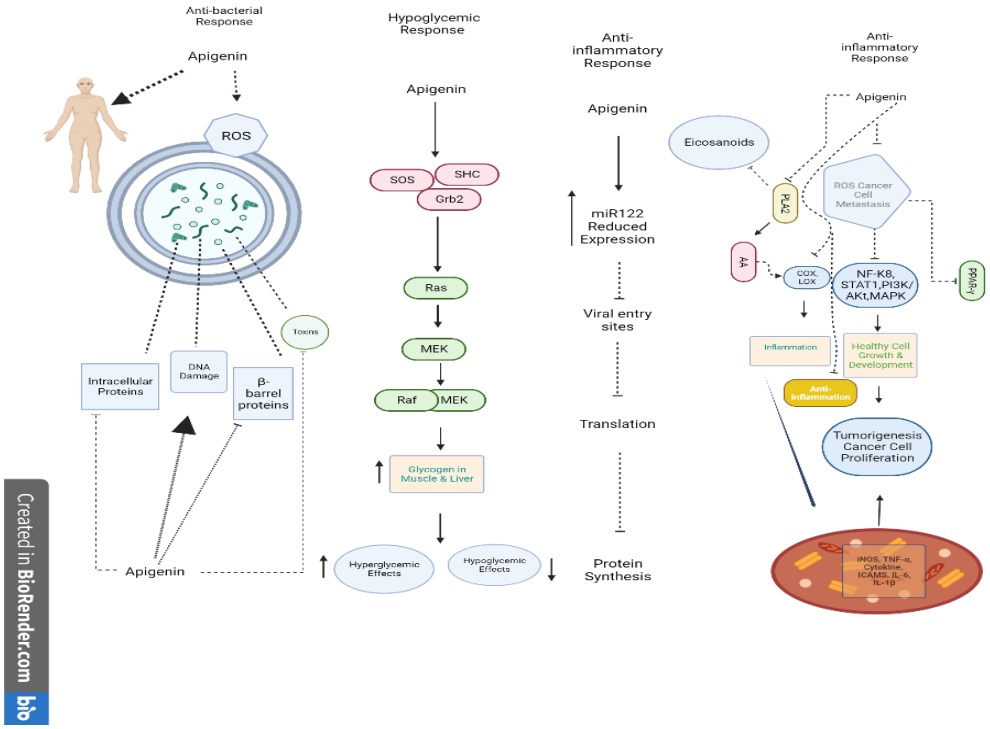


Figure 5: Various neuro inflammatory diseases get triggered due to the immunomodulation of different inflammatory pathways.

API induces apoptosis in cancer cells by targeting the PI3K/AKT pathway nodes. The nodal points considered in the network represent the major signalling mechanisms leading to cell survival gene expression with different approaches, such as Ras-Raf1/MEK/ERK, mTOR, and NF-B, which lead to upregulation of inflammation, cell progression, protein synthesis, and angiogenesis (Figure 4E). Numerous cell functions are regulated by these phytochemicals, including cell apoptosis and survival, protein synthesis, cell growth, cell cycle, proliferation, and metabolism.

JAK-STAT Pathway

JAK-STAT signalling is activated by cytokines during the inflammatory process and coordinates immune cell proliferation and differentiation. Various STAT proteins are either pro- or anti-inflammatory. The JAK1/STAT3 signalling pathway is important in inflammation, cell transformation, and carcinogenesis (Figure 4F). Through a positive feedback loop, pro-inflammatory cytokines can increase STAT3 expression. This chain of events has a number of immune suppressive effects. API and other bioactive compounds improve immune response by reducing JAK2 and STAT5 phosphorylation in cancer-associated cell lines. API also inhibits STAT3 and its direct target, VEGF, which has anti-inflammatory properties.[42] They can also reduce tumour cell proliferation, apoptotic pathways, and VEGF expression. API has shown growth inhibitory properties in breast cancer cells with HER2-overexpression by promoting apoptosis by blocking STAT3 signalling.[52] BA, another bioactive compound, can inhibit STAT3 activation and affect the STAT3/HIF-1/VEGF signal pathway.[39]

Various neuro inflammatory diseases get triggered due to the immunomodulation of different inflammatory pathways. Bioactive compounds have shown significant effects on these pathways, which proved helpful in curing diseases. Some of them are discussed as follows:

Anti-Inflammatory and Antioxidant Potential of Apigenin

According to a different study, rats given adequate doses of apigenin (10, 20, and 40 mg/kg) are protected from oxidative and membrane protein damage,[53] Lipid Peroxidation (LPO) is reduced, and blood serum enzyme markers are secreted via lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, and aspartate transaminase.[51,54] Apigenin inhibits the COX-2 and NOS inhibitor activity that is produced by lipopolysaccharide in mouse white blood cells, which results in an anti-inflammatory reaction in the animals' bodies.[55] By increasing the amount of their expression, these ROS help to activate a number of transcription factors, including as PPAR-, HIF-1, Sp-1, STAT-3, AP-1, and Nrf2, as well as to raise a number of genes, including those for inflammatory cytokines and various chronic diseases (Figure 5).[56,57]

Antibacterial Potential of Apigenin

It is well known that phytochemicals like apigenin have antibacterial and antimicrobial properties.[58] It is important to note that future studies will focus on the connection between flavone structural traits and antibacterial activity. [54] According to numerous studies, apigenin, which has potent antibacterial characteristics, is highly advised for the treatment of oral bacteria (Figure 5). Apigenin has been found to have the strongest antibacterial effects against the gram-negative bacterium Proteus mirabilis.[27] Both gram-positive and gram-negative bacterial species are bactericidal to it.[55,60-62]

Antiviral Beneficiary Effects

According to studies, consumption of apigenin reduces the production of mature miR122, which prevents post-entry infections from the viruses causing hepatitis C and foot-and-mouth disease. The host factor modulation of apigenin's antiviral effects on the Hepatitis C Virus (HCV) led to a reduction in the synthesis of miR122, which aids *in vitro* HCV infection.[53] When apigenin was administered to vetro cells for an hour following infection, ASFV was reduced by more than three logs (Figure 5). In cells infected with ASFV, ongoing apigenin therapy can lessen cytopathic effects.[63]

Hypoglycemic Effects of Apigenin

The apigenin complex 6-C-(200-O—L-rhamnopyranosyl)—L-fucopyranoside) is a strong approach to boost insulin production and lower blood levels of $C_6H_{12}O_{6,}$[64] claims the study. Apigenin has been shown to speed up the metabolism of glucose by slowing down the activity of liver gluconeogenic enzymes. After using apigenin for several days, the rats' body weight and blood sugar levels decreased.[65] Particular vitexin components in apigenin notably reduced body weight and blood sugar levels in rats. Apigenin reduced the signs and symptoms of diabetes by preventing the caspase 3 and Nitric Oxide (NO) signaling pathway axis from activating (Figure 5).

DISCUSSION

The present review provides valuable mechanistic insights into the multifaceted actions of apigenin, a natural bioactive compound belonging to the flavone class. The urgent need to strengthen healthcare systems and combat infectious diseases has become increasingly apparent due to the widespread prevalence of viral infections without adequate treatment and the emergence of drug-resistant viral strains. In this context, the potential of apigenin as an innovative agent for the treatment of various viral infections has been extensively explored.

Apigenin's role as a potent antioxidant stands out as one of its key mechanisms of action. By scavenging free radicals and Reactive Oxygen Species (ROS), apigenin helps mitigate oxidative stress and cellular damage. This property is particularly relevant in the

context of various chronic diseases, including cardiovascular conditions and neurodegenerative disorders, where oxidative stress plays a crucial role. Furthermore, apigenin's ability to modulate inflammation by inhibiting pro-inflammatory mediators makes it a promising candidate for managing conditions characterized by excessive inflammation, such as arthritis and Inflammatory Bowel Disease (IBD).

A noteworthy area of research is apigenin's potential in cancer chemoprevention. The evidence suggesting its ability to inhibit cancer cell proliferation, induce apoptosis, and reduce cancer cell invasiveness and metastatic potential highlights its potential as a therapeutic agent for cancer management. Moreover, apigenin's role in promoting DNA repair and genoprotection provides additional support for its anticancer properties, as maintaining genomic stability is essential in preventing cancer development and progression.

Apigenin's antiviral properties have garnered significant attention. Studies have demonstrated its efficacy against various viral infections, including the Hepatitis C Virus (HCV), Epstein-Barr virus (EBV), poliovirus, and African Swine Fever Virus (ASFV), among others. Its ability to interfere with different stages of viral replication, including virus-cell adhesion and protein production, contributes to its antiviral effects. Notably, apigenin has been shown to inhibit the expression of miR122, a crucial factor in the propagation of certain viral infections. These findings open up new possibilities for the development of apigenin-based antiviral therapies.

The non-hazardous and non-virulent nature of apigenin further adds to its appeal as a potential therapeutic agent. The absence of significant side effects or cytotoxicity suggests that apigenin may be a safe and well-tolerated treatment option. Additionally, its ability to act as a Reactive Oxygen Species (ROS) scavenger and reduce cytokine levels associated with infections supports its potential in managing viral infections.

While the potential of apigenin as an antiviral agent is promising, there are challenges that need to be addressed. Some viruses, such as Coxsackie Virus A16 (CAV16), appear to be unaffected by apigenin treatment. This highlights the need for further investigation into the specific mechanisms of viral inhibition and potential limitations in its efficacy against certain viral strains. Additionally, more comprehensive clinical studies are necessary to validate its antiviral effects in humans and determine appropriate dosages and treatment regimens.

Furthermore, the research on apigenin's antiviral properties is still in its early stages, and many studies have been conducted *in vitro* or in animal models. To translate these findings into clinical applications, extensive research on human subjects is required. The challenges in bioavailability and pharmacokinetics of apigenin also need to be addressed for effective therapeutic use.

CONCLUSION

In conclusion, apigenin, a natural bioactive compound, has been found to possess various pharmacological activities, including anti-inflammatory, antioxidant, anticancer, and antibacterial effects. Mechanistic insights suggest that apigenin exerts its biological effects through various pathways and cellular processes, such as modulation of PI3K/PTEN/AKT/mTOR signaling pathway, inhibition of NF-κB signaling pathway, and modulation of phase II detoxification enzymes.

Apigenin has shown promising results in preclinical studies for the prevention and treatment of various diseases, including cancer, cardiovascular disease, and neurodegenerative diseases. Moreover, apigenin has been demonstrated to enhance the activity of conventional therapies and overcome drug resistance. Therefore, apigenin has the potential to be developed as a natural alternative or adjunct to conventional therapies.

However, the translation of preclinical findings to clinical practice requires further studies to determine the safety, efficacy, and optimal dosages of apigenin. Moreover, the bioavailability and pharmacokinetics of apigenin need to be considered for the development of effective formulations. Therefore, future studies should focus on clinical trials to evaluate the potential of apigenin as a therapeutic agent for various diseases. Overall, apigenin represents a promising natural compound with potential therapeutic benefits that warrant further investigation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

APAF: Apoptotic Protease Activing Factors; **NF-B:** Necrosis Factors; B**TNF:** Tumor Necrosis Factors; **IL-6:** Interleukin-6; **IL-12:** Interleukin-12; **IL-1:** Interleukin-1; **LPS:** Lipopolysaccaride; **IRAK:** Interleukin-1 receptor associated kinase; **TAK1:** Transforming growth factor activated kinas-1; **TLR4:** Toll-like receptor-4; **API:** Apigenin; **QU:** Quercetin; **PBMCs:** Peripheral blood mononuclear cells; **MMPs:** Metalloproteinases; **ARE:** Antioxidant response element; **NQO1:** NAD(P)H quinine oxidoreductase-1; **GPCRs:** G- Protein coupled receptors; **PI3K:** Phosphoinositide 3-kinases; **HIF 1:** Hypoxia Inducible factors; **HCV:** Hepatitis C Virus; **EBV:** Epstein-Barr virus; **DNA:** Deoxyribonucleic Acid.

SUMMARY

Apigenin, a natural flavone compound, emerges as a promising soldier in the fight against various diseases. This review delves into its multifaceted power, highlighting its key mechanisms of action: **Antioxidant Shield:** Apigenin scavenges free radicals and reactive oxygen species, minimizing oxidative stress and cellular damage. This shields against chronic diseases like cardiovascular issues and neurodegenerative disorders. **Inflammation Tamer:** By modulating pro-inflammatory mediators, apigenin tackles conditions like arthritis and IBD, offering relief from their inflammatory grip. **Cancer Chemoprevention Champion:** Apigenin inhibits cancer cell growth, triggers apoptosis, and curbs their spread, making it a potential ally in cancer management. Its ability to promote DNA repair adds another layer of defense against cancer. **Viral Threat Neutralizer:** The star of the show - apigenin's antiviral potential shines against infections like HCV and EBV. By interfering with viral replication at various stages, it offers a safe and non-toxic safeguard. **Antibacterial Potential of Apigenin:** Apigenin has been shown to exhibit antibacterial activity against a variety of bacterial strains, including both Gram-positive and Gram-negative bacteria. This activity is attributed to several mechanisms, including, Inhibition of DNA synthesis and Inhibition of protein synthesis. **Antiprotozoal** Potential of Apigenin: Apigenin has also demonstrated activity against some protozoan parasites, such as Trypanosoma cruzi (the causative agent of Chagas disease) and Leishmania donovani (the causative agent of visceral leishmaniasis). The mechanisms of action for this activity are still being investigated, but may involve similar mechanisms to its antibacterial activity.

While challenges remained, like its ineffectiveness against certain viruses and the need for extensive human trials, apigenin's potential to strengthen healthcare systems and combat infectious diseases is truly thrilling. It holds promise as a natural warrior against a diverse range of threats, waiting to be harnessed for improved human health.

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