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REVIEW

The Protective Activity of Apigenin Against Bone and Cartilage Diseases

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Abstract: Bone and cartilage diseases have become the leading causes of joint disability due to the destruction of bone and cartilage. No effective drugs are available to cure bone and cartilage diseases. Exploring natural compounds as therapeutic alternatives shows promise. Apigenin, a naturally occurring flavonoid, exhibits various pharmacological activities, such as anti-inflammation, antioxidant, and immune modulation. Apigenin acts as a phytoestrogen and mediates the balance of bone remodeling by inducing osteogenic differentiation, promoting osteoblast-associated bone formation, and inhibiting osteoclast-related bone resorption. In addition, apigenin exhibits protective effects against osteoporosis (OP), rheumatoid arthritis (RA), osteoarthritis (OA), gouty arthritis (GA), and intervertebral disc degeneration (IDD). Apigenin can be a promising agent in treating bone and cartilage. However, the application of apigenin is limited due to its low water solubility and bioavailability. More efforts are still needed.

Keywords: apigenin, osteogenic differentiation, osteoporosis, rheumatoid arthritis, osteoarthritis, gouty arthritis

Introduction

The skeletal system provides the framework for body structure and movement. Bones undergo continuous remodeling by replacing old bones with new bones, and bone remodeling is maintained by the balance between osteoblast-mediated bone formation and osteoclast-regulated bone resorption. The incidence of degenerative bone and cartilage diseases is increasingly high due to the aging population.[1] Aging and estrogen deficiency may lead to the development of bone diseases, such as osteoporosis (OP),[2] rheumatoid arthritis (RA),[3] and osteoarthritis (OA).[4] The prevalence of bone and cartilage diseases has caused economic and social stress worldwide. Currently, most therapeutic pharmaceuticals for OA, OP, and RA management are prescribed for symptom improvement.[5,6] For example, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for joint pain alleviation. Some disease-modifying anti-rheumatic drugs (DMARDs), such as tofacitinib, have been developed for treating RA.[7] However, no effective drugs are available to cure them. This can be explained by the absence of a full understanding of the underlying molecular mechanisms. Thus, it is urgent to explore potential targets and effective drugs for managing bone and cartilage diseases.

The dynamic metabolism of bone is balanced by osteoblasts and osteoclasts. Osteoclast-mediated bone resorption is essential for the maintenance, repair, and remodeling of bone tissues. Osteoblasts activate the expression of receptor activator of nuclear factor (NF)-κB ligand (RANKL), which interacts with the RANKL receptor to mediate the differentiation, activation, and survival of osteoclasts.[8] Osteoblasts secrete collagen and promote the deposition of calcium, phosphate, and other ions, leading to the formation of new bones. Osteoclasts digest proteins and minerals by upregulating the expression of tartrate-resistant acid phosphatase (TRAP).[9] Chondrocytes, the unique cell type in the articular cartilage, maintain the structure and function of cartilage as well as extracellular matrix (ECM) metabolism.[10] The pathological alterations of OA cartilage are associated with excessive chondrocyte cell death and ECM degradation.[11] The main components of ECM include type II collagen and aggrecan. Particularly, type II collagen forms a network by interacting with proteoglycan aggregate, which is constituted by the large aggregating proteoglycan

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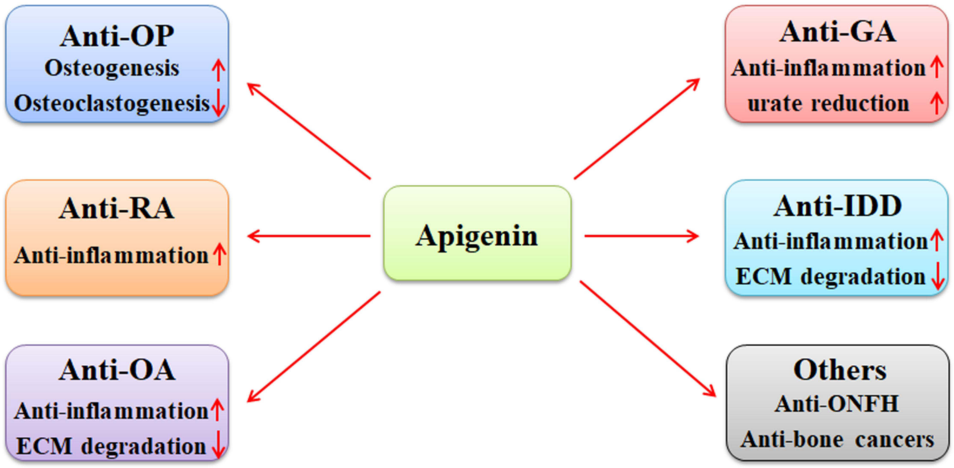
Graphical Abstract



and aggrecan to a hyaluronan (HA) filament.[12] The catabolic factor matrix metalloproteinases (MMPs), particularly MMP-13, are mainly responsible for the degradation of type II collagen, and a disintegrin and metalloproteinases with thrombospondin motifs (ADAMTSs) can degrade aggrecan.[13]

Flavonoids, the secondary metabolites in natural plants and nutraceuticals, have a common carbon skeleton of diphenylpropane, which is characterized by two benzene rings (A and B rings) connected by a three-carbon linking chain that forms a heterocyclic ring (C ring) containing oxygen. The B ring is commonly attached to position 2 in the C ring. However, position 3 or 4 can also be available for the B ring.[14] Flavonoids exhibit protective effects on bone remodeling.[15] Apigenin, also called 4',5,7-trihydroxyflavone with the formula of $C_{15}H_{10}O_5$ and a molecular weight of 270.05 g/mol, has been abundantly found in vegetables and fruits, such as celery, parsley, pistachio, onions, apple, oranges, and chamomile.[16] In nature, apigenin is mainly present in O- and C-glycosidic forms, such as apigenin-8-C-glucoside (also known as vitexin), and apigenin-6-C-glucoside (also known as isovitexin)[17–19] (Figure 1).

Botanical preparations have been proven to be safe and effective in treating bone and cartilage diseases.[15,20] Supplemental natural flavonoids as nutraceuticals are increasingly recognized for treating many diseases. Ramesh et al have reviewed the functions and molecular mechanisms of flavonoids in mediating bone remodeling and suggested flavonoids as the promising agents in treating bone-related ailments in the future.[15] Some flavonoids can function as phytoestrogens due to their structural similarity to estrogen and their ability to interact with estrogen receptor. The estrogen-like effects of flavonoids favor anabolism in the tissues of bone and cartilage.[21] Apigenin is one of the important natural phytoestrogens derived from plants and foods.[22] Phytoestrogens can interact with estrogen receptors due to their

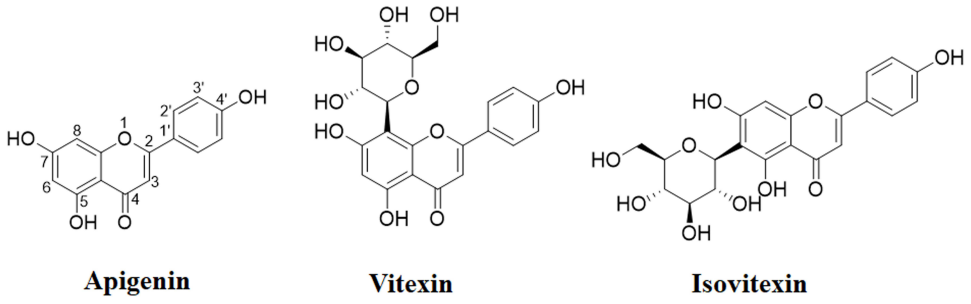


Figure 1 The chemical structures of apigenin, vitexin, and isovitexin.

structural similarity with 17β-estradiol.[23] Apigenin has various pharmacological activities, such as anti-inflammation,[24,25] antioxidant,[26] immune modulation,[27] and bone protection effects.[17] In this article, we mainly discuss the protective effects of apigenin and its glycosides against bone diseases.

The Protective Activities of Apigenin Against OP Development

OP is associated with decreased bone mass and increased bone fragility, and it is marked as a progressive systemic skeletal disease by the World Health Organization (WHO). Approximately 536,000 OP patients with fragility fractures develop annually. In the European Union, about 22,000,000 women and 5,500,000 men were affected by OP in 2010.[28] It has been reported that the total medical expenses for OP increased by 51% from 2015 to 2019 (from USD 155 million to USD 234 million), while the medical expenses per patient increased by 3.7% annually, reaching USD 216.[29] OP and the fragility fracture significantly challenge individuals and have become a public health concern worldwide.[28]

Estrogen deprivation in postmenopausal women induces high bone turnover and loss, resulting in primary OP.[30] It is reported that hormone therapy shows efficacy in reduction or suppression of OP-associated fracture and most of the other symptoms related to menopause.[30] However, long-term hormone therapy has been associated with a high risk of breast cancer and other diseases.[31] Several medications in the clinic include anti-resorptive drugs, such as bisphosphonates, calcitonin, and denosumab, and anabolic agents, such as abaloparatide, romosozumab, and teriparatide. Healthy lifestyle, including nutrition (calcium, protein, vitamin C, and vitamin D) and suitable physical activity, exhibits relative small efficacy, but it may slow bone loss and prevent OP.[32] Currently used therapy includes those that inhibit bone resorption, promote bone formation, and dual-action therapies.[33] Combinational therapy of anabolic and anti-resorptive agents can produce synergistic effects and become the ideal strategy for OP treatment. However, this therapeutic strategy is not recommended due to the combined adverse effects.[34] An alternative therapeutic strategy for OP management is essential.

In ovariectomized (OVX) mice, apigenin treatment can significantly reduce trabecular bone loss in the femurs, maintaining bone homeostasis.[35] The protective activity of apigenin against bone loss has been confirmed in OVX rats, as shown by the increased mineral content and density of the trabecular bone and improved trabecular bone microarchitecture.[36] Apigenin is one of the bioactive components of *Cirsium setidens* water extracts (CSEs), which has been shown to promote osteoblastic bone matrix mineralization and suppress osteoclastic bone resorption in OVX mice.[37] (Table 1) It has been reported that the apigenin glycosides vitexin and isovitexin are the bioactive components of *Acer palmatum* hot water extract (APE), which promotes osteoblastogenesis and inhibits osteoclastogenesis in MC3T3-E1 cells.[38]

Apigenin Induces Osteogenic Differentiation

Mesenchymal stem cells (MSCs) have multiple directional differentiation potential. Under specific conditions, MSCs can differentiate into osteoblasts, adipocytes, and chondrocytes, and they can be used as important seed cells for gene therapy, regenerative medicine, and tissue engineering.[62] Particularly, MSCs derived from bone marrow (BMSCs) can easily differentiate into osteoblasts, stimulate bone formation, and increase bone mass. The introduction of BMSCs into the therapeutic management of bone diseases has shown promising results.[63] However, the potential of osteogenic differentiation of BMSCs in OP patients is reduced.[64]

Various signaling pathways have been involved in mediating osteogenic differentiation.[65] For example, Wnt/β-catenin signaling is believed to be integral to osteoblastic differentiation by transcriptionally upregulating the gene expression of runt-related transcription factor 2 (Runx2) via binding to its promoter.[66] Activation of β-catenin stimulates the formation of osteoblasts by inducing an increase in alkaline phosphatase (ALP) activity.[67] Similarly, activation of the Hedgehog signaling pathway relieves the inhibitory effects of Ptch1 on Smo and activates the expression of nuclear transcription factor Gli1, promoting the osteogenic differentiation of BMSCs.[65] BMP pathway is critical for promoting ossification by mediating osteogenic differentiation marker expression, such as ALP, osteopontin (OPN), and OCN.[68] Another study shows that Sirt1 activation promotes angiogenesis and osteogenic differentiation in BMP9-induced MSCs.[69]

It has been reported that apigenin can significantly increase the activity of ALP and mineralization and upregulate the expression of OPN, osterix (OSX), and Runx2. Apigenin promotes osteogenic differentiation of human MSCs by activating the JNK and p38 MAPK signaling pathways.[39] (Table 1) Consistently, apigenin can rescue the potential

Table 1 Summary of the Effects of Apigenin, Vitexin, and Isovitexin on Bone and Cartilage Diseases

Flavonoids	Models	Doses	Biological Actions	Effects	Ref.
Apigenin	OVX mice	20 mg/kg of CSEs	RANKL↓, OPG↑, BMD↑, TRAP↓, OC↑, PINP↑, CTX-1↓, mineralization↑	Promotes bone formation and inhibits bone resorption	[37]
Apigenin	Human MSCs	0.1, 1, and 5 μM	ALP↑, mineralization↑, Runx2↑, OPN↑, OSX↑, BMP2↑, Wnt/β-catenin↑,	Promotes osteogenesis	[39]
Apigenin	Human MSCs	1 μM	ALP↑, mineralization↑, FAK↑, ERK↑, TGFβ↑, Smad2↑, senescence↓, ROS↓	Promotes osteogenic differentiation	[40]
Apigenin	HPDL cells	40 μM	REX1↓, OCT4↓, ALP↑, mineralization↑, HIF1α↓,	Promotes osteogenesis	[41]
Apigenin	Human MSCs	25 and 50 μM	NLRP3↓, IL-1↓, ALP↑, Runx2↑, p-p65↓	Inhibits inflammation, enhances osteogenic differentiation	[42]
Apigenin	MG63 cells	10^{-6} M	TGFβ1↑, TGFβ-R1↑, TGFβ-R2↑, TGFβ-R3↑, BMP-2↑, BMP-7↑, RUNX-2↑, ALP↑, COL-I↑, OSX↑, OSC↑, OPG↑, RANKL↑	Promotes bone formation and maintains bone metabolism	[43]
Apigenin	MC3T3-E1 cells	1 μM	ALP↑, collagen↑, OPN↑, OPG↑, bone sialoprotein↑, OSX↑, OC↑, BMP-2↑, BMP-4↑, BMP-7↑, SOD1↑, SOD2↑, GPx1↑, ERK2↑, PI3K/AKT↑	Inhibits oxidative stress and promotes osteoblast differentiation	[44]
Isovitexin	OVX mice	5 mg/kg	Bone mass↑, Runx2↑, BMP-2↑, collagen I↑, PINP↑, CTX-1↓	Promotes osteoblast differentiation	[45]
Apigenin	MC3T3-E1 cells	10 and 20 μM	IL-6↓, MCP-1↓, MCP-3↓, and RANTES↓, CXCL-9↓, CXCL-10↓	Suppresses osteoclastogenesis	[46]
Apigenin	3T3-L1 cells	5 and 10 μM	IL-6↓, MCP-1↓, leptin↓		
Apigenin	RAW 264.7	10 μM	RANKL↓, TRAP↓, c-Fms↓		
Apigenin	Collagen-induced arthritis mice	20 mg/kg	Improved histological changes↑, TNFα↓, IL-1β↓, IL-6↓, CXCR4↓	Suppresses DC cell maturation and migration	[47]
Apigenin	DC cells	20 μM	TNFα↓, IL-10↓, IL-12p70↓, CXCR4↓		
Apigenin	RA-FLSs	15, 25, and 50 μM	Apoptosis↑, VEGF↓, VEGFR↓	Inhibits angiogenesis	[48]
Apigenin	Collagen-induced arthritis mice	20 mg/kg	Synovial hyperplasia↓, inflammatory cell infiltration↓, dilatation↓, congestion↓, RANKL↓, RANK↓, OPG↑	Improves arthritis symptoms and inhibits osteoclastogenesis	
Apigenin	CFA rats	43.61 μg/g	Paw swelling↓, NF-κB↓, TNFα↓, NOx↓, IL-23↓, IL-17↓, IL-22↓, IL-1β↓, IL-6↓, IL-36↓, IFNγ↓, JAK1↓, STAT3↓	Exhibits anti-inflammatory and anti-rheumatic effects	[49]
Apigenin	CFA rats	20 and 40 mg/kg	IL-1β↓, TNFα↓, IL-6↓, P2X7↓, p-p65↓, p-IKKα↓, p-IKKβ↓, p-IκBα↓	Alleviates inflammation	[50]
Apigenin	SW982 cells	40 μM	IL-6↓, IL-1β↓, TTR↓, RAGE↓, p65↓	Alleviates inflammation	[51]
Apigenin	RA-FLSs	0.25, 0.5, and 1 mM	Cell proliferation↓, NO↓, IL-6↓, p-p65↓, p-IKK↓, p-IκBα↓	Alleviates inflammation	[52]
Apigenin	CFA rats	10 mg/kg	Paw edema↓, arthritis scores↓, weight loss↑, SOD↑, GSH-Px↑, NO↓, MDA↓	Inhibits oxidative stress and improves RA	[53]
Apigenin	RAW 264.7	10 μM	IL-1↓, IL-6↓, TNFα↓, IL-12↓, MG-L1↑, MG-L2↑, ARG-1↑, IL-10↑, TRPM7↓, p-mTOR↓	Inhibits macrophage M1 polarization and promotes M2 polarization	[54]
Apigenin	Mouse chondrocytes	10 μM	IL-1↓, IL-6↓, TNFα↓, MMP-13↓, p-p38↓, p-JNK↓, p-ERK↓, apoptosis↓	Inhibits inflammation	

(*Continued*)

Table 1 (Continued).

Flavonoids	Models	Doses	Biological Actions	Effects	Ref.
Apigenin	Mouse chondrocytes	25 μM	CD38↓, Sirt1↑, p-p65↓, NAD+/NADH levels↑, collagen II↑, MMP-3↓, MMP-13↓	Inhibits inflammation and ECM degradation	[55]
Vitexin	Human OA chondrocytes	5 μM	IL-6↓, TNFα↓, HIF-1α↓, COX-2↓, PGE2↓, MMP-1↓, MMP-3↓, MMP-13↓	Inhibits inflammation and ECM degradation	[56]
Vitexin	BMDMs	100 μM	NAD+↑, IL-1β↓, CXCL1↓, NLRP3↓, Sirt3↑, SOD2↑	Inhibits inflammation and oxidative stress	[57]
Isovitexin	MSU-treated rats	100 mg/kg	IL-1β↓, IL-6↓, TNFα↓, TLR4↓, MyD88↓, p-p65↓	Inhibits inflammation	[58]
Apigenin	IDD rats	15 mg/kg	TNFα↓, IL-1β↓, IL-2↓, IL-6↓, IL-8↓, IL-17↓, COX-2↓, PGE2↓, MMP-3↓, MMP-9↓, ADAMTS-4↓, syndecan-4↓	Inhibits inflammation and ECM degradation	[59]
Apigenin	Rat NP cells	10, 25, and 50 μM	Bax↓, cleaved caspase-3↓, Bcl2↑, p21↓, p16INK4a↓, β-gal↓, collagen II↑, aggrecan↑, MMP-13↓, ADAMTS5↓, LC3-II↑, p62↓, TFBE↑	Inhibits apoptosis, senescence, and ECM degradation	[60]
Apigenin	SOSP-9607 cells	10, 20, and 40 μM	Proliferation↓, migration↓, invasion↓, Nanog↓, OCT4↓, Warburg effect↓, p-PI3K↓, p-AKT↓, p-mTOR↓	Inhibits OS development	[61]

Notes: ↑ indicates an increase, and ↓ is a decrease.
Abbreviations: RANKL, receptor activator of nuclear factor (NF)-κB ligand; BMD, bone mineral density; OC, osteocalcin; ALP, alkaline phosphatase; Runx2, runt-related transcription factor 2; OPN, osteopontin; OSX, osterix; BMP-2, bone morphogenetic protein-2; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase; TGFβ, transforming growth factor-β; ROS, reactive oxygen species; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor kappa-B; MAPK, mitogen-activated protein kinase; IL-1β, interleukin-1β; TNFα, tumor necrosis factor-α; MMPs, matrix metalloproteinases; ADAMTSs, a disintegrin and metalloproteinases with thrombospondin motifs; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2.

osteogenic differentiation of human BMSCs obtained from elderly patients with OP. Microarray-based gene expression profile in apigenin-treated human BMSCs has been explored. Apigenin promotes osteogenic differentiation by activating the focal adhesion kinase (FAK), ERK, and TGFβ/Smad2 signaling pathways. In addition, apigenin decreases senescence and oxidative stress in TBHP-treated human BMSCs.[40] It is well known that Wnt/β-catenin signaling plays a critical role in cellular differentiation and ECM production during skeletal formation and development.[70] One study reports that apigenin at the doses of 0.05 and 0.5 μM induces osteogenic differentiation of human MSCs by enhancing the Wnt/β-catenin signaling. Similar effects of apigenin (at the dose of 45 ng/kg for 6 weeks) on osteogenesis in a rat (male and 3-month old) femoral fracture model have been shown.[71]

Hypoxia plays a critical role in maintaining the pluripotency of stem cells. In human periodontal ligament (HPDL) cells, cobalt chloride ($CoCl_2$) treatment upregulates the mRNA expression of stem-cell markers REX1 and OCT4, downregulates the expression of osteogenesis-related factors, and suppresses the activities of ALP and mineralization. However, apigenin compromises the effects of $CoCl_2$ on HPDL cells by inhibiting HIF1α activity.[41] (Table 1) Increased inflammation regulated by the NLRP3 inflammasome and NF-κB signaling can suppress osteogenesis but promote adipogenesis. In LPS/palmitic acid (PA)-treated human MSCs, apigenin may significantly enhance the osteogenic activity by downregulating the expression of NLRP3, caspase-1, IL-1β, and NF-κB[42] (Table 1).

Apigenin Promotes Osteoblast-Mediated Bone Formation

Quantitative structure-activity relationship (QSAR) has been explored to evaluate the bone-forming ability of flavonoids by activating the voltage-gated calcium (CaV) channel in osteoblasts. Apigenin has been predicted to be the bioactive compound in modulating the CaV channel and promoting osteoblast-mediated bone formation.[72] Apigenin can enhance the mRNA expression of TGFβ1, TGFβ-R1, TGFβ-R2, TGFβ-R3, BMP-2, BMP-7, RUNX-2, ALP, COL-I, OSX, and OSC in MG63 osteoblasts. In addition, apigenin treatment also increases the mRNA expression of osteoprotegerin (OPG) and RANKL, compared to that in the negative control group. These indicate that apigenin treatment plays a role in maintaining the metabolism homeostasis of osteoblasts.[43] (Table 1) Apigenin is one of the bioactive compounds in the leaf extract of *Blainvillea acmella* (L). Philipson, which shows bone anabolic effects in MC3T3-E1 cells by suppressing

oxidative stress.[73] Another study reports that an apigenin glycoside from *Uraria crinita* (L). Desv. ex DC. can promote osteoblast differentiation and stimulate new bone formation and regeneration by upregulating the expression of ALP, Runx2, OPN, and BMP-2 in HOb cells.[74]

Oxidative stress is associated with the imbalance between antioxidant defenses and ROS production. Oxidative stress has become a cause of various degenerative diseases, such as OP. Particularly, oxidative stress induces bone loss by inducing lipid peroxidation, inhibiting the expression of antioxidant enzymes, suppressing osteoblast differentiation, increasing osteoblast apoptosis, and enhancing osteoclast formation.[75] In H_2O_2-treated MC3T3-E1 cells, apigenin prevents oxidative stress-induced cell damage and promotes osteoblast differentiation, as shown by increased expression of ALP, collagen, OPN, OPG, bone sialoprotein, OSX, osteocalcin (OC), and BMPs (BMP-2, BMP-4, and BMP-7) (Figure 2). Mechanically, the protective activity of apigenin might be associated with activation of the PI3K/AKT and ERK signaling pathways, which are inhibited by H_2O_2 treatment.[44] (Table 1) Osteoblasts have been implicated in mineral formation by promoting ECM protein expression and releasing matrix vesicles. The processes of mineralization require the involvement of many factors, such as annexins (Anx) and tissue-nonspecific alkaline phosphatase (TNAP). Apigenin mediates the mineralization processes by regulating the expression of AnxA6 and TNAP.[76]

It has been reported that isovitexin promotes bone formation at the osteotomy site and exhibits bone regenerative effects in a femur osteotomy mouse model. Isovitexin promotes osteoblast differentiation by stimulating mitochondrial biogenesis and respiration. In OVX osteopenic mice, isovitexin rescues bone mass and structure of trabecular bones and cortical bones, as demonstrated by the upregulation of the expression of Runx2, BMP-2, and type I collagen in bones, an increase in serum procollagen type I N-terminal propeptide (PINP), and a decrease in sclerostin and type I collagen cross-linked C-telopeptide (CTX-1).[45] (Table 1) Consistently, vitexin promotes the osteoblast differentiation of MC3T3-E1 preosteoblasts, mouse calvarial primary cells, C3H10T1/2, and BMSCs, as shown by enhanced expression of Dlx5, Runx2, ALP, and Smad1/5/9.[77]

Apigenin Inhibits Osteoclast-Mediated Bone Resorption

Osteoclasts are derived from the hematopoietic bone marrow monocytic/macrophage (BMM) cell lineage and they are known to be capable of resorbing bone. Osteoblasts and osteocytes can produce and secrete RANKL, which can interact

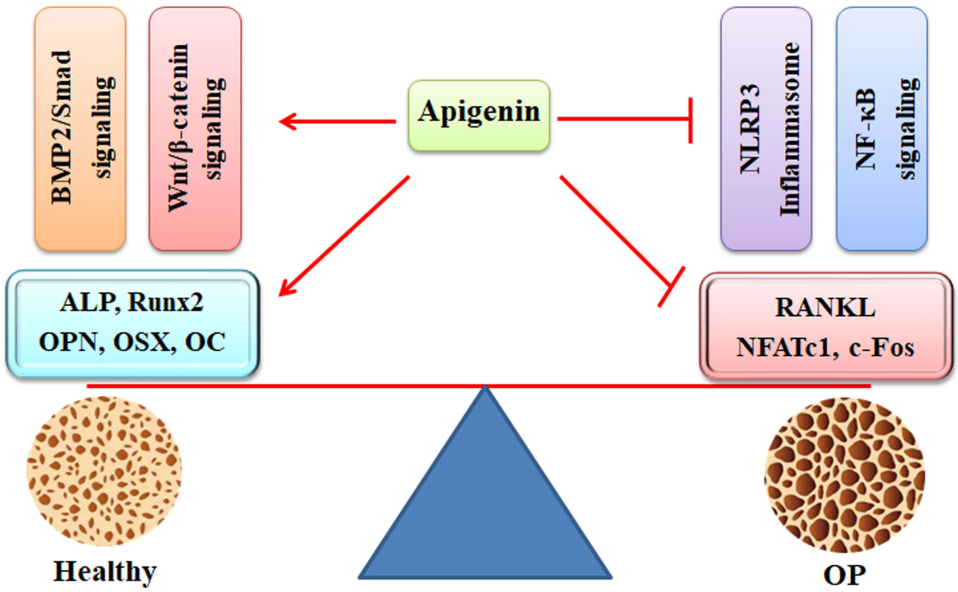


Figure 2 The protective activity of apigenin against OP development. Apigenin promotes bone formation by activating the BMP-2/Smad and Wnt/β-catenin signaling pathways, as shown by increased expression of ALP, Runx2, OPN, OSX, and OC. In contrast, apigenin inhibits bone resorption by suppressing the NLRP3 inflammasome and NF-κB signaling pathways, as indicated by decreased expression of RANKL, NFATc1, and c-Fos.

Abbreviations: OP, osteoporosis; BMP-2, bone morphogenetic protein-2; ALP, alkaline phosphatase; Runx2, runt-related transcription factor 2; OPN, osteopontin; OSX, osterix; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor kappa-B; RANKL, receptor activator of nuclear factor (NF)-κB ligand; NFATc1, nuclear factor of activated T-cells cytoplasmic 1.

with the receptor RANK on BMM precursors, activating the bone-resorbing machinery and the downstream factors NFATc1 and c-Fos.[78] (Figure 2) One study shows that inhibition of RANKL may lead to suppression of the NF-κB signaling pathway and NFATc1 expression, leading to attenuation of osteoclast-derived bone resorption.[79] OP is a bone disorder with dysregulated inflammatory responses. Estrogen insufficiency may favor Th2 over Th1 in the immune profile, inducing the alteration of inflammatory cytokine ratio, the initiation of bone loss, and the promotion of OP pathogenesis.[80] Inflammatory immune regulation can be a potential target for OP management.

Apigenin, one of the bioactive components from *Cephalotaxus koreana* Nakai, has been reported to inhibit osteoclast differentiation.[81] In MC3T3-E1 cells, apigenin suppresses TNFα-induced expression of osteoclastogenic factors, such as IL-6, MCP-1, MCP-3, and RANTES, and inhibits IFNγ-induced secretion of osteoclastogenic monokines CXCL-9 and CXCL-10. In 3T3-L1 cells, apigenin downregulates the expression of IL-6, MCP-1, and leptin. In RAW 264.7 cells, apigenin inhibits RANKL-induced formation of multinucleated cells and suppresses osteoclastogenesis.[46] (Table 1) It has been reported that vitexin (a glucoside of apigenin) can significantly inhibit RANKL-induced osteoclast formation and bone resorption by inhibiting the p38 MAPK and ERK signaling pathways and suppressing the expression of NFATc1 and c-Fos in LPS-treated BMM cells. Thus, apigenin and its glucoside may suppress RANKL-mediated osteoclastogenesis and bone resorption.[82]

The Protective Activities of Apigenin Against RA Development

RA, an autoimmune disease, is correlated with the deregulation of immune cells and synovial fibroblasts, which increase inflammatory responses, induce cartilage destruction, and promote osteoclast differentiation and bone erosion.[83,84] Research indicates that the incidence of RA increases with age, peaking between 60 and 70 years. In 2020, an estimated 17.6 million people had RA worldwide, and it is forecasted that the number of RA patients will be 31.7 million by 2050.[85] A significant upward trend in the global age-standardised incidence rate (ASIR) of RA is observed for both sexes from 1990 to 2019 (average annual percent change (AAPC): 0.214.[86] One study reports that the global RA-related incidence rate increases from 11.66 to 13.48 per 100,000 people from 1990 to 2021. RA-related disability-adjusted life years (DALYs) rate increases from 26.37 to 30.71 per 100,000 people, with females bearing a higher burden.[87] RA diagnosis (during the 5 years after diagnosis) has been associated with lower earnings, particularly for older individuals and those with lower education level, by about 5%.[88] The annual average cost is $2337.73 per patient with RA in Morocco.[89]

Various potential biomolecular mechanisms have been proposed. However, the exact cause of RA remains unclear.[90] Four classes of drugs, such as NSAIDs, DMARDs, glucocorticoids (GCs), and botanical preparations, have been used for treating RA. DMARDs are recommended by the American College of Rheumatology (ACR) to preserve joint functions.[91] NSAIDs and GCs have become supplementary therapies to alleviate inflammatory responses in RA patients. Apigenin has been reported to inhibit the inflammatory responses in LPS-treated RAW 264.7 cells and the angiogenesis in TNFα-treated human umbilical vein endothelial cells (HUVECs).[19]

It has been reported that apigenin exhibits immunosuppressive activity against collagen-induced arthritis, as shown by reduced severity of pathological alterations and decreased production of pro-inflammatory cytokines in the serum and supernatants from the lymph nodes of the mice with collagen-induced arthritis. In lipopolysaccharide (LPS)-treated bone marrow-derived dendritic cells (DCs), apigenin restrains cell phenotype and maintains cell phagocytotic capability. Apigenin becomes a potent suppressor of DC maturation and migration.[47] (Table 1) Consistently, apigenin can significantly reduce the infiltration of inflammation cells, edema formation, and paw thickness and decrease arthritis score in collagen antibody-induced arthritis-induced rat models. In addition, apigenin also decreases the neutrophil-to-lymphocyte ratio (NLR) in whole blood.[92] Additionally, it is reported that apigenin can alleviate the arthritic symptoms by inhibiting synovial hyperplasia, angiogenesis, and osteoclast activation in the mice with collagen-induced arthritis. Mechanically, apigenin inhibits the expression of VEGF and VEGFR, suppresses the proliferation of RA-FLSs, promotes the apoptosis of RA-FLSs, and mediates the RANKL/RANK/OPG system in CIA mice[48] (Table 1).

It has been reported that apigenin exhibits anti-inflammatory activity and inhibits LPS-activated collagenase activity by decreasing nitric oxide (NO)-mediated cyclooxygenase-2 (COX-2) expression and monocyte adherence.[93] One study reports that apigenin can effectively inhibit cyclooxygenase 2 (COX-2) and nuclear factor κB (NF-κB) expression,

induce lupus immune cell apoptosis, and suppress lupus development by inhibiting autoantigen presentation for expansion of autoreactive Th1 and Th17 cells. Apigenin may exhibit protective activities against inflammation- or immune-associated diseases, such as RA and OA.[94] Apigenin is one of the bioactive compounds from the polar extract of *Phoenix dactylifera* L., which shows anti-inflammatory and anti-rheumatic effects in CFA-induced arthritis rat models by mediating the IL-23/IL-17/IL-22 axis and the NF-κB/IL-6/JAK1/STAT3 signaling pathway.[49] (Figure 3) In addition, apigenin is the bioactive compound of *Mansoa alliacea* extract, which exhibits anti-inflammatory and anti-nociceptive activities in CFA-treated mice.[95] Consistently, isovitexin-contained crude aqueous extract of *Cecropia hololeuca* Miq. also shows anti-inflammatory and anti-nociceptive effects in zymosan-induced mouse arthritis.[96]

P2X7 plays a role in the immune system and inflammatory diseases by mediating the efflux of Na^+, Ca^{2+}, and K^+ and activating the MPAK/NF-κB signaling pathways (Figure 3). The P2X7/NF-κB signaling has been implicated in the pathological development of arthritis.[50] Apigenin has been shown the protective activity against CFA-induced arthritis by suppressing the P2X7/NF-κB signaling and its downstream factors, such as IL-1β, TNFα, and IL-6 in rats.[50] (Table 1) TNFα-triggered progressive inflammation has been implicated in the pathogenesis of RA. TNFα treatment increases the expression of IL-6, IL-1β, TTR, and receptors for advanced glycation end products (RAGE) by activating the NF-κB signaling pathway, compared to that in the negative control group in human synovial fibroblast SW982 cells. Apigenin can interact with TNFα and exhibit anti-inflammatory effects against TNFα-stimulated deregulation associated with RA pathogenesis[51] (Table 1).

RA fibroblast-like synoviocytes (RA-FLSs) are different from normal FLSs due to their aggressive and invasive phenotype. RA-FLSs can grow in soft agarose in an anchorage-independent manner, and they can invade the articular cartilage in mouse RA models.[97] RA-FLSs play a critical role in the pathological development of RA by promoting the synthesis of pro-inflammatory cytokines and upregulating the expression of matrix-degrading enzymes.[98] Apigenin suppresses the aberrant proliferation of RA fibroblast-like synoviocytes (RA-FLSs) and decreases the production of NO and IL-6. Apigenin exhibits anti-RA effects by attenuating the activation of the NF-κB signaling and the expression of pro-inflammatory cytokines.[52] (Table 1) TNF-related apoptosis-inducing ligand (TRAIL) can promote FLS proliferation by activating the MAPK and PI3K/AKT signaling pathways. However, TRAIL-induced apoptosis only accounts for

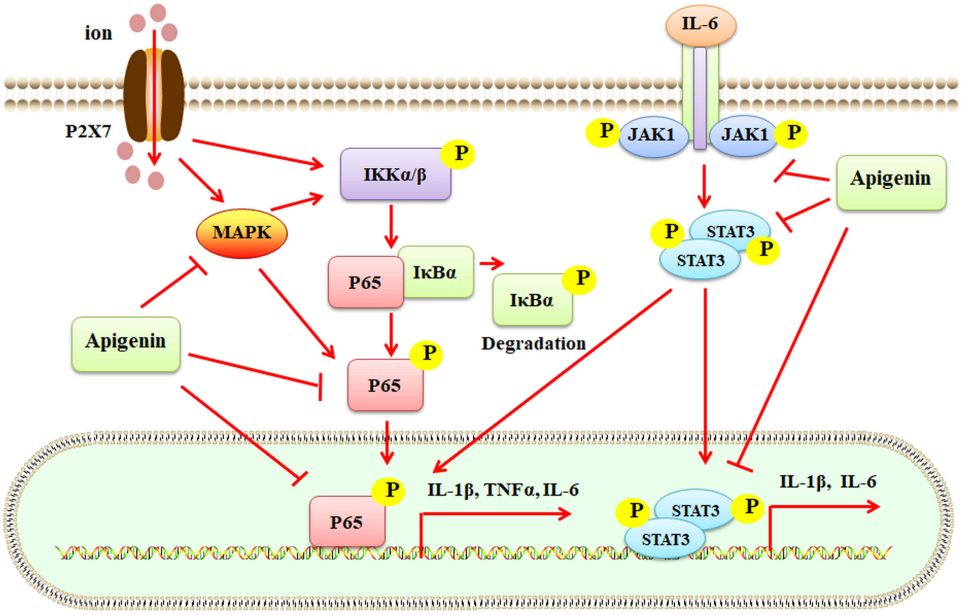


Figure 3 Apigenin suppresses inflammatory responses mediated by the P2X7/MAPK/NF-κB and IL-6/JAK1/STAT3 signaling pathways. Ion-activated P2X7 stimulates MAPK and IKKα/β, which induced the activation of p65. Phosphorylated p65 (p-p65) enters the nucleus for transcription regulation of IL-1β, TNFα, and IL-6 expression. IL-6 induces the phosphorylation of JAK1, which promotes the activation of STAT3. Phosphorylated STAT3 (p-STAT3) enters the nucleus for transcription regulation. Apigenin suppresses the activities of MAPK, p-p65, and p-STAT3, leading to inhibition of inflammatory responses.

Abbreviations: MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; IL-1β, interleukin-1β; TNFα, tumor necrosis factor-α; JAK1, Janus kinase 1; STAT3, signal transducer and activator of transcription 3.

a small amount of RA-FLSs. This might be associated with the death resistance of RA-FLSs, which exhibit high expression levels of Bcl-2 and Mcl-1. Apigenin can significantly suppress TRAIL-induced RA-FLS proliferation, restore the expression of p21 and p27, and inactivate the PI3K/AKT signaling pathway.[99] Apigenin-4'-O-α-L- rhamnoside can decrease the expression of MMP-1, MMP-3, RANKL, and TNFα in RA-FLS cells and inhibit the MAPK signaling pathway.[100]

In human RA-FLSs, the effects of apigenin (at the dose of 10, 25, 50, and 100 μM) on cell apoptosis have been studied. Particularly, the activity of apigenin (at the dose of 100 μM) at the time-point of 1, 2, 4, and 8 h in promoting cell apoptosis is also investigated. Consequently, apigenin treatment may stimulate a large amount of ROS, stimulate the MAPK-ERK1/2 signaling pathway, and induce cell apoptosis.[101] Apigenin, the effective compound of a Chinese herbal medicine *Genkwa flos*, can inhibit paw edema, decrease arthritis scores, and induce weight loss in complete Freund's adjuvant (CFA)-treated rats by enhancing the levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and decreasing the production of NO and malondialdehyde (MDA). The protective effects of apigenin against CFA-induced RA might be associated its antioxidant activity[53] (Table 1).

The Protective Activities of Apigenin Against OA Development

OA, characterized by chronic low-grade inflammation, degenerative cartilage erosion, osteophyte hyperplasia, and synovitis, is the leading cause of musculoskeletal pain, disability, and socioeconomic burden. Epidemiological data show that OA affects more than 300 million individuals worldwide, with higher incidence and prevalence in middle-aged and elderly populations.[102] The number of years lived with disability (YLDs) for hip and knee OA has been ranked 11th highest in the 2010 Global Burden of Diseases (GBD) survey.[103] In the USA, musculoskeletal diseases affect over 121 million people and account for the highest rate of disability among all disease groups.[104] The traditional treatment for OA are mainly systemic administration of drugs (such as NSAIDs or opioid-strength painkillers) or end-stage total joint replacement-related surgery.[105]

Macrophage polarization plays a critical role in OA development.[106] It has been reported that apigenin can inhibit macrophage M1 polarization and promote M2 polarization, as shown by reduced levels of IL-1, IL-6, TNFα, and IL-12 and enhanced levels of MG-L1, MG-L2, ARG-1, and IL-10 in cultured bovine articular cartilage explants. Mechanically, apigenin inhibits macrophage polarization-mediated inflammatory response and chondrocyte apoptosis by inhibiting the MAPK and TRPM7/mTOR signaling pathways.[54] (Figure 4) One study reports the co-culture of bovine articular cartilage explants with cytokine combinations (including IL-1α, IL-1β, IL-6, IL-17, TNFα, and oncostatin M). The aggrecanase-mediated cleavage of aggrecan is promoted by all cytokine mixtures via MMPs. Particularly, oncostatin M can synergize with IL-1 and TNFα to induce a rapid cleavage of aggrecan and HA. Interestingly, apigenin acts as an inhibitor of hyaluronidase to suppress HA release. This suggests that hyaluronidase has been involved in cartilage matrix degradation, and HA release is associated with high levels of concomitant proteolysis.[107]

Cluster of differentiation 38 (CD38), the principal NADase, is ubiquitously expressed in immune cells. CD38-mediated NAD^+ degradation is linked to reduced activity of Sirts, and the expression of CD38 is associated with increased inflammatory responses.[108] The expression of CD38 is upregulated in human OA cartilage and IL-1β-treated chondrocytes. Overexpression of CD38 decreases cellular NAD^+/NADH levels and promotes IL-1β-induced cartilage degradation, synovial inflammation, osteophyte formation, and subchondral bone sclerosis. Apigenin attenuates IL-1β-induced catabolic activities and exhibits chondroprotective effects by mediating the CD38 activity and the Sirt1/NF-κB signaling pathway.[55] (Figure 4) (Table 1) Apigenin is one of the bioactive compounds in *Vernonia amygdalina* (VA), which has been shown to increase the expression of IL-10 and collagen 2a1 and decrease the expression of MMP-3, MMP-13, ADAMTS5, collagen type II degradation biomarker (CTX-II), NF-κB, COX-2, and PGE2.[109] OA commonly co-exists with OP in the elderly. Apigenin glycosides can effectively decrease cartilage erosion, bone loss, serum levels of biomarkers, such as IL-1β and osteocalcin (OCN), and mRNA expression of NF-κB, IL-1β, cyclooxygenase-2 (COX-2), and matrix metalloproteinase-13 (MMP-13) in rats.[18]

The hypoxia-inducible factor 2α (HIF2α) is a transcription factor for mastering OA pathogenesis by upregulating the expression of MMP-3, MMP-13, COX-2, and other catabolic factors via binding to hypoxia-responsive elements (-CGTG-) in their promoter specifically.[110] Apigenin, one of the main bioactive compounds in *Cirsium japonicum* var.

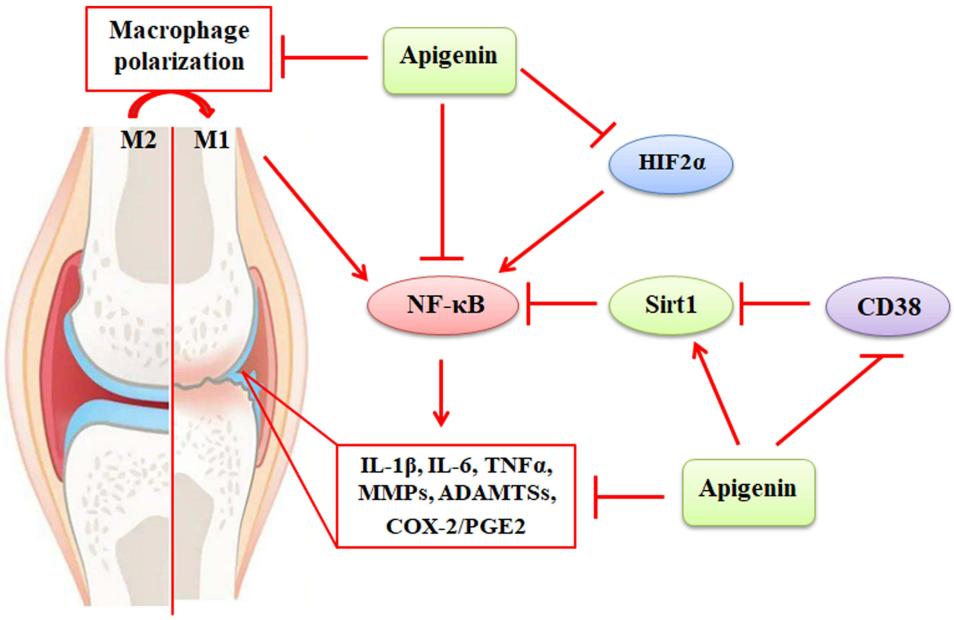


Figure 4 The protective activity of apigenin against inflammatory responses in OA. Activation of the NF-κB signaling enhances the expression of IL-1β, IL-6, TNFα, MMPs, ADAMTSs, COX-2, and PGE2, leading to destruction of joint cartilage. The NF-κB signaling can be activated by macrophage M1 polarization, HIF2α, and CD38. These can be compromised by apigenin, which exhibits protective activity against NF-κB-mediated inflammatory responses.
Abbreviations: NF-κB, nuclear factor kappa-B; IL-1β, interleukin-1β; TNFα, tumor necrosis factor-α; MMPs, matrix metalloproteinases; ADAMTSs, a disintegrin and metalloproteinases with thrombospondin motifs; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2.

maackii (CJM), has been demonstrated to alleviate HIF2α-induced cartilage destruction and improve DMM-induced mouse OA progression. Apigenin downregulates HIF2α-mediated expression of MMP-3, MMP-13, COX-2, and ADAMTS4 by inhibiting the NF-κB and JNK signaling pathways.[111] (Figure 4) Vitexin exhibits anti-inflammatory effects on IL-1β-treated human OA chondrocytes by reducing the levels of pro-inflammatory cytokines, such as IL-6, TNFα, HIF-1α, COX-2, PGE2, MMP-1, MMP-3, and MMP-13.[56] (Table 1) In addition, vitexin suppresses IL-1β-induced rat chondrocyte apoptosis by inhibiting the expression of GRP78, PDI, and CHOP, which are the key factors in endoplasmic reticulum (ER) stress. Vitexin also inhibits ER stress-related activation of the NF-κB signaling, inflammation, and ECM degradation in rat chondrocytes. Thus, the protective activity of vitexin, a glucoside of apigenin, might be associated with the inhibition of ER stress in OA chondrocytes.[112]

The Protective Activities of Apigenin Against Gouty Arthritis (GA)

Gouty arthritis (GA) has been associated with the deregulation of purine metabolism and uric acid excretion. GA is characterized by the accumulation of uric acid crystals in the articular cavity, synovium, cartilage, and bone tissues, leading to joint deformation and stiffness.[113] The development of GA might be associated with the interaction of genetic and environmental factors, such as obesity, purine-rich diets, and alcohol consumption. Monosodium urate (MSU) in the joints or urate in the serum may activate the inflammatory responses.[114] NSAIDs, GCs, allopurinol, probenecid, and colchicine have been intensively used in the clinic for GA treatment. However, they are limited due to the adverse effects.[115] Novel effective therapeutic strategies, such as anti-inflammation, urate reduction, and xanthine oxidase (XOD) inhibition, have been explored.

MSU-induced CD38 expression has been associated with NAD^+ degradation and IL-1β and CXCL1 release in gouty mice. However, apigenin acts as an inhibitor of CD38 and reverses CD38-induced activation of the NLRP3 inflammasome and suppression of the Sirt3/SOD2 signaling pathway in bone marrow derived macrophages (BMDMs).[57] (Table 1) It has been demonstrated that apigenin exhibits the strongest activity in inhibiting XOD functions (an IC_{50} value of 30 μM) among the isolated compounds. The aqueous extract of *Selaginella moellendorffii* Hieron containing apigenin has been reported to improve hyperuricemia, reduce gouty joint inflammatory responses, and suppress oxidative stress in

potassium oxonate-treated mice.[116] Another study reports that apigenin-7-O-glucoside reduces the serum levels of uric acid, creatinine, and MDA and enhances the activity of SOD in hyperuricemic mice. Mechanically, apigenin-7-O-glucoside inhibits the expression of XOD (an IC_{50} value of 0.24 μM) and promotes the excretion of uric acid by mediating the renal urate transporters URAT1, GLUT9, OAT1, and ABCG2.[117] Isovitexin, a glucoside of apigenin, has been shown to alleviate the joint inflammatory responses in MSU-induced rat GA models by inhibiting the TLR4/MyD88/NF-κB signaling pathway. However, the mechanism of apigenin underlying the anti-inflammatory activity of independent pathways, such as JNK, MAPK, and other signaling pathway, still needs further investigation[58] (Table 1).

The Protective Activities of Apigenin Against IDD Development

Intervertebral disc degeneration (IDD), an age-associated musculoskeletal disease, causes low-quality life and high clinical and socioeconomic burdens. The intervertebral disc (IVD), a cylindrical avascular connective tissue, is constituted by a central nucleus pulposus (NP), a peripheral annulus fibrosus (AF), and a cartilage endplate (CEP). The NP cells are responsible for the production of ECM metabolism by regulating the expression of proteoglycan and type II collagen. This indicates that the NP cells play a critical role in maintaining the function and flexibility of the discs.[118] It has been reported that the dysfunction of NP and AF cells has been correlated with the pathological development of IDD by inducing abnormal ECM metabolism.[119] A variety of factors, such as inflammation, oxidative stress, abnormal mechanical stress, and immune deregulation contribute to IVD cell apoptosis and ECM composition alterations.[120]

One study reports that the levels of the pro-inflammatory cytokines, such as TNFα, IL-1β, IL-2, IL-6, IL-8, and IL-17 are significantly enhanced in IDD rats. In addition, the catabolic factors, such as MMP-3, MMP-9, ADAMTS-4, syndecan-4, and COX-2/PGE2, are also upregulated. Apigenin has been reported to inhibit inflammatory responses and ECM degradation in the IDD rats and NP cells.[59] (Table 1) Autophagy is a dynamic process for scavenging the senescent organelles and misfolded proteins. One study reports that impaired lysosomal biogenesis and autophagic flux promote IDD development.[121] Tert-butyl hydroperoxide (TBHP) may induce autophagosome and lysosome fusion interruption and lysosomal dysfunction by decreasing the nuclear translocation of TFEB, the controller of autophagosome. Apigenin can reverse the decreased nuclear translocation of TFEB induced by TBHP. Particularly, apigenin can inhibit TBHP-induced NP cell apoptosis and senescence and ECM degradation by activating the AMPK/mTOR/TFBE signaling pathway and restoring autophagic flux.[60] Thus, increasing autophagy has become a potential strategy for IDD treatment, and this suggests a new insight into understanding the potential of apigenin in the treatment of IDD (Table 1).

The Protective Activities of Apigenin Against Other Bone Diseases

Osteonecrosis of the femoral head (ONFH) is characterized by progressive alterations in the hip structure affected by various factors, such as GC use. The bioinformatics analysis shows that thirty-one hub genes are enriched in the AMPK pathway, TLR pathway, and immunity. Two ferroptosis-related factors NCF2 and SLC2A1 have been identified the potential diagnostic biomarkers. Vitexin, an apigenin glucoside, has been reported to promote osteoblast differentiation by inhibiting oxidative stress and the HIF-1 signaling pathway in dexamethasone (Dex)-treated MC3T3-E1 cells.[122]

Osteosarcoma (OS), the most common bone cancer, affects children and adolescents worldwide. The etiology of OS remains unclear, and the prognosis is poor due to the recurrence and metastasis.[123,124] Apigenin has been shown to promote the mitochondrial apoptosis of OS U2OS cells and exhibit anticancer activity.[125] The Wnt/β-catenin signaling plays a role in cell morphogenesis, differentiation, and proliferation. It has been reported that apigenin suppresses cell proliferation and reduces cell invasion by inhibiting the Wnt/β-catenin signaling in U2OS and MG63 cells.[126] Consistently, apigenin suppresses the proliferation and epithelial-mesenchymal transition (EMT) of SOSP-9607 cells by inhibiting the PI3K/Akt/mTOR signaling-mediated Warburg effects[61] (Table 1).

Clinical Perspectives

There are several clinical trials for apigenin reported on the website of clinicaltrials.gov. A single-center, single-blind, randomized, placebo-control pilot clinical trial (NCT05999682) in elderly septic patients has been performed to determine whether apigenin improves organ dysfunction scores. However, no results have been posted. Similarly, the clinical trial (NCT06560216) to study cryopreservation medium with apigenin in post-thaw human sperm has been

conducted. The clinical trial on the protective effects of apigenin against neurodegenerative disorder (NCT05696665) has been documented. However, apigenin has low water solubility and poor oral bioavailability (less than 5% of the oral administered dose), which may significantly limit its clinical applications. Isovitexin has appropriately three-fold higher bioavailability than apigenin and has an osteogenic EC_{50} value of 620 nM in cultured osteoblasts.[45,127] To improve the bioavailability of apigenin, several strategies have been explored. Nanoparticles, such as liposomes, lipid nanocapsules, and polymer-based nanocapsules have been prepared to improve the bioavailability of apigenin.[16] For example, a novel formulation of apigenin loaded into nanoparticles has been developed for treating dry eye diseases.[128] The self-nanoemulsifying drug delivery system (SNEDDS) has been employed to improve the dissolution and permeability of apigenin and promote its antioxidant activity.[129] However, the new strategies for improving apigenin bioavailability in treating bone diseases are rarely reported.

The effects of apigenin on bone healing of critical-size defects in rat calvaria have been investigated. Apigenin treatment by gavage promotes the new formation of bone trabeculae, as shown by increased secretion of osteoid matrix and mineralization. Mechanically, apigenin enhances the expression of Runx-2, Smad5, Coll1, Coll4, and Coll5 in human dental pulp stem cells (hDPSCs).[130] Bioactive mesoporous glasses (MBGs) have been used for treating bone defects. One study shows that the 3D scaffolds using MBGs loaded with extracts, rich in apigenin and kaempferol, promote bone metabolism, as indicated by improved cytocompatibility and enhanced expression of Runx-2, ALP, and biomineralization in MC3T3-E1 cells.[131]

MSC administration has been used as a cell-based therapeutic strategy for OA treatment, and it shows promising effects on cartilage regeneration. One study reports that a combination of apigenin and synovial membrane-derived MSC (SMMSCs) can enhance the therapeutic efficiency of cell therapy with a potential mechanism of anti-inflammation and antioxidant of apigenin. It shows that apigenin decreases the expression of IL-1β, TNFα, inducible nitric oxide synthase (iNOS), MMP-3, and MMP-13 and increases the expression of SOD, MDA, SOX-9, collagen 2a1, and aggrecan, compared to that in the negative control group.[132] Co-treatment of MSC and apigenin in the rat knee by intra-articular injection can enhance the production of ECM components and improve histological changes by inhibiting inflammation and oxidative stress.[133]

One study shows that Sirt3- and SHMT2-mediated mitochondrial pathways have become the potential targets of apigenin in promoting caspase-3-dependent apoptosis in colorectal cancer cells.[134] Apigenin is an anti-inflammatory agent that could induce the death of cancer cells using radiotherapy methods with X-ray. The presence of sensitizers and high atomic number nanoparticles coated with apigenin biomaterials can prevent DNA damage repair and increase the likelihood of cancer cell death. A biocompatible gold nanoparticle coated with apigenin (Api@AuNPs) as a sensitizer has been introduced.[135]

Conclusions

Apigenin, a naturally occurring flavonoid, has been shown the protective activities against bone diseases, such as OP, RA, OA, GA, and IDD, in cells and animals. Apigenin is a phytoestrogen that inhibits bone loss and improves bone microarchitecture. It is valuable that apigenin promotes osteogenic differentiation, induces osteoblast-associated bone formation, and suppresses osteoclast-related bone resorption. The anti-inflammation and antioxidant effects of apigenin facilitate its protection against OP, RA, OA, GA, and IDD. However, many issues still need to be addressed. For example, more potential targets and the related molecular mechanisms of apigenin should be explored. The clinical trials of apigenin in treating human bone diseases should be studied. The different chemical forms of apigenin, such as apigenin glycosides, might be linked to the distinct biological activities, although the sugar parts of these glycosides can be removed and converted into their aglycone moiety apigenin. The effects of apigenin on NAD^+ elevation need more investigation, although apigenin acts as an inhibitor of CD38. The novel strategies for improving the bioavailability of apigenin should be further studied, particularly in the field of bone and cartilage diseases.

Data Sharing Statement

The data used to support the findings of this study are included within the article.

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Disclosure

The authors declare no conflicts of interest in this work.

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