Formononetin: a review of its anti-inflammatory properties and mechanisms

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REVIEW ARTICLE

Abstract

Formononetin, an isoflavone phytoestrogen widely present in legumes, has garnered significant attention for its diverse health-promoting functions, particularly its antioxidant, neuroprotective, and antihypertensive properties. However, the complex connection between these health benefits and its potent anti-inflammatory mechanisms remains largely unexplored. This comprehensive review, covering the period from 1994 to 2024, aims to bridge this gap by elucidating formononetin's potential as a therapeutic agent for a variety of inflammatory-mediated diseases, such as cancer, obesity, and neurodegenerative disorders. By interacting with key inflammatory signaling pathways (NF-κB, MAPK, JAK-STAT, PI3K-AKT, and TLRs) and through estrogen-dependent mechanisms, formononetin exerts strong anti-inflammatory effects that contribute to its overall health benefits. Our synthesis consolidates the latest findings, emphasizing the mechanisms underlying formononetin's anti-inflammatory actions and their implications for various pathological conditions. This review not only fosters a deeper understanding of formononetin's health-promoting potential but also encourages further research to harness its therapeutic benefits for enhancing human health.

Keywords: anti-inflammatory effect; formononetin; isoflavone; network pharmacology; pathological condition

Introduction

Flavonoids, ubiquitous secondary metabolites found in various plant parts, including stems, leaves, flowers, and fruits, exhibit a wide range of biological activities that significantly contribute to healthy bodily functions. Not only do these compounds possess anti-inflammatory, antioxidant, anti-tumor, and cardiovascular disease treatment effects, but they also boast excellent safety profiles with minimal side effects. Importantly, flavonoids are diverse and easily obtainable through our daily diets, being abundant in common fruits, vegetables, and beverages like berries, grapes, tea, and herbal plants. Their accessibility enhances their value and practicality in promoting healthy bodily functions. By integrating flavonoid-rich foods into our diets, we can leverage their multifaceted biological activities to bolster overall health and well-being (Dias *et al.*, 2021). Natural flavonoids

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encompass a diverse range of subclasses, including flavones, flavonols, flavanones, flavanonols, isoflavones, isoflavanones, chalcones, dihydrochalcones, aurones, anthocyanidins, flavan-3-ols, flavan-3,4-diols, bisflavonoids, and xanthones. Their classification is based on the oxidation level of the three-carbon bridge linking the A and B rings, the presence of a ring in this bridge, hydroxyl substitution at position 3, and the attachment site of the B ring (the chemical structure of flavonoids is shown in Figure 1) (Wang *et al.*, 2021).

Formononetin ($C_{16}H_{12}O_4$, FMN) is a flavonoid component within the isoflavone family, also known as 7-hydroxy-4′-methoxyisoflavone or biochanin B, with a molecular weight of 268 g·mol^{-1}. The hydroxy group is located on the A ring, while the methoxy group is located on the B ring. The discovery of FMN has a long history, first reported in 1855. However, FMN was not demonstrated to be extracted from red clover until 1975 and has since been utilized in research on cancer prevention, osteogenesis, wound healing, hypertension, neuroprotection, and diabetes from 2008 to 2018 (Dutra *et al.*, 2021). Meanwhile, FMN is abundant in nature and predominantly found in legume plants. It can be extracted from a diverse array of functional foods, including *Glycyrrhizae Radix Et Rhizoma* (Xie *et al.*, 2007), *Sophorae Flavescentis Radix* (Gu *et al.*, 2020), *Astragali Radix* (Chu *et al.*, 2022), *Dalbergia ecastophyllum* (de Mendonça *et al.*, 2015), and *Trifolium pratense* (Mu *et al.*, 2009) (Table 1). These sources reflect the wide distribution of FMN within the legume family.

From the perspective of food function, FMN's presence in leguminous plants enhances their nutritional profile and health-promoting attributes. The incorporation of these plants or their extracts into food products can potentially amplify FMN's various health benefits. Specifically, FMN exhibits antioxidant, anti-inflammatory, and estrogenic activities, all of which contribute to its diverse health functions. For instance, FMN undergoes metabolic transformation in living organisms, and its metabolic byproducts can influence the quantity and function of gut microbiota, thereby enhancing immune function (Danciu *et al.*, 2018).

Hence, FMN's diverse sources within leguminous plants and its multitude of health functions make it a valuable component in functional foods and nutritional supplements. Notably, when FMN is incubated with *Eubacterium limosum*, a common acetogenic bacterium in the human digestive system, it undergoes a time-dependent conversion to daidzein, which is further metabolized into equol, a potent estrogenic derivative (Hur & Rafii, 2000). Additionally, specific microbial strains, such as *Eggerthella* sp. Julong 732 and YY7918, exhibit selective conversion abilities, transforming daidzein or dihydrodaidzein into equol or S-equol, respectively (Kim *et al.*, 2009; Yokoyama & Suzuki, 2008). Equol has been shown to mitigate LPS-induced NET formation via PAD4 inhibition (Murakami *et al.*, 2024) and quell neuroinflammation through the TLR4/NF-κB pathway (Lu *et al.*, 2021). In addition to the downstream products of FMN producing biological activity, the glucoside form of FMN, ononin, can produce FMN, FMN glucuronide, and FMN sulfate, among other products, which work synergistically in intra-body metabolic conversion to exert effects. (Li *et al.*, 2020). These metabolic transformations mediated by intestinal microbiota convert FMN into bioactive compounds like daidzein and equol, underpinning its therapeutic potential and enhancing immune function to reverse inflammatory storms.

Various diseases, including digestive disorders, diabetes, and atherosclerosis, are linked to inflammation (Gasaly *et al.*, 2021; Hu *et al.*, 2021; Libby, 2021; Luc *et al.*, 2019). Inflammation is closely related to immunity and is a fundamental pathological process primarily characterized by the defensive response of living tissues with a vascular system to various damaging factors. Successful inflammatory responses typically eliminate the cause of inflammation (e.g., pathogens), which should, in principle, terminate the response. However, it is well known that eliminating the pathogen alone is not sufficient to control inflammation. In the absence of negative regulators (e.g., IL-10), the inflammatory response often becomes overwhelmingly excessive, to the point of being pathological. While acute inflammation responds to immediate threats like injury or infection, chronic inflammation—characterized by persistent immune cell infiltration and cytokine production—can lead to tissue damage, fibrosis, and granuloma formation, disrupting immune homeostasis (Furman *et al.*, 2019; Medzhitov, 2021; Schmid-Schönbein, 2006). Therefore, the inflammatory response requires timely management and control to alleviate its adverse effects on the body.

FMN has been successfully employed in inflammation models to elucidate its mechanisms. For example, in LPS-induced murine macrophages, FMN upregulated SIRT1 via PPAR-δ, while inhibiting NF-κB and cell apoptosis in IL-1β-treated cells (Hwang *et al.*, 2018). Furthermore, FMN exerts anti-inflammatory effects by modulating the MAPK, JNK, and NF-κB pathways, reducing inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ), and enhancing IL-10 levels (Luo *et al.*, 2019; Wang *et al.*, 2012). As mentioned above, it can be seen that FMN mediates pathways such as NF-κB, PPAR-δ, and MAPK, and regulates the levels of inflammatory cytokines to intervene in inflammation, indicating that FMN has a fundamental ability to combat inflammation. To further understand the anti-inflammatory mechanisms of FMN, we have summarized how FMN exerts its effects across various

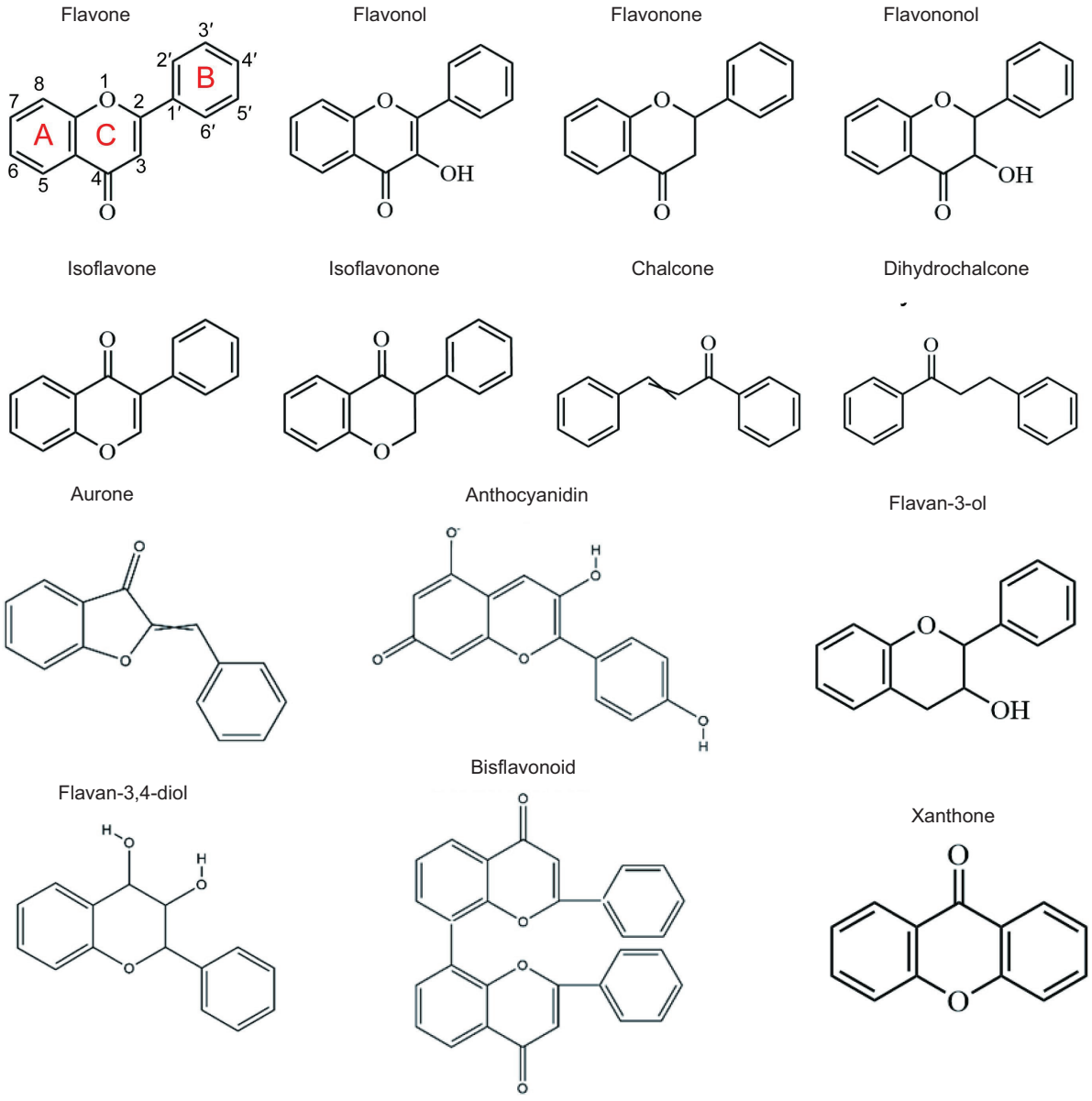


Figure 1. Chemical structure of flavonoids. (A & B) rings belong to Benzene; (C) ring is a three-carbon bridge. The other chemical structures of the flavonoids are transformed based on the skeleton structure of the flavone.

Table 1. Modern function of herbal plants related to Formononetin.

Latin name	Family	Function (modern)
Glycyrrhizae Radix Et Rhizoma	Fabaceae	Antitumor, Antimicrobial, Antiviral, and Anti-inflammation (Wahab *et al.*, 2021)
Astragali Radix	Fabaceae	Antimicrobial, Antiviral, Antifungal, and Antiparasitic (Salehi *et al.*, 2021)
Sophorae Flavescentis Radix	Fabaceae	Antitumor, Antivirus, Antioxidation, Analgesia, and Anti-inflammation (Chen *et al.*, 2017)
Dalbergia ecastophyllum	Fabaceae	Antioxidant, Antibacterial, Anti-inflammation, and Antitumor (Moise & Bobis, 2020)
Trifolium pratense	Fabaceae	Antioxidant, Antivirus, Anti-inflammation, and Antitumor (Antonescu *et al.*, 2021)
Radix Puerariae	Fabaceae	Antioxidant, Hepatoprotective, Antidiabetic, and Neuroprotective (Wang *et al.*, 2020)
Spatholobus Suberectus Dunn	Fabaceae	Antioxidation, Antitumor, Anti-diabetes, and Anti-inflammation (Huang *et al.*, 2023)
Hedysari Radix	Fabaceae	Antioxidation, Antiaging, Antitumor, and Anti-diabetes (Mo *et al.*, 2022)
Dalbergiae Odoriferae Lignum	Fabaceae	Antioxidation, Antibacterial, Antiosteosarcoma, and Anti-inflammation (The, 2017)

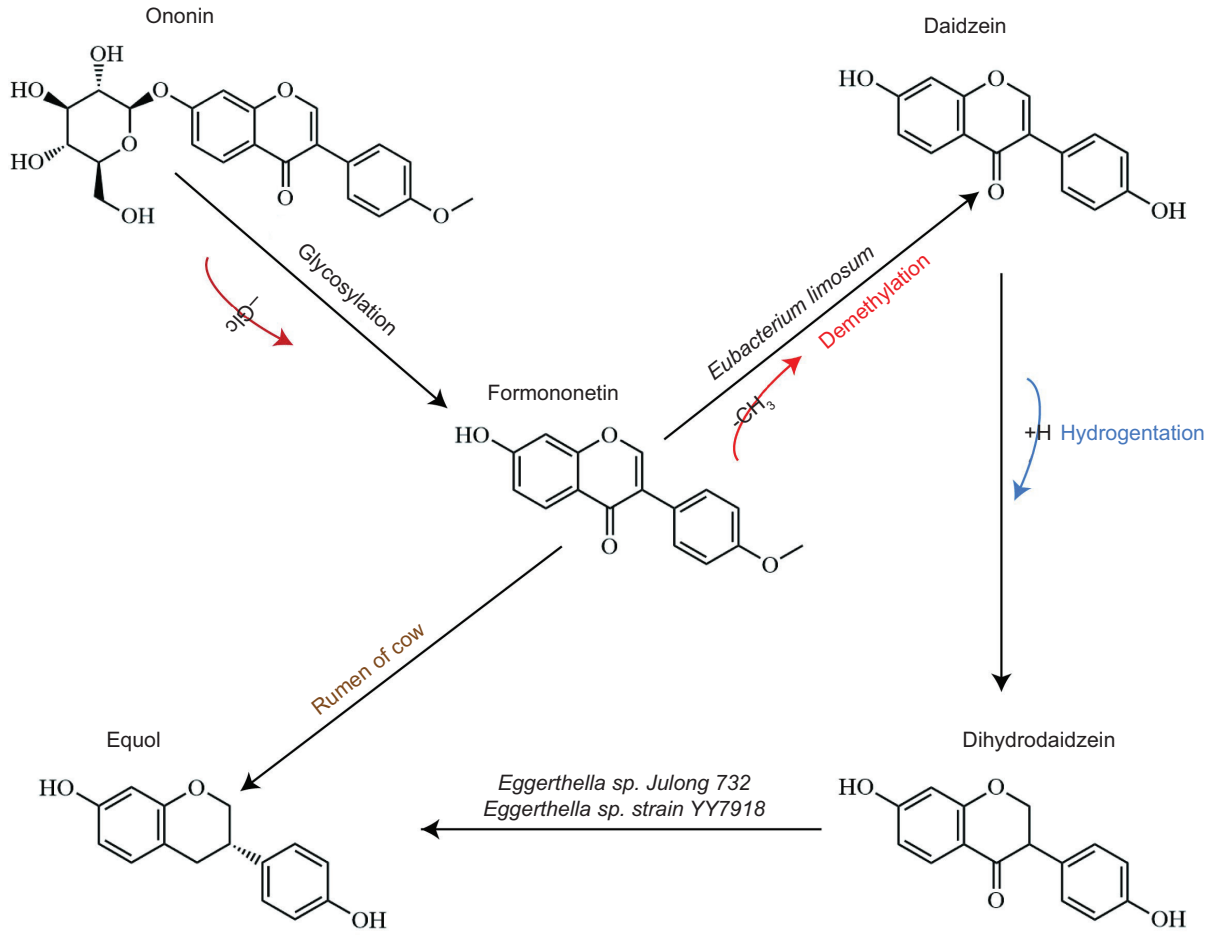


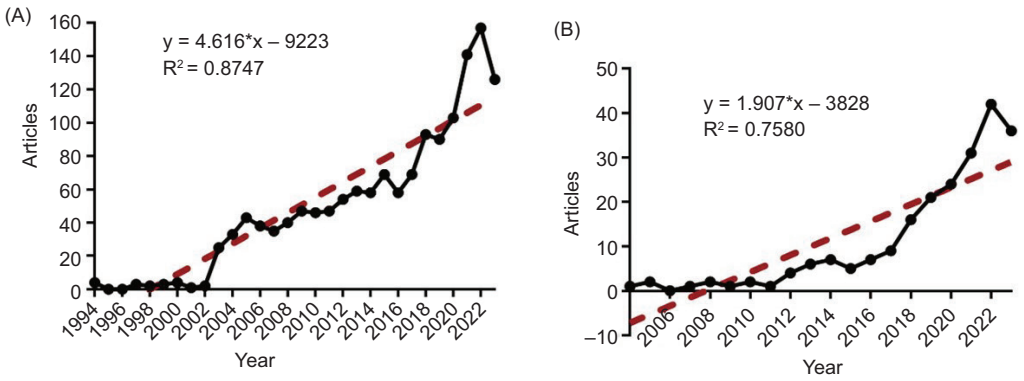
Figure 2. The metabolic conversion of Formononetin in vivo. "Glc" in the chemical structure indicates a glycoside. "CH3" in the chemical structure indicates a methyl. "H" in the names of chemical constituents indicates hydrogenation. Red line represents glycosylation and demethylation; blue line represents hydrogenation.

systems (skeletal, digestive, endocrine, immune, nervous, cardiovascular, and others) during inflammation. This is essential because inflammation can cause dysfunction in any system, impacting overall health. Therefore, exploring natural anti-inflammatory components in food and herbal plants with good safety profiles and fewer side effects is of utmost importance.

Anti-Inflammatory Research Hotspots of FMN

To understand the research hotspots on the anti-inflammatory effects of FMN over the past thirty years, we used Clarity Analytics' Web of Science Core Collection (WoSCC) as our primary data source to analyze the research trends of FMN. From 1994 to 2002, a nascent yet foundational phase emerged, marked by a handful of articles elucidating the physical and chemical properties of FMN, laying the groundwork for future advancements. Subsequently, between 2003 and 2016, a steady growth trajectory was observed, with an average of 46 articles per year published on FMN, signifying the second stage of its bioactivity evolution, such as its anti-cancer effects. Notably, since 2017, FMN research has surged into a third booming phase, totaling 1485 articles, accounting for an impressive 54.81% of all FMN-related publications to date. These studies have thoroughly examined the biological activities of FMN, including neuroprotection and anti-cardiovascular disease effects. Parallelly, research on FMN's role in inflammation began in 2004, initially progressing at a moderate pace but experiencing a pivotal shift after 2017, mirroring the accelerated pace of FMN research and reaching an 83.11% contribution rate. The fitting curve analysis underscores the escalating interest among researchers in both FMN and its inflammation-related facets in recent years (Figure 3A, B).

Utilizing Citespace's burst analysis, we delved into the keywords that underpin FMN research, revealing a preponderance of focus on its inherent characteristics. Our analysis uncovered keyword clusters centered on chemical components (genistein, daidzein, glycoside), sources



(C)

Top 25 keywords with the strongest citation burst

Keywords	Year	Strength	Begin	End	1994–2024
genistein	1998	12.2	1998	2010	
quantification	2006	4.68	2006	2017	
red clover	2003	14.98	2003	2012	
diadzein	1999	7.95	1999	2008	
estrogen	1999	7.68	1999	2008	
performance liquid chromatography	2005	6.92	2006	2015	
phytoestrogen	2002	14.16	2002	2010	
soy isoflavone	2003	8.34	2003	2011	
isoflavonoid	2002	6.2	2007	2015	
glycoside	2005	5.6	2005	2013	
inflammation	2013	4.74	2017	2024	
radix, astragali	2005	4.22	2010	2017	
flavonoid	2003	7.64	2007	2013	
trifolium pratense 1	2003	5.53	2003	2009	
metabolism	2005	9.73	2008	2013	

(D)

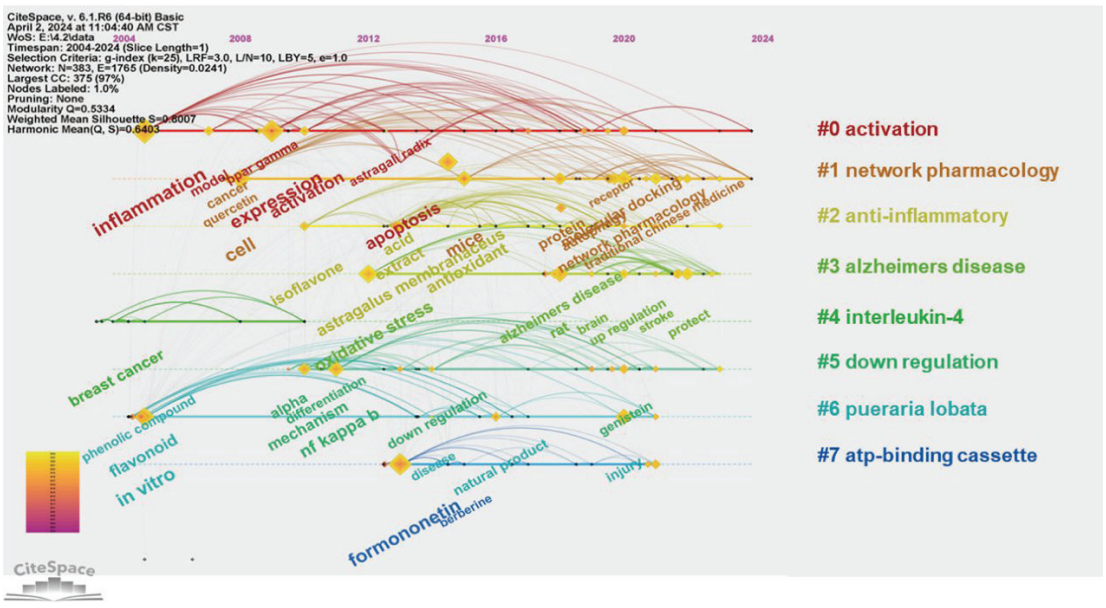


Figure 3. The main research trends of Formononetin at various stages. (A) Publication articles of FMN in WoSCC; (B) Publication articles of FMN on inflammation in WoSCC; (C) Keywords burst analysis of FMN. (D) Timeline cluster analysis of FMN.

(*Astragali Radix*, *Trifolium pratense*), chemical structures (isoflavonoid, soy isoflavone, flavonoid), and biological properties (estrogen, phytoestrogen). Inflammation emerged as a prominent theme, with its emergence and prevalence aligning neatly with our search findings (Figure 3C). These results highlighted the basic FMN properties and activity studies, suggesting that further analysis of its potential, unexplored pharmacological activities would be worthwhile.

To further illustrate the multifaceted nature of FMN research, we constructed a timeline cluster, showcasing its primary concentration areas. The analysis of the various clusters reveals intriguing insights into the diverse research trends surrounding FMN. First, early investigations from 2004 focused on the role of IL-4 in breast cancer research, likely due to its estrogenic properties, highlighting the broader biological implications of FMN beyond inflammation (Cluster #4, Figure 3D). Next, many studies emphasized the phenolic compounds and flavonoids found in *Pueraria lobata*, a leguminous plant, underscoring the natural product chemistry underpinning FMN's bioactivity and its potential applications in addressing injuries, showcasing the enduring interest in the plant's constituents (Cluster #6, Figure 3D). Subsequently, research between 2008 and 2012 centered prominently on inflammation, PPAR-γ activation, and the potential of *Astragali Radix*. This cluster marked early explorations into the anti-inflammatory mechanisms mediated by FMN, setting the stage for further investigations (Cluster #0, Figure 3D). During the mid-2010s, two parallel trends emerged. One trend focused on downregulating inflammatory pathways involving NF-κB, differentiation, and the effects of genistein, demonstrating FMN's ability to modulate inflammation (Cluster #5, Figure 3D). Meanwhile, other studies emphasized the anti-inflammatory and antioxidant properties of isoflavones and extracts from *Astragalus membranaceus*, reinforcing the link between flavonoid components and anti-inflammatory effects (Cluster #2, Figure 3D). Within this same timeframe, another cluster specifically targeted FMN and berberine in the context of ATP-binding cassette transporters, highlighting the specificity of FMN's interactions with cellular transport mechanisms (Cluster #7, Figure 3D). Recent years have witnessed a shift towards advanced methodologies in understanding the complex interactions of FMN. Cluster #1 underscores the emergence of network pharmacology, receptor studies, molecular docking, and the integration of traditional Chinese medicine (TCM), reflecting contemporary research trends. Simultaneously, Cluster #3 highlights FMN's neuroprotective effects, particularly in neurodegenerative disorders such as Alzheimer's disease and stroke, which are accompanied by inflammatory responses (Cluster #1 and 3, Figure 3D).

Collectively, these clusters underscore the intricate connections between FMN and inflammatory processes, involving PPAR-γ, apoptosis, autophagy, oxidative stress, and NF-κB. This comprehensive body of research solidifies FMN's potential as a promising anti-inflammatory candidate, warranting further investigation into its therapeutic potential. Furthermore, as network pharmacology continues to flourish, the integration of molecular docking techniques offers a promising avenue to unravel the intricate mechanisms of TCM in addressing diverse pathologies, presenting a valuable alternative approach.

Anti-Inflammatory Effects of FMN

Based on the findings discussed in the previous section, we assert that elucidating the anti-inflammatory actions and mechanisms of FMN across various systemic disorders would significantly enhance our understanding of this compound's biological activities. The main biological activities of FMN in systemic disorders are analyzed, with further details listed in Table 2.

Anti-inflammatory effect of FMN in the skeletal system disorders

Osteoarthritis (OA), a complex and multifaceted disorder, is characterized by the deterioration of articular cartilage and the subsequent thickening of the subchondral plate, significantly impeding patients' daily activities (Sharma, 2021). Research (Huh *et al.*, 2010) demonstrated that FMN exhibited biphasic and beneficial effects by modulating biological synthesis pathways. A human normal osteoblast and osteoarthritis subchondral osteoblast cell model treated with various concentrations of FMN (1 and 10 $\mu g \cdot mL^{-1}$) resulted in a reduction in IL-6, VEGF, BMP-2, OCN, and Col I levels compared to OA-affected samples, while reversing these trends towards normalcy in healthy controls. VEGF, BMP-2, OCN, and Col I are genes associated with the pathological process of OA. For instance, VEGF is involved in intra-articular inflammation and cartilage destruction processes by promoting neovascularization and increasing vascular permeability (Wang *et al.*, 2020). While BMP-2 has a dual role: it promotes cartilage repair by increasing chondrocyte Col II expression and stimulating chondrocyte proliferation, while also exacerbating cartilage destruction by inducing chondrocyte apoptosis (Whitty *et al.*, 2022). Col I, like Col II, provides strength and structural support, essential for maintaining the strength and stability of bones and tendons, whereas Col II mainly provides elasticity, reducing the impact on the joint and protecting it from damage (Mazor *et al.*, 2022; Orhan *et al.*, 2021). Additionally, OCN decarboxylation changes to ucOCN, which can inhibit chondrocyte hypertrophic degeneration and delay

Table 2. Biological effects of Formononetin.

Related systems	Type of diseases	Involved mechanism	Reference
Skeletal System	Osteoarthritis	Decreasing ALP, IL-6, VEGF, BMP-2, OCN, and Col I level.	(Huh *et al.*, 2010)
	Osteoarthritis	Reducing IL-1β, MMP-3, and MMP-13 levels, increasing Col2al levels.	(Xiong *et al.*, 2021)
	Knee injury	Suppressing NK-κB and blocking phosphorylation of the ERK and JNK proteins in the MAPK signaling pathway.	(Ni *et al.*, 2023)
	Multiple myeloma	Inhibiting phosphorylation of AKT to constrain the expression of HIF-1α and reduce cytokines TNF-α, IL-6, and IL-8 production.	(Wu *et al.*, 2016)
Digestive System	Gastric ulcer	Downregulating TNF-α, IL-1β, IL-6, ET-1, MPO, and p-P65 levels, upregulating VEGF, NO, CD34, p-IκBα, ZO-1, and occludin contents in a dose- dependent manner.	(Yi *et al.*, 2022)
	Acute colitis	Improving intestinal issue morphology, boosting tight junction proteins recovery, falling down apoptosis-related genes expressions (NLRP3, ASC, and IL-1β).	(Wu *et al.*, 2018)
	Colon cancer	Slicing PI3K/AKT and STAT3 signaling pathways to suppress cyclin and MMP expression.	(Wang *et al.*, 2018)
	Acute pancreatitis	Activating the Keap/Nrf2 signaling pathway to reduce ROS levels, inhibiting the NLRP3 inflammasome activation, and reversing injury tight junction proteins.	(Yang *et al.*, 2023)
	Hepatotoxicity	Attenuating the RIT-induced Bax, caspase-3, NF-κB, and eNOS activation and persuading the Bcl2 and pAkt levels in hepatic tissue.	(Alauddin *et al.*, 2018)
	Hepatic cholestasis	Upregulating expression of SIRT1 and activating PPARα, maintaining the hepatic bile acid metabolism in an FXR-SIRT1-dependent manner	(Yang *et al.*, 2019)
Endocrine System	Obesity	Changing body weight, hyperglycemia, insulin resistance, and leptin levels and improving the HDL-to-LDL ratio.	(Naudhani *et al.*, 2021)
	Type 2 diabetes mellitus	Blocking the phosphorylation of JNK 2 and STAT3, reversing the increasing expressions of p-JAK2, p-STAT3, IL-1β, ICAM-1, and NO.	(Zhou *et al.*, 2019)
	Diabetic nephropathy	Improving antioxidant enzymes levels (SOD, GSH, and CAT) to protect against lipid peroxidation, downregulating pro-inflammatory cytokines TNF-α, and IL-6 contents.	(Jain *et al.*, 2020)
	Diabetic cardiomyopathy	Alleviating oxidative stress, increasing SIRT1 expression, and reducing glucose, triglycerides, low density lipoprotein, lactate dehydrogenase, cholesterol, aspartate aminotransferase, and creatine kinase MB levels.	(Oza & Kulkarni, 2020)
	Diabetic neuropathy	Controlling and improving hyperglycemia, and insulin resistance, increasing SIRT1 and NGF expression in nerve tissue.	(Oza & Kulkarni, 2020)
Nervous System	Neuroinflammation	Preventing activated microglia-produced neurotoxicity through ERβ pathway.	(El-Bakoush & Olajide, 2018)
	Depression	Improving the depression-model behavior parameters, fluorescence intensity of Iba-1 in hippocampus, and reducing the levels of IL-6, IL-1β, and TNF-α.	(Li *et al.*, 2023)
	Spinal cord injury	Preventing microglial inflammatory response, promoting SCI repair via the EGFR/p38 MAPK signaling pathway.	(Fu *et al.*, 2023)
	Spinal cord injury	Corporation within multi-walled carbon nanotubes exhibited excellent photopolymerized characteristic to image SCI site.	(de Vasconcelos *et al.*, 2020)
Cardiovascular System	Endothelial injury	Enhancing PPAR-γ activity to protect against oxidative stress (ROS, MDA, and SOD), apoptosis, and inflammatory response (TNF-α, IL-1β, and COX2).	(Zhang *et al.*, 2021)
	Atherosclerosis	Regulating KLF4 and SRA to promote ApoE-deficient mice atherosclerosis dysfunction recovery.	(Ma *et al.*, 2020)
	Thrombosis	Considering as a NOS agonist to against increasing IL-1β, IL-18, NF-κB levels, and average weights of thrombosis. Boosting p-eNOS and promoting the morphology of injury lesions recovery.	(Zhou *et al.*, 2022)
	Endothelial function	Involved in promoting growth, proliferation, migration, and tube formation in association with the activation of eNOS and he promotion of intracellular nitric oxide production through AKT and Erk1/2 signaling pathway.	(Wu *et al.*, 2020)

(*continues*)

Table 2. Continued.

Related systems	Type of diseases	Involved mechanism	Reference
	Angiogenesis	Reversing deficiency of intersegmental vessels in a concentration-dependent manner, enriching the decreasing levels of kdr, flt1, and kdrl which involved in VEGF/PI3K/Akt/MAPK signaling pathways.	(Zhou *et al.*, 2019)
	Angiogenesis	Recovering subintestinal vessels sproutings via ERα and ROCK interactions.	(Li *et al.*, 2015)
	Myocardial ischemia/ reperfusion injury	Suppressing the ROS-TXNIP-NLRP3 pathway to constrain pro-inflammatory cytokines TNF-α, IL-6, and IL-1β overexpression.	(Wang *et al.*, 2020)
	Cerebral ischemia/ reperfusion injury	Constraining activation of JAK2/STAT3 pathway to inhibit related apoptosis pathway (NLRP3, cl-IL-1β, cl-Caspase-1, and ASC) and cytokines production (IL-18, TNF-α, IL-6 and IL-1β).	(Yu *et al.*, 2022)
	Cerebral ischemia/ reperfusion injury	Diminishing NO and MDA contents, increasing SOD levels, and enhancing energy metabolism via Na^+-K^+-ATPase, Ca^{2+}-Mg^{2+}-ATPase, and Ca^{2+}-ATPase activities.	(Wang *et al.*, 2022)
	Myocardial infarction	Targeting GSK-3β to regulate macrophage/microglial polarization, and blocking IL-6 and IL-17A overexpression caused neuroinflammation.	(Yang *et al.*, 2023)
Immune System	Allergic diseases	Decreasing TSLP/IL-33 production via regulation of E-cadherin.	(Li *et al.*, 2018)
	Allergic inflammation	Reducing TSLP production via regulating NF-kB activation to attenuate allergic inflammation	(Shen *et al.*, 2014)
	Allergic diseases	Alleviate pseudoallergic responses via the inhibition of IgE-independent MC degranulation and NF-κB signaling.	(Zhou *et al.*, 2023)
	Allergic inflammation	Suppressing IgE-induced NF-κB and MAPK activity, reducing the FcεRIγ chain expression via increased proteasome-mediated degradation, and induced FcεRIγ ubiquitination by inhibiting USP5 and/ or USP13.	(Zhou *et al.*, 2023)
	Allergic asthma	Elevating HO-1 levels to constrain ROS expression and boosting SOD content, dramatically inhibiting the activation of NF-kB and JNK, and restraining the overexpression of cytokines (IL-4, IL-5, IL-13, and IL-17A) and chemokines (CCL5 and CCL11).	(Yi *et al.*, 2020)
Other Systems	Acute kidney injury	Activating PPARα/Nrf2/HO-1/NQO1 pathway to reduce the levels of blood urea, nitrogen, creatinine, TNF-α, IL-1β, MDA, and MPO activity.	(Hao *et al.*, 2021)
	Acute lung injury	Attenuating inflammatory cell numbers, increasing PPAR-γ gene expression and improving SOD activity and inhibiting MPO activity.	(Ma *et al.*, 2013)
	Acute lung injury	Reversing the reduction of M2 macrophage polarization, increasing HO-1 expression via Nrf2.	(Chen *et al.*, 2021)
	Pulmonary arterial hypertension	Suppressing pulmonary vascular remodeling, and activation of ERK and NF-κB signaling pathway.	(Wu *et al.*, 2020)

OA progression (Zappia *et al.*, 2023). Beyond in vitro studies, in vivo research has also investigated the anti-OA mechanism of FMN. Oral administration of FMN at a dosage of 10 $mg{\cdot}kg^{-1}$ has been shown to effectively mitigate the impact of partially removed medial meniscus in rats, leading to OA-related pathological manifestations. Notably, it reduces cartilage matrix degradation, overall articular cartilage wear, and the levels of the proinflammatory cytokine IL-1β within chondrocytes (Barreto *et al.*, 2022).

In a surgical model of OA established through anterior cruciate ligament transection, the injection of 1.25 $\mu g{\cdot}mL^{-1}$ FMN-poly(ethylene glycol) for 4 or 8 weeks was shown to downregulate the expression of inflammatory cytokines such as IL-1β, MMP-3, and MMP-13, while simultaneously upregulating Col2a1. Notably, both MMP-13 and MMP-3 contribute to the degradation of various cartilage extracellular matrix components during OA progression, with MMP-13 exhibiting a specific preference for Col II (Xiong *et al.*, 2021), consistent with findings from earlier studies (Huh *et al.*, 2010).

Knee injury, similar to OA, falls under the category of skeletal system disorders. To further explore FMN's anti-inflammatory mechanisms, research (Ni *et al.*, 2023) has demonstrated that FMN exerts protective effects against knee injuries in a dose-responsive manner. In an IL-1β-stimulated primary chondrocyte cell model, FMN at concentrations of 5, 10, 20, and 40 μM was found

to suppress the NF-κB signaling pathway and modulate the MAPK cascade. This modulation specifically involved inhibiting the phosphorylation of extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinases (JNK) proteins, effectively dampening the inflammatory cascade.

The MAPK family, a critical signaling pathway, translates extracellular cues such as stress signals and growth factors into intracellular responses. Comprising at least four subfamilies (ERKs, JNKs, p38 isoforms, and ERK5), MAPKs are regulated by upstream kinases and phosphatases, which modulate their phosphorylation status. Activated MAPKs phosphorylate specific serine and threonine residues on target proteins, triggering a range of cellular responses, including proliferation, differentiation, and apoptosis (Yue & López, 2020). Importantly, MAPKs can indirectly regulate NF-κB activity by phosphorylating the IκB kinase (IKK) in the NF-κB pathway, while NF-κB can influence MAPK activity by regulating the transcription of certain genes within the MAPK pathway (Kramer & Goodyear, 2007). Meanwhile, the NF-κB family of transcription factors, which includes p50, p52, p65, RelB, and c-Rel, governs the expression of numerous genes central to immune and inflammatory processes. These proteins are typically sequestered in the cytoplasm by inhibitory proteins like IκB but are released upon stimulation, forming dimers that translocate to the nucleus to regulate gene transcription by binding to κB enhancer elements (Yu *et al.*, 2020).

Multiple myeloma, a highly aggressive malignancy and a leading cause of global mortality, highlights the intricate link between inflammation and cancer progression (Rajkumar, 2011). In a xenograft model induced by subcutaneous injection of 1×10^7 U266 cells in mice, intragastric administration of FMN (20 and 50 mg·kg^{-1}) for 25 days was shown to hinder tumor growth by decreasing AKT phosphorylation. Additionally, FMN restricted the expression of HIF-1α, a key regulator of tumor metabolism and angiogenesis, and curtailed the production of inflammatory cytokines such as TNF-α, IL-6, and IL-8. This multi-faceted approach effectively targets the inflammatory milieu that fosters myeloma development (Wu *et al.*, 2016). (The potential mechanism of action of FMN in relieving skeletal system diseases is shown in Figure 4).

Anti-inflammatory effect of FMN in the digestive system disorders

The gastrointestinal tract serves as a pivotal hub in the intricate processes of food and medicine absorption,

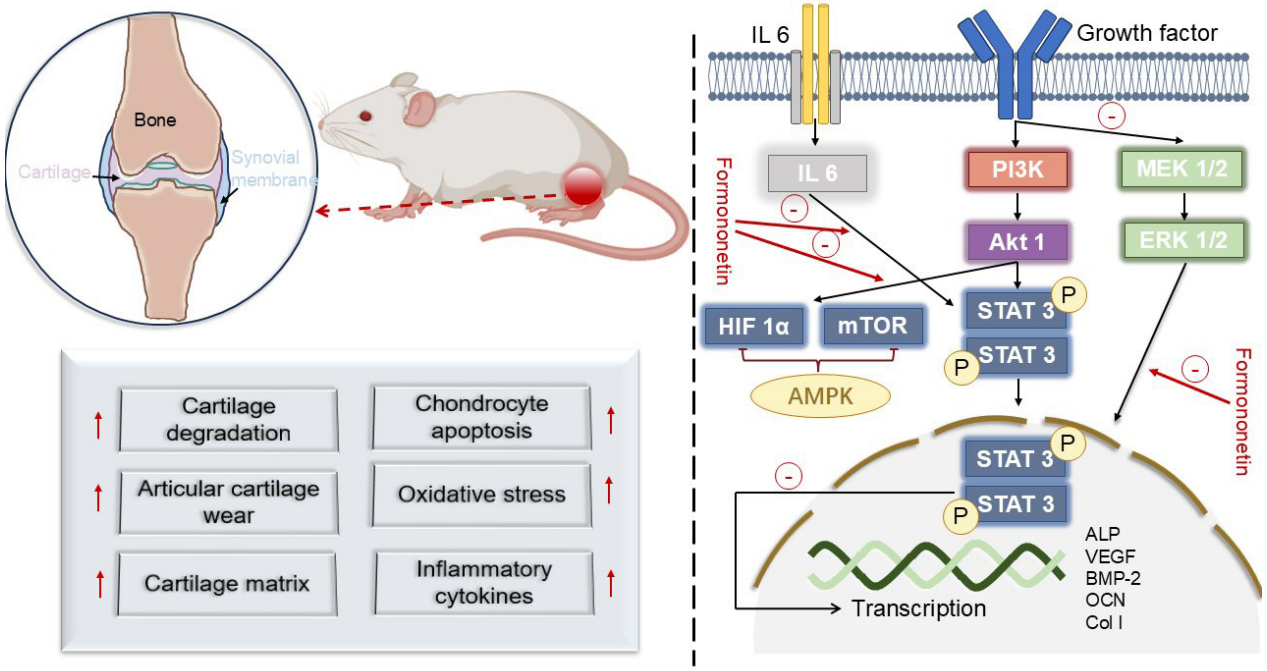


Figure 4. Potential mechanism of action of FMN in relieving skeletal system diseases. IL-6: Interleukin-6; PI3K: Phosphoinositide 3-kinase; Akt: Serine/threonine-protein kinase Akt; MEK: MAP kinase kinase; ERK: Extracellular regulated protein kinases; STAT: Signal transducer and activator of transcription; mTOR: Mammalian target of rapamycin; HIF-1α: Hypoxia inducible factor-1α; ALP: Alkaline phosphatase; VEGF: Vascular endothelial growth factor; BMP-2: Bone morphogenic protein-2; OCN: Osteocalcin; Col I: Type I collagen. Red circle within minus represents inhibition.

distribution, metabolism, and excretion, ultimately shaping the health-promoting or mitigating effects of their bioactive components (Ruan *et al.*, 2020). Notably, the intestinal barrier stands as a vital sentinel, safeguarding the body's well-being through multifaceted functions. It not only facilitates nutrient absorption but also forms a formidable line of defense against the infiltration of bacteria, their toxins, and metabolic byproducts, as well as harmful substances present in ingested foods (Chang, 2020). Furthermore, the intestinal barrier contributes to maintaining immunological balance within the gastrointestinal tract and plays a pivotal role in regulating crucial aspects of energy metabolism and expenditure (Oteiza *et al.*, 2018).

Intragastric administration of FMN over a 14-day period, at concentrations of 25, 50, and 100 mg·kg^{-1}, was shown to effectively ameliorate gastric mucosal pathology in a rat model of gastric ulcer induced by 100% glacial acetic acid. The treatment exhibited a dose-dependent reduction in pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as ET-1, MPO, and p-P65 levels. Simultaneously, FMN upregulated VEGF, NO, CD34, p-IκBα, and critical tight junction proteins like ZO-1 and Occludin. CD34, VEGF, ET-1, and NO are closely associated with angiogenesis (Yi *et al.*, 2022). CD34, a highly glycosylated type I transmembrane glycoprotein, serves as a marker for vascular endothelial cells (Hassanpour *et al.*, 2023). ET-1, a potent vasoconstrictor, and NO, an endothelial relaxing factor, play crucial roles in maintaining vascular permeability and improving gastrointestinal tract function under ischemic and hypoxic conditions (Brewster *et al.*, 2020; Cyr *et al.*, 2020). Meanwhile, p-P65 and p-IκBα reflect the activation state of the NF-κB signaling pathway. MPO, which originates from neutrophils, macrophages, monocytes, and microglia, plays a role in killing microorganisms and is primarily involved in the body's inflammatory response (Lin *et al.*, 2024). Furthermore, ZO-1 is connected with the myosin light chain to form a precise intestinal barrier structure, while Occludin closes the pore between intestinal cells through tight junctions, lower wall junctions, and desmosomes, thus maintaining the integrity of the intestinal barrier. ZO-1 and Occludin not only serve as the main mode of connection between intestinal epithelial cells but also participate in the regulation of intestinal immune and inflammatory responses (Kuo *et al.*, 2022). The above-mentioned genes involved in angiogenesis, the NF-κB signaling pathway, and tight junction proteins reinforce the gastrointestinal tract barrier's integrity.

IBD has been increasingly linked to the NLRP3 inflammasome (Zhen & Zhang, 2019). Upon activation by pathogenic signals, NLRP3 undergoes deubiquitination, binds to the adaptor protein ASC, and activates caspase-1. This process leads to the maturation of IL-1β and IL-18 and triggers pyroptosis via GSDMD (Song *et al.*, 2021). NLRP3 plays a critical role in maintaining intestinal stability by responding to microbial and danger signals, and its dysfunction can increase susceptibility to IBD (Chen *et al.*, 2021). In a study using a 2.5% DSS-induced IBD model, intraperitoneal administration of FMN at concentrations of 25, 50, and 100 mg·kg^{-1} over 9 days significantly alleviated pathological symptoms. FMN inhibited NLRP3 inflammasome activation, reduced levels of NLRP3, ASC, and IL-1β, and demonstrated potential in managing acute colitis (Wu *et al.*, 2018).

Intestinal homeostasis is also crucial in the treatment of acute pancreatitis. In a caerulein-induced acute pancreatitis mouse model, intragastric administration of FMN (25, 50, and 100 mg·kg^{-1}) for 7 days activated the Keap1/Nrf2 signaling pathway. This activation reduced ROS levels, inhibited NLRP3 inflammasome activation, and reversed damage to tight junction proteins, further highlighting FMN's role in maintaining gastrointestinal health and protecting against inflammatory insults (Yang *et al.*, 2023).

Keap1 is the primary negative regulator of Nrf2. Under normal physiological conditions, Keap1 binds to Nrf2, mediating its ubiquitination and degradation, which results in low intracellular levels of Nrf2. However, when cells are exposed to oxidative stress, Keap1 undergoes a conformational change, causing it to dissociate from Nrf2. This dissociation allows Nrf2 to become activated and translocate to the nucleus. Inside the nucleus, Nrf2 forms heterodimers with small Maf proteins, which then bind to antioxidant response elements (AREs), initiating the transcription of downstream antioxidant enzymes. This process enhances the cell's ability to combat oxidative stress (Yu & Xiao, 2021). Therefore, FMN not only modulates the NLRP3 signaling pathway to prevent further inflammatory responses in the gastrointestinal tract but also activates the Keap1/Nrf2 pathway to maintain redox balance and protect against the excessive accumulation of ROS.

Diving deeper into its mechanisms, FMN modulates key signaling pathways that govern cellular behavior. The phosphoinositide 3-kinases (PI3Ks), which belong to the lipid kinase superfamily, play a pivotal role in regulating cellular processes. A key aspect of PI3K regulation involves negative modulators such as PTEN, a lipid phosphatase that converts PIP3 to PIP2, effectively dampening the activation of downstream effectors like AKT and maintaining cellular homeostasis (Acosta-Martinez & Cabail, 2022). The PI3K/AKT axis is closely linked to vital physiological processes, including cell survival, metabolic regulation, and growth. This pathway is activated or inhibited through the binding of PI3K to EGFR and subsequent phosphorylation events. Similarly, the

JNK/STAT3 axis, which is activated by IL-6 engagement with its receptors, regulates gene transcription via phosphorylation and nuclear translocation of STAT3. Intriguingly, studies in zebrafish larvae have underscored the importance of Class III PI3K in gut morphogenesis and maintenance. Defects in this pathway lead to a pathological condition resembling inflammatory bowel disease, further highlighting the complex interplay between PI3K/AKT signaling and autophagy (Zhao *et al.*, 2018).

In colon carcinoma cell lines SW1116 and HCT116, 100 μM FMN inhibited both PI3K/AKT and STAT3 signaling pathways, resulting in reduced cancer cell growth, invasion, and the expression of cyclins and matrix metalloproteinases (MMPs) (Wang *et al.*, 2018). Furthermore, FMN has demonstrated broad-spectrum cytoprotective effects in hepatic tissue. A 14-day treatment with 100 $mg{\cdot}kg^{-1}$ FMN mitigated ritonavir-induced hepatotoxicity by modulating cell death pathways (Bax, caspase-3, NF-κB, and eNOS) and promoting survival signals (Bcl2, pAkt) (Alauddin *et al.*, 2018). Additionally, FMN (10, 20, and 50 $mg{\cdot}kg^{-1}$) alleviated α-naphthylisothiocyanate-induced hepatic cholestasis by upregulating SIRT1 and activating PPAR-α, thereby maintaining bile acid homeostasis in an FXR-SIRT1-dependent manner (Yang *et al.*, 2019). These findings underscore FMN's potential as an anti-cholestatic agent and highlight its role in hepatic protection.

In summary, FMN exhibits significant anti-inflammatory effects in digestive diseases by modulating key signaling pathways. It enhances gastric mucosal health, inhibits its NLRP3 inflammasome activation (crucial in IBD), reduces ROS levels, and reverses tight junction damage in pancreatitis. Additionally, FMN attenuates colon cancer cell growth by modulating the PI3K/AKT and STAT3 pathways, and regulates FXR-SIRT1 to maintain hepatic bile acid homeostasis. These actions collectively highlight FMN's complex role in supporting digestive health. (The potential mechanisms of FMN in alleviating digestive system disorders are shown in Figure 5).

Anti-inflammatory effect of FMN in endocrine system disorders

Excessive accumulation of body fat can lead to obesity, which has numerous adverse effects on health. Obese individuals often experience chronic inflammation, which in turn heightens the body's stress response and triggers a cascade of metabolic diseases. This chronic inflammatory state is closely linked to the development of various metabolic disorders, including cardiovascular diseases and diabetes (Smith *et al.*, 2020).

A Western-style diet, administered for two months, was used to induce obesity in mice. Researchers found

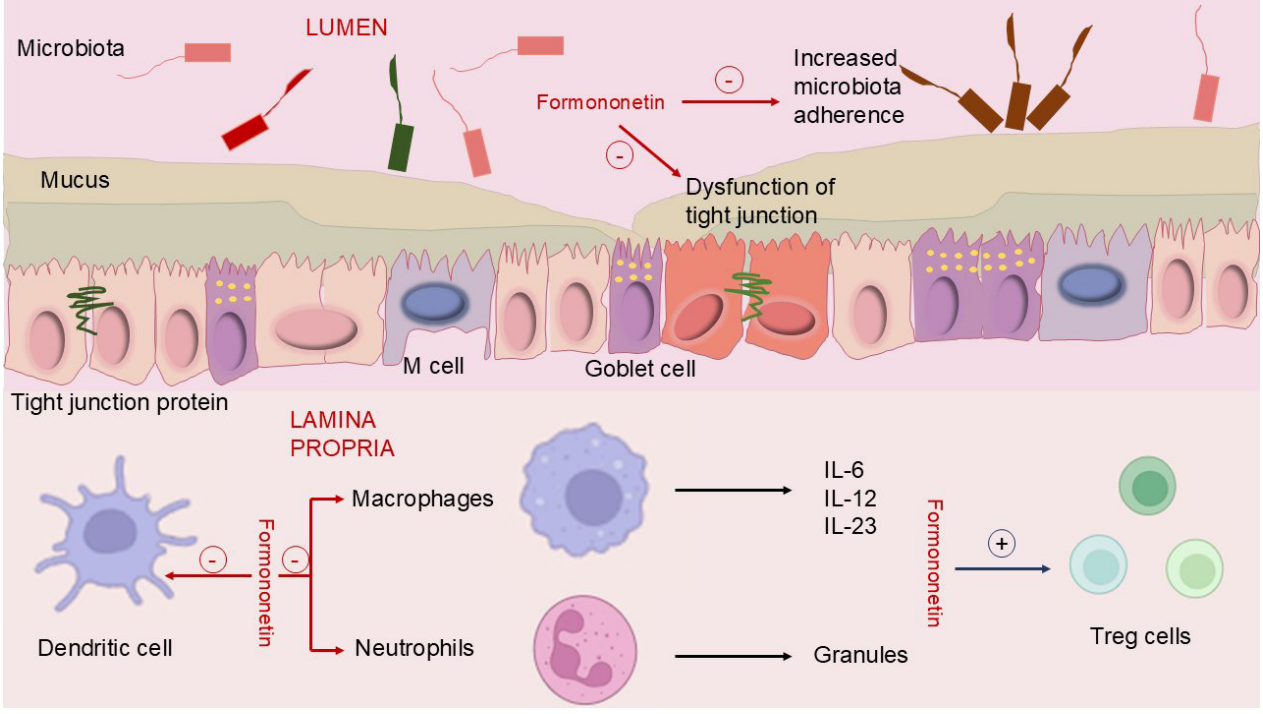


Figure 5. Potential mechanism of action of FMN in relieving digestive system diseases. IL-6: Interleukin-6; IL-12: Interleukin-12; IL-23: Interleukin-23; Red circle within minus represents inhibition; Blue circle within plus represents facilitation.

that intragastric administration of FMN at doses ranging from 20 to 100 mg/kg effectively modulated body weight, hyperglycemia, insulin resistance, and leptin levels. Furthermore, FMN favorably altered the ratio of HDL to LDL cholesterol (Naudhani *et al.*, 2021). LDL is primarily responsible for transporting cholesterol from the liver to peripheral tissues, while HDL facilitates the reverse transport of cholesterol from peripheral tissues back to the liver for metabolism and excretion (Stadler *et al.*, 2021). Therefore, the shift from LDL to HDL helps maintain cholesterol homeostasis in the body, improving cholesterol metabolism in obesity, aiding in weight loss, and promoting a healthier metabolic state.

Diabetes mellitus, characterized by weight loss despite increased appetite, thirst, and urination, poses a significant health threat due to its chronic inflammatory nature and the severe complications that arise (Cole & Florez, 2020). These complications include vascular damage, dyslipidemia, and a range of conditions such as diabetic nephropathy, diabetic foot, neuropathy, cardiomyopathy, and retinopathy (Ciarambino *et al.*, 2022). The JAK/STAT signaling cascade is a complex network involving tyrosine kinase-related receptors, JAKs, and STATs. These receptors, capable of recognizing over 50 cytokines, act as conduits for transmitting extracellular signals. Upon cytokine binding, JAKs undergo autophosphorylation or transphosphorylation, which then phosphorylates the receptors. This phosphorylation creates docking sites for STATs, which, upon phosphorylation, form dimers and translocate to the nucleus to regulate gene transcription by directly binding to DNA. This pathway governs a broad spectrum of biological responses, particularly in immune regulation (Hu *et al.*, 2021). Studies have shown that FMN, acting as a JNK2 inhibitor, can attenuate the phosphorylation of JNK2 and STAT3. Similar to tyrphostin AG 490, FMN reverses the elevated expression of p-JAK2, p-STAT3, IL-1β, ICAM-1, and NO in HUVECs exposed to high glucose conditions, thereby mitigating the vascular complications commonly observed in diabetes (Zhou *et al.*, 2019).

Furthermore, research has shown that intraperitoneal injection of 55 mg/kg streptozotocin (STZ) induces a diabetic nephropathy rat model. Subsequent intragastric administration of FMN at doses of 10, 20, and 40 mg/kg for 14 days demonstrated remarkable efficacy in enhancing antioxidant enzyme activity, including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). This intervention protected against lipid peroxidation and downregulated inflammatory markers such as TNF-α and IL-6. SOD, CAT, and GSH together form a powerful antioxidant system that neutralizes reactive oxygen species (ROS), thereby protecting cells from oxidative damage (Gui *et al.*, 2022). SOD catalyzes the conversion of superoxide anions into hydrogen peroxide and oxygen, while CAT and GSH catalyze the decomposition and reduction of hydrogen peroxide, respectively, further mitigating its reactivity and maintaining cellular health (Yang *et al.*, 2020).

Moreover, SIRT1, the mammalian counterpart of SIR2, functions as an NAD^+-dependent histone deacetylase, with its activity closely linked to lifespan extension under calorie restriction. SIRT1 plays a crucial role in regulating glucose-dependent insulin secretion from pancreatic β-cells and directly activates insulin signaling pathways in insulin-responsive tissues. This multifaceted regulation includes the modulation of adiponectin secretion, inflammatory responses, gluconeogenesis, and ROS levels, all of which contribute to the development of insulin resistance (Liang *et al.*, 2009).

Notably, intraperitoneal injection of 35 mg/kg STZ induces a type 2 diabetes rat model. Subsequent intragastric administration of FMN at doses of 10, 20, and 40 mg/kg for 16 weeks significantly mitigates oxidative stress, enhances SIRT1 expression, and reduces levels of glucose, triglycerides, cholesterol, LDL, creatine kinase MB, lactate dehydrogenase, and aspartate aminotransferase in STZ-induced diabetic cardiomyopathy (Oza & Kulkarni, 2020). Beyond its cardiovascular benefits, FMN also protects against diabetic neuronal damage by managing hyperglycemia, increasing SIRT1 and NGF expression in nerve tissue, and improving hypoglycemia and insulin resistance (Oza & Kulkarni, 2020).

Thus, FMN emerges as a promising therapeutic agent for the comprehensive management of metabolic diseases (such as obesity and diabetes mellitus) by influencing lipid metabolism, SIRT1, the JAK/STAT signaling pathway, and oxidative stress levels, thereby preventing endocrine system disorders and mitigating inflammatory responses. (The potential mechanism of action of FMN in relieving endocrine system disorders is shown in Figure 6).

Anti-inflammatory effect of FMN in the nervous system disorders

The intricate network formed by the peripheral and central nervous systems, in connection with other bodily systems, creates a unique platform for regulating and coordinating various physiological functions. At the core of this network lies the central nervous system, which exerts a profound influence on maintaining homeostasis, preserving structural integrity, and balancing internal processes with external environmental stimuli (Macpherson *et al.*, 2023). This complex orchestration facilitates advanced cognitive and behavioral abilities, including language, thought, learning, and memory

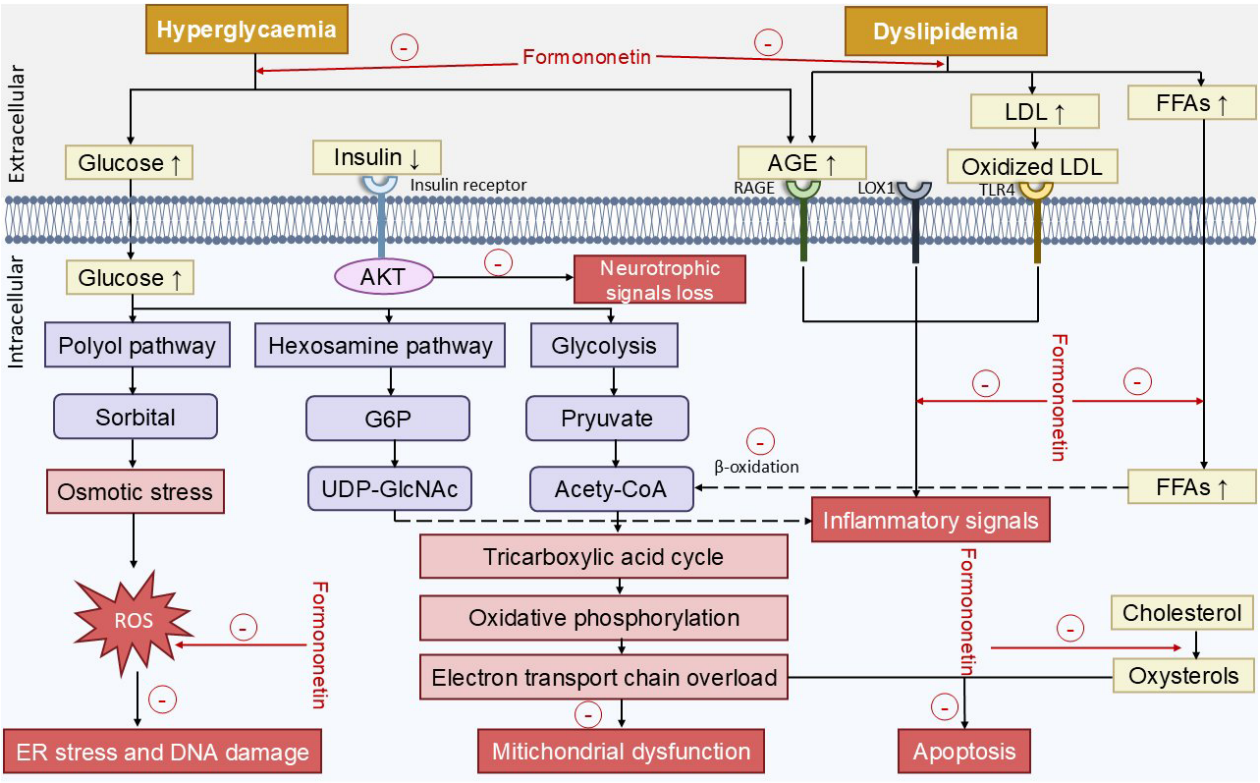


Figure 6. Potential mechanism of action of FMN in relieving the endocrine system diseases. AGE: Advanced glycation endproduct; AKT: Serine/threonine-protein kinase akt; RAGE: The receptor for advanced glycation endproduct; LOX1: Lysyl Oxidase 1; LDL: Low density lipoprotein; FFAs: Free fatty acid; G6P: Glucose 6-phosphate; Red circle within minus represents inhibition.

formation (Alves de Lima *et al.*, 2020). Consequently, nerve injury—especially in conditions like depression, spinal cord injury, and neuroinflammation—can have devastating effects on these vital functions (Li *et al.*, 2022).

FMN, in a dose-dependent manner at concentrations of 2.5, 5, and 10 μM, conclusively demonstrates a neuroprotective effect by alleviating neuroinflammation. It achieves this by modulating the microglia ERβ pathway, whether the neuroinflammatory state is induced by LPS-stimulated BV2 microglial cells or TNF-α-stimulated HEK293 cells. As a result, FMN mitigates the neurotoxic consequences associated with activated microglia, showcasing its protective efficacy against neuroinflammatory processes (El-Bakoush & Olajide, 2018).

Long-term neuroinflammation can trigger the body's stress response, impairing the normal functioning of the nervous system. This disruption may, in turn, increase the risk of depression or exacerbate existing symptoms. Intragastric administration of FMN (20, 40 mg·kg^{-1}) for 3 weeks has been shown to alleviate depressive-like behaviors in mice induced by subcutaneous injection of 10 mL·kg^{-1} corticosterone. Evidence of this improvement includes increased sucrose preference, enhanced activity and exploration in the central area, and reduced levels of pro-inflammatory cytokines, as well as decreased ionized calcium-binding Iba-1 fluorescence intensity in the hippocampus's CA1, CA3, and DG regions (Zhang *et al.*, 2022). Iba-1, a protein specifically expressed in microglia within the hippocampus, is widely recognized as a marker for microglial activation. When microglia are activated, Iba-1 interacts with cytoskeletal proteins to promote cell movement, facilitating the dynamics of the cell membrane and the activation of RAC-1. Moreover, Iba-1 is involved in the RAC-1 signaling pathway and the process of phagocytosis, contributing to the morphological changes that characterize microglia/macrophage activation (Ansari *et al.*, 2024; Shikata *et al.*, 2022). Consequently, Iba-1 has become a crucial marker in the study of neuroinflammation and neurodegenerative diseases.

The EGFR signaling pathway, which plays a critical role in regulating microglial activation and the MAPK cascade, is pivotal in modulating the inflammatory response and subsequent secondary injury following spinal cord injury (SCI). As a key downstream effector of EGFR, MAPK is essential for orchestrating these inflammatory and

biological responses. For example, in an SCI model where rats were subjected to 20 seconds of spinal cord compression at the T10 level to induce lower extremity paralysis, intraperitoneal injection of FMN (20, 40 mg·kg^{-1}) for 4 weeks effectively suppressed microglial inflammation and promoted SCI repair by targeting the EGFR/p38 MAPK signaling pathway (Fu *et al.*, 2023).

Furthermore, integrating FMN into functionalized carbon nanomaterials not only enhances their safety but also enables their incorporation into photocrosslinkable formulations. When these advanced formulations are photopolymerized at the site of spinal injury, they demonstrate excellent cell viability, underscoring their potential as therapeutic agents for spinal cord injury (SCI) and other neuroinflammatory conditions (de Vasconcelos *et al.*, 2020). This innovative approach paves the way for the development of targeted, effective, and safe treatments for a broad range of neurological disorders.

Anti-inflammatory effect of FMN in the cardiovascular system disorders

The circulatory system, an intricate network of extracellular fluids—including plasma, lymph, and interstitial tissue fluids—along with their respective circulatory pathways, serves as the lifeline of transportation within living organisms. It diligently delivers essential nutrients absorbed from the digestive tract and oxygen obtained through the gills or lungs to every tissue and organ, ensuring their proper function and vitality (Hillyer & Pass, 2020). Simultaneously, the system efficiently removes metabolic waste products from tissues and organs, transporting them through the lungs and kidneys for excretion. In addition to its crucial role in substance exchange, the circulatory system maintains homeostasis by regulating body temperature through heat distribution and fine-tuning organ functions by transporting hormones to their specific targets (Batool *et al.*, 2020).

Notably, the protective effects of 40 μM FMN against ox-LDL-induced endothelial damage are mediated through the activation of PPAR-γ, underscoring its anti-inflammatory, anti-oxidative stress, and anti-apoptotic properties (Zhang *et al.*, 2021). In the context of atherosclerosis, FMN has shown therapeutic potential by modulating KLF4 and SRA in ApoE-deficient mice, thereby effectively restoring vascular function (Ma *et al.*, 2020). Additionally, a concentration gradient of FMN (10, 20, and 40 mg·kg^{-1}) has demonstrated efficacy as a NOS agonist, alleviating deep vein thrombosis by increasing p-eNOS levels, suppressing inflammatory cytokines such as IL-1β, IL-18, and NF-κB, and promoting vascular healing (Zhou *et al.*, 2022). FMN's pro-angiogenic properties are further evidenced by its ability to stimulate endothelial cell growth, proliferation, migration, and tube formation—processes closely linked to endothelial nitric oxide synthase activation and nitric oxide production. These effects, however, are contingent upon intact AKT and Erk1/2 signaling pathways (Wu *et al.*, 2020).

Recent studies on the Shuxinyin formula, enriched with FMN, have demonstrated its ability to significantly enhance the growth of sub-intestinal vessel plexuses in zebrafish models. This formula effectively reversed vessel deficiencies induced by VRI and modulated key angiogenesis-related genes, including *kdr*, *flt1*, and *kdrl*. The underlying mechanism appears to involve the VEGF/PI3K/Akt/MAPK signaling cascade, highlighting the complexity of FMN's angiogenic effects (Zhou *et al.*, 2019). Additionally, FMN's interactions with ERα and ROCK play a critical role in promoting angiogenic sprouting in the zebrafish sub-intestinal vessels. These findings provide valuable insights into the mechanisms by which phytoestrogens, particularly through the regulation of ERα and ROCK interactions, influence actin assembly and cell migration during angiogenesis (Li *et al.*, 2015).

FMN has demonstrated notable cardioprotective properties in the context of ischemia-reperfusion injuries (IRI). It attenuates cardiac dysfunction, reduces infarct size, and suppresses biomarker release by inhibiting inflammatory cytokines such as TNF-α, IL-1β, and IL-6, primarily through the ROS-TXNIP-NLRP3 and JAK2/STAT3 signaling pathways. These actions contribute to neuronal recovery and inhibit pro-inflammatory cascades (Wang *et al.*, 2020; Yu *et al.*, 2022). In studies on cardiac ischemia-reperfusion injury (CIRI), FMN (20 mg·kg^{-1}) mitigated oxidative stress by reducing NO and MDA levels, increasing SOD activity, and enhancing energy metabolism. It achieved this by modulating the activities of key enzymes, including Na^+-K^+-ATPase, Ca^{2+}-Mg^{2+}-ATPase, and Ca^{2+}-ATPase, which are essential for energy conversion, ion transport, and the maintenance of cellular ionic balance. These findings highlight FMN's ability to restore energy metabolism and alleviate CIRI-related damage (Wang *et al.*, 2022).

Moreover, FMN has shown promise in addressing post-myocardial infarction depression, a significant comorbidity that negatively impacts prognosis. By targeting GSK-3β, FMN modulates macrophage and microglial polarization, reducing neuroinflammation and offering potential therapeutic benefits for this condition. Collectively, these findings highlight FMN's multifaceted role in vascular protection, angiogenesis, and the mitigation of ischemia-reperfusion injuries, underscoring its potential as a versatile therapeutic agent for both cardiovascular and neurological disorders (Yang *et al.*, 2023).

In conclusion, FMN's multifaceted biological activities—ranging from metabolic regulation and vascular protection to neuromodulation—highlight its potential as a versatile therapeutic agent across a broad spectrum of pathological conditions. (The potential mechanism of action of FMN in alleviating cardiovascular system disorders is illustrated in Figure 7).

Anti-inflammatory effect of FMN in the immune system disorders

The immune system, intricately designed, serves three fundamental functions: immune defense, immune surveillance, and immune homeostasis (Alves de Lima *et al.*, 2020). "Immune defense" is the body's first line of resistance, warding off pathogenic microorganisms and eliminating invading pathogens and harmful biomolecules to protect the body from external threats (Diamond & Kanneganti, 2022). "Immune surveillance", on the other hand, plays a vigilant role by continuously monitoring for and promptly eliminating mutated cells that could potentially lead to disease. Lastly, "immune homeostasis", or self-regulation, maintains the body's equilibrium by distinguishing between self and non-self entities, effectively differentiating between "friendly" and "harmful" components to preserve overall stability (Wu *et al.*, 2022). Allergic diseases arise when this delicate balance of the immune system is disrupted. At the core of allergic reactions are "leukocytes", white blood cells originating from pluripotent stem cells in the bone marrow. These cells play a pivotal role in both innate and acquired immunity, mediating allergic responses just as they do in other immune reactions (Wang *et al.*, 2023).

Remarkably, a concentration gradient of FMN (0.4, 2, and 10 mg·kg^{-1}) has shown effectiveness in the 0.6% FITC-induced atopic contact dermatitis mouse model, positioning FMN as a promising agent for managing allergic diseases (Li *et al.*, 2018). Its protective effects are linked

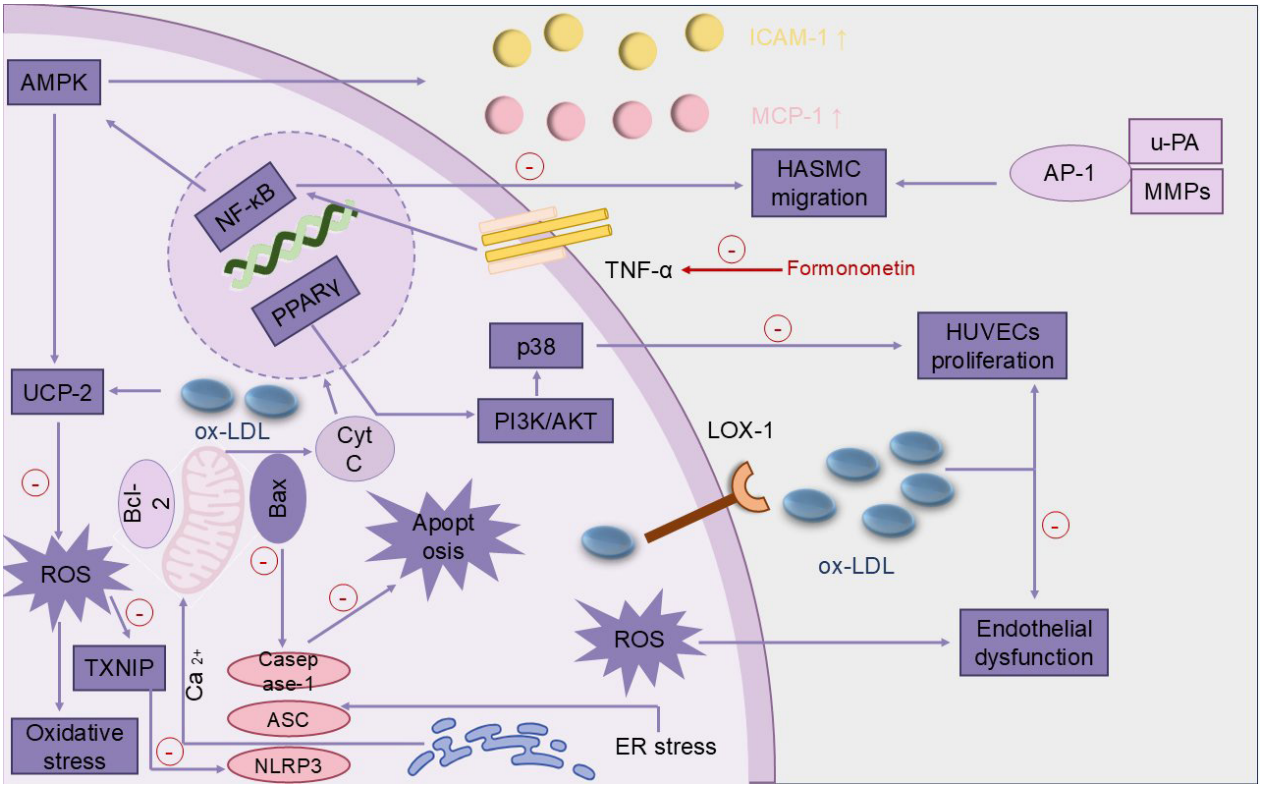


Figure 7. Potential mechanism of action of FMN in relieving cardiovascular system diseases. AMPK: Adenosine 5'-monophosphate-activated protein kinase; AP-1: Activating protein-1; UCP-2: Uncoupling Protein 2; ROS: Reactive oxygen species; TXNIP: Thioredoxin interacting protein; NLRP3: NOD-like receptor thermal protein domain associated protein 3; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma-2; ICAM-1: Intercellular cell adhesion molecule-1; MCP-1: Monocyte chemoattractant protein 1; CytC: Cytochrome c oxidase; TNF-α: Tumor necrosis factor-α; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1; ER: Endoplasmic reticulum; NF-κB: Nuclear factor kappa-B; PPAR-γ: Peroxisome proliferators-activated receptor γ; AKT: Serine/threonine-protein kinase akt; PI3K: Phosphoinositide 3-kinase; MMP: Matrix metalloproteinase; u-PA: Urokinase-type plasminogen activator; Red circle within minus represents inhibition.

to the modulation of "E-cadherin", leading to a reduction in the production of TSLP and IL-33, which are key mediators of allergic inflammation (Shen *et al.*, 2014). In related studies, consistent dosages of FMN have been used in the induced atopic contact dermatitis mouse model, with results demonstrating that FMN attenuates allergic inflammation, likely by reducing TSLP production through the regulation of NF-κB activation (Li *et al.*, 2018).

Intriguingly, FMN (10, 20, and 40 μM) exerts dose-dependent protective effects against compound C48/80-stimulated mouse bone marrow-derived mast cells and RBL-2H3 cells, effectively suppressing the resulting inflammatory response. These findings suggest that FMN could be a promising novel anti-allergic therapeutic. It inhibits IgE-independent mast cell degranulation and the NF-κB signaling pathway, providing a multifaceted approach to managing allergic reactions (Zhou, *et al.*, 2023).

FMN exerts its effects by suppressing IgE-induced NF-κB and MAPK pathways. It decreases FcεRIγ chain expression through enhanced proteasome-mediated degradation and promotes FcεRIγ ubiquitination by inhibiting ubiquitin-USP 5 and/or USP 13 enzymes (Zhou, *et al.*, 2023). When an allergen binds with IgE, the formed immune complex interacts with FcεRI, triggering signal recognition by FcεRIα. This leads to the activation of FcεRIβ and FcεRIγ, which are phosphorylated by Src family kinases through the intracellular immune receptor tyrosine activation motif. The phosphorylation cascade subsequently activates the Syk family kinases, initiating a signaling pathway that culminates in the degranulation of effector cells like mast cells and basophils. This degranulation releases histamine and other inflammatory mediators, contributing to the onset of allergic reactions (Li *et al.*, 2022; Nagata & Suzuki, 2022).

In addition, a concentration gradient of FMN (10, 20, and 40 $mg \cdot kg^{-1}$) administered over a 28-day period can enhance antioxidant defenses. This is achieved by elevating HO-1 levels, which in turn reduce ROS production and increase SOD content. As a result, FMN significantly inhibits the activation of NF-κB and JNK pathways, leading to a reduction in inflammatory cytokines (IL-4, IL-5, IL-13, and IL-17A) and chemokines (CCL5 and CCL11). These effects further dampen the allergic response in a 0.5 $mg \cdot mL^{-1}$ ovalbumin-induced murine model of allergic asthma (Yi *et al.*, 2020).

In summary, these findings highlight the complex mechanisms underlying immune regulation and allergic responses. They also emphasize the promising potential of targeted interventions, such as FMN, in alleviating the burden of allergic diseases by modulating inflammatory pathways and immune distribution.

Anti-inflammatory effect of FMN in other system disorder

The kidneys in the human body are not only responsible for producing urine and regulating fluid balance, but also have endocrine and detoxification functions (Oshima *et al.*, 2021). Meanwhile, the lungs are the main site for gas exchange, providing the body with the necessary oxygen by inhaling oxygen and expelling carbon dioxide, while also removing waste gases produced by metabolism (Okyere *et al.*, 2021). When early signs of disease appear in the lungs and kidneys, it can severely jeopardize the body's health. Therefore, protecting kidney and lung health is crucial for maintaining the body's normal physiological functions. For instance, in a 12 $mg \cdot kg^{-1}$ cisplatin-induced acute kidney injury rat model, treatment with 75 $mg \cdot kg^{-1}$ FMN for 5 days was found to be effective (Hao *et al.*, 2021). In an acute lung injury model where mice were exposed to hyperoxia for 72 hours, intraperitoneal injection of FMN (10, 100 $mg \cdot kg^{-1}$) for 3 days prevented further damage (Chen *et al.*, 2021). In a 4 $mg \cdot kg^{-1}$ LPS-induced acute lung injury mouse model, FMN (10, 20 $mg \cdot kg^{-1}$) also showed therapeutic effects (Ma *et al.*, 2013). Notably, FMN's efficacy extends to both lung and kidney injuries, which are inflammatory conditions. It achieves this by modulating the PPAR-α/Nrf2/HO-1/NQO1 pathway. This modulation helps counteract oxidative stress and reduce pro-inflammatory cytokines. The transcription factor Nrf2 is fundamental in coordinating cellular antioxidant defenses. By regulating genes related to drug metabolism, detoxification, and antioxidant responses, Nrf2 maintains a delicate balance within the cell. This regulatory mechanism is closely associated with Keap1, an adapter protein in the Cullin 3-based E3 ubiquitin ligase complex that controls Nrf2 degradation. In response to oxidative and inflammatory stimuli, HO-1, a stress-inducible protein in the Keap1/Nrf2 pathway, is activated, triggering anti-inflammatory cascades. The Keap1/Nrf2/HO-1 signaling axis is recognized as a key antioxidant stress signaling pathway and a promising therapeutic target for inflammation-related disorders (Wu *et al.*, 2020). Significantly, FMN modulates this pathway, adjusting the intracellular oxidant status and balancing energy metabolism. In the case of PAH, in a 60 $mg \cdot kg^{-1}$ monocrotaline-induced PAH rat model, the 2-week therapeutic effects of FMN (10, 30, and 60 $mg \cdot kg^{-1}$) were investigated. The results revealed that FMN suppressed pulmonary vascular remodeling, potentially mediated by ERK and NF-κB signals, highlighting its therapeutic potential in this challenging condition (Wu *et al.*, 2020).

In summary, these findings suggest that FMN can be involved in PPAR-α, Keap/Nrf2/HO-1, MAPK, and NF-κB signaling pathways to alleviate the burden of kidney and lung injury. Its intricate anti-inflammatory mechanisms position it as a promising candidate for effectively

targeting inflammation and potentially becoming a better therapeutic option for inflammation-related conditions.

Coupling with Network Pharmacology and Molecule Docking to Reveal FMN's Anti-Inflammatory Properties

Network pharmacology, an advanced and versatile methodology, has become a powerful tool in drug discovery and development, particularly within the context of Traditional Chinese Medicine (TCM). It enables the efficient identification of bioactive chemical components and their corresponding therapeutic targets within classical Chinese medicine formulas or individual herbal remedies (Muhammad *et al.*, 2018). This approach highlights its potential in uncovering the complex mechanisms that underlie the therapeutic efficacy of herbal treatments.

Further enhancing this process, the integration of molecular docking with network pharmacology has enabled the identification of potential protective agents against ulcerative colitis, including quercetin, FMN, kaempferol, licochalcone A, oroxylin A, and wogonin from the *Gegen Qinlian decoction* (Xu *et al.*, 2021). This synergy exemplifies the power of combining computational techniques with traditional knowledge to fully unlock the therapeutic potential of herbal medicines. In the case of *Hedysarum multijugum Maxim*, studies have highlighted its remarkable immunostimulatory properties, primarily attributed to quercetin, kaempferol, FMN, and isorhamnetin. These compounds exhibit a high affinity for targeted genes related to ulceration (Zhang *et al.*, 2022). This underscoring the importance of identifying key active ingredients and their mechanisms of action in herbal remedies. Moreover, a study analyzing the ethyl acetate extract of *Sophora flavescens* in DSS-induced rat models, combined with network pharmacology and metabolic profiling, identified a range of highly active compounds, including genistein, FMN, isokurarinone, kurarinone, maackiain, kushenol N, trifolirnizin, kuraridin, and norkurarinone (Chen *et al.*, 2020). This comprehensive approach sheds light on the intricate interactions between herbal constituents and their metabolic effects, providing valuable insights into the design of novel therapeutic strategies.

The recurring theme of FMN as an anti-inflammatory agent in these network pharmacology studies highlights its significance and the potential of modern technologies to tap into the rich resources of Traditional Chinese Medicines (TCMs). However, these studies did not delve deeper into the specific activity of FMN. In contrast, we applied network pharmacology to analyze the potential bioactive components of *Huangqin decoction*, and through molecular docking, we identified FMN as a promising candidate. Furthermore, to validate FMN's anti-inflammatory effects, our research on FMN in a DSS-induced zebrafish larvae IBD model demonstrated that FMN treatment effectively inhibited the recruitment of intestinal neutrophils, while also expanding intestinal length and area (Figure 8).

Looking ahead, it is essential to further explore the synergies between computational methodologies and traditional knowledge, encouraging innovative drug development strategies that harness the distinct strengths of both areas. By doing so, we can open up new pathways for treating complex diseases and advancing global health, ultimately leading to more effective and holistic healthcare solutions.

Future perspectives

Currently, extensive research has been conducted on the anti-inflammatory activity of Formononetin, with a focus on understanding its underlying mechanisms. These studies mainly employ molecular biology techniques such as Western blotting, immunofluorescence staining, cell biological assays, histopathological examinations, and physiological markers in in vivo animal models. As research continues to advance, a growing body of evidence supports the idea that Formononetin's anti-inflammatory effects may involve multiple targets and complex layers of action. Consequently, future studies could benefit from the incorporation of omics technologies—particularly the integration of transcriptomics, proteomics, and metabolomics—to provide a more comprehensive understanding of its mechanisms. Additionally, it is crucial to focus on improving the bioavailability of Formononetin, exploring the potential development of nanomedicine delivery systems and targeted drug delivery methods to enhance its therapeutic efficacy. High-throughput screening using zebrafish models could also reveal more potential targets and applications for Formononetin. These efforts will be instrumental in advancing Formononetin's development, offering promising prospects for improving human health.

Conclusions

In our comprehensive review, we highlight FMN as an effective functional isoflavone component, whose natural abundance in edible sources and functional foods offers a compelling opportunity to harness its health benefits through dietary interventions. Additionally, we have meticulously summarized the anti-inflammatory attributes of FMN. Despite challenges related to its inherently low water solubility, FMN demonstrates strong anti-inflammatory regulation in combating inflammatory responses linked to conditions such as tumors,

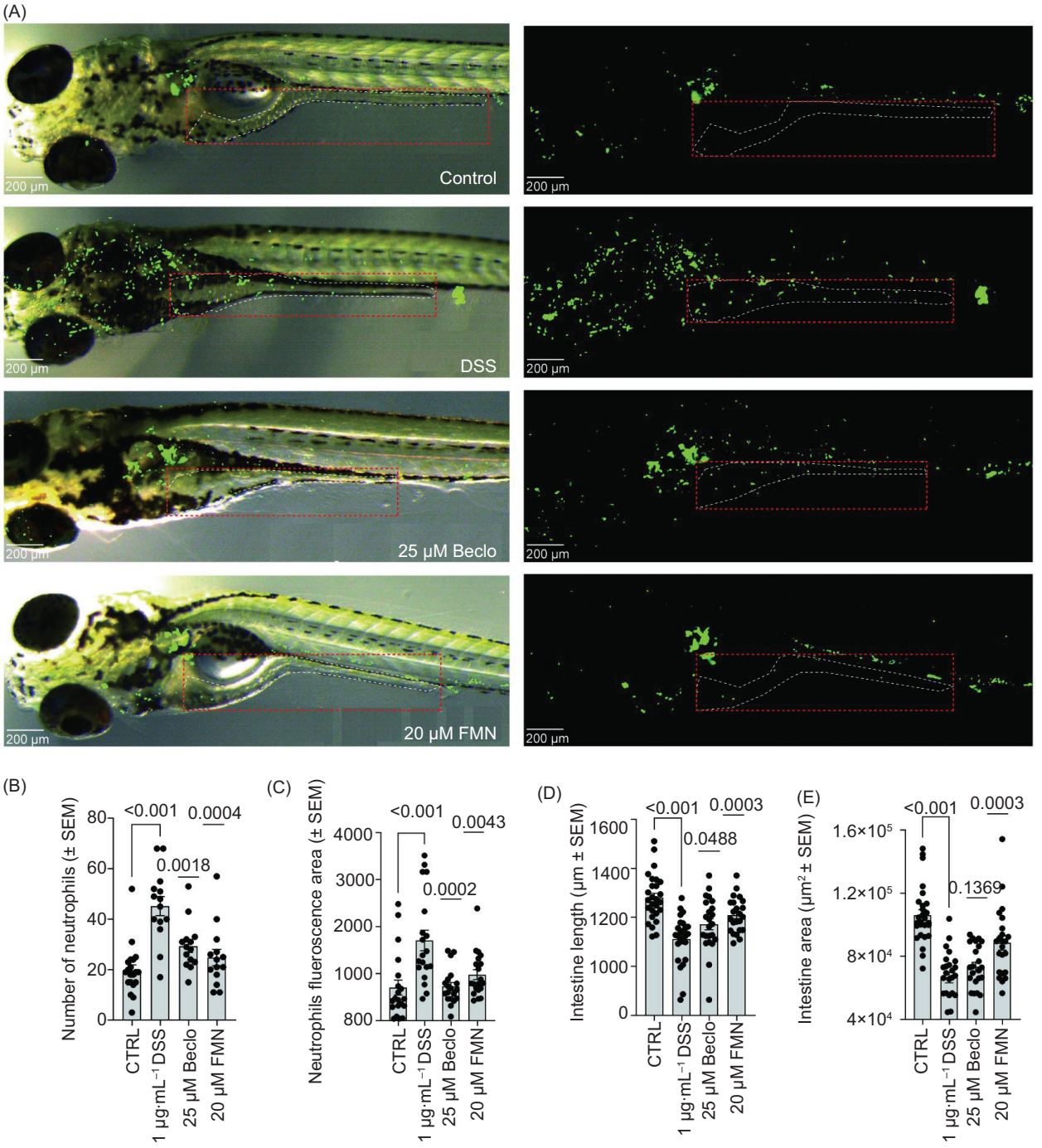


Figure 8. Formononetin in the treatment of DSS-induced zebrafish larvae IBD model. (A) Representative Mshot fluorescence microscopy images of DSS-induced zebrafish larvae IBD model intestinal migration of neutrophils in combination with CTRL, Beclo (Beclomethasone), and FMN treatments; (B) Fluorescence and bright field photos are merged by image J software, which indicates the intestinal recruitment of neutrophils; (C) Number of neutrophils; (D) Neutrophils fluorescence area; (E) Zebrafish larvae intestinal length; (F) Zebrafish larvae intestinal area. Green fluorescence represents neutrophils of zebrafish larvae in vivo. White dotted line represents statistical zebrafish larvae intestinal area, red dotted line represents zebrafish larvae intestinal area. CTRL represents control group; Beclo represents positive drug beclomethasone group; FMN represents formononetin group. The statistical method uses the Student's test. P < 0.05 represents significance; P > 0.05 represents no significance; the significance is compared in CTRL and Model, Model versus Treatment (Beclo and FMN).

osteoporosis, diabetes, cardiovascular disease, and excessive immunity. This underscores the importance of deeply exploring the complex mechanisms that regulate key genes or pathways associated with various diseases. The anti-inflammatory effects of FMN are linked to pathways including NF-κB, MAPK, JAK-STAT, PI3K-AKT, TLRs, and estrogen, which involve preventing diseases caused by inflammation and protecting the body's health by inhibiting apoptosis, autophagy, and oxidative stress. Future research could focus on unraveling the intricate interplay between FMN and its co-existing bioactive molecules, as well as their collective impact on cellular signaling cascades and gene expression patterns, to fully unlock their therapeutic potential. In conclusion, exploring FMN's multifaceted pharmacological properties, coupled with its availability through dietary sources, holds great promise for developing novel therapeutic strategies and health promotion programs aimed at preventing and mitigating inflammatory conditions and their associated sequelae. By leveraging the anti-inflammatory and health-promoting attributes of FMN, we can pave the way for innovative approaches to maintaining and improving human health.

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Consent for Publication

The manuscript is approved by all authors for publication.

Author Contributions

Conceptualization, Min He and Mengmeng Sun; formal analysis, Jiawen Dou; funding acquisition, Min He and Mengmeng Sun; investigation, Jiawen Dou and Yongping Li; project administration, Min He and Mengmeng Sun; visualization, Jiawen Dou; writing-original draft, Jiawen Dou; Writing-review & editing, Fiodar Pryvalau, Liudmila Goncharova, Min He and Mengmeng Sun.

Conflicts of Interest

The authors declare no conflict of interest.

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