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*Review*

# Fucoidan: Modulating Post-Myocardial Infarction Inflammation via the Gut-Heart Axis

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**Abstract**

Myocardial infarction (MI) remains a major cause of global morbidity and mortality, with post-MI inflammation significantly exacerbating tissue damage and adverse cardiac remodeling. Recent advancements have highlighted the gut microbiota as a crucial regulator of cardiovascular health via the gut-heart axis. This review introduces a novel therapeutic perspective by exploring the potential mechanisms through which fucoidan, a sulfated polysaccharide derived from marine algae, may alleviate post-MI inflammation. Fucoidan demonstrates unique anti-inflammatory and antioxidant properties and has been shown to modulate the gut microbiota. Specifically, it enhances the abundance of beneficial gut bacteria, boosts short-chain fatty acids (SCFA) production, and reduces bacterial endotoxin translocation. Additionally, fucoidan directly inhibits inflammatory signaling pathways, decreases pro-inflammatory cytokine secretion, and protects cardiomyocytes through antioxidant effects. These multifaceted actions position fucoidan as a promising novel therapeutic strategy for mitigating post-MI inflammation and promoting cardiac recovery. Future research should focus on optimizing fucoidan extraction methods, identifying effective dosing regimens, and developing targeted delivery systems to maximize clinical efficacy.

**Keywords:** fucoidan; myocardialinfarction; intestinal flora; mechanisms

## 1. Introduction

Heart attack or myocardial infarction is the primary cause of morbidity and death worldwide. If the supply of the portion of the heart gets blocked, it results in the blockage of the supply of the blood that results in the death of the myocardial cells. The post-myocardial infarction (MI) inflammatory response, triggered by a double hit, leads to excessive inflammation that worsens tissue injury and can cause heart failure. This excessive inflammation also contributes to other conditions such as stroke, which are difficult to repair and regenerate. Therefore, modulating the inflammatory response after myocardial infarction is an important therapeutic target [1].

The gut microbiota has recently been recognized as a central regulator of cardiovascular health. The gut-heart axis, a bidirectional communication system between the gut and the heart, plays a significant role in various cardiovascular diseases, including MI [2]. Fucoidan, a sulfated polysaccharide derived from algae, exhibits a broad range of biological activities, particularly anti-inflammatory and antioxidant effects [3]. Fucoidan obtained from brown algae has been shown to regulate the release of inflammatory cytokines from macrophages [4]. Previous studies have demonstrated that fucoidan extracted from Undaria pinnatifida can improve dyslipidemia and modulate the gut microbiota of BALB/c mice (BALB/c mice are an inbred strain of laboratory mice, widely used in biomedical research) [5]. It has been found that the addition of fucoidan can enhance the bile salt hydrolase (BSH) activity of Lactobacillus casei DM8121 in culture media [6]. Fucoidan from sea cucumber can inhibit hyperlipidemia, obesity, and inflammation caused by a high-fat diet (HFD). Fucoidan can reverse gut microbiota dysbiosis, especially colonic microbiota dysbiosis, by reducing the abundance of Firmicutes and increasing the abundance of Bacteroidetes [7]. Fucoidan from kelp can significantly reduce the body weight, hepatic steatosis, and systemic inflammation in diet-induced metabolic syndrome mice. After oral administration of fucoidan, beneficial microbial groups (including Akkermansia muciniphila) and short-chain fatty acid-producing bacteria (such as alloprevotella, blautia, and other bacteria) are highly enriched [8]. However, the anti-inflammatory effects of fucoidan in post-myocardial infarction inflammatory responses have not been thoroughly investigated, and the existing research on its impact on gut microbiota is also not comprehensive.

In this review, the focus is on the manner in which fucoidan could influence post-MI outcomes. Specifically, it examines how fucoidan may affect the levels of post-MI inflammation, its anti-inflammatory effects on the gut microbiota, and its potential cardioprotective benefits, as detailed further in the present review.

## 2. The Gut-Heart Axis and Myocardial Infarction

### *2.1 The Role of Gut Microbiota in Cardiovascular Health*

The human gastrointestinal tract is home to a dynamic and intricate trillions of bacteria community called the gut microbiota. The population of the microbiota consists of bacteria, archaea, viruses, and fungi, with Firmicutes and Bacteroidetes phyla of bacteria being the most dominant ones [9]. The microbiota of the gut plays a critical function in favor of the health of the host by way of a variety of mechanisms, including the facilitation of the digestion of complex carbohydrates, the production of vital vitamins (such as vitamin K and a few B vitamins), and the modulation of local and systemic immunity [10]. Dysbiosis, a state of imbalance of the microbiota that is characterized by the loss of microbiota diversity or overgrowth of pathogenetic species, has increasingly been shown to be connected with a variety of diseases, including cardiovascular diseases (CVDs).

The gut microbiota affects cardiovascular health through various mechanisms, including the production of bioactive metabolites such as short-chain fatty acids (SCFAs), for example, acetate, butyrate, and propionate by fermentation of polyphenols and dietary fiber and the expression of systemic anti-inflammatory and cardioprotective effects by stimulating the G-protein-coupled receptors (GPR) such as GPR41 and GPR43, enhancing endothelial function, reducing blood pressure, and preventing histone deacetylases to suppress the expression of pro-inflammatory genes [11]. Some of the intestinal microbes degrade the diet components such as choline, L-carnitine, and phosphatidylcholine to trimethylamine (TMA), which in the liver is converted to trimethylamine N-oxide (TMAO), a harmful metabolite that plays a role in atherosclerosis, MI, and other CVDs by mechanisms such as inducing foam cell formation by stimulating the endocytosis of oxidized low-density lipoprotein (oxLDL), stimulating the activation of the pro-inflammatory mechanisms such as the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, and interfering with the process of the reverse cholesterol transport [12]. The intestinal microbiota also modulates systemic inflammation by modulating the interaction between the pro- and anti-inflammatory cytokines such as inducing the suppression of the inflammation by inducing the cytokine interleukin-10 (IL-10), or inducing the promotion of the inflammation by inducing the cytokine tumor necrosis factor-alpha (TNF-$\alpha$), and interleukin-6 (IL-6), as well as interacting with the toll-like receptors to modulate the nuclear factor-kappa B (NF-$\kappa$B)-dependent signaing mechanisms [13]. The intestinal microbiota also plays an important function in the bile acid homeostasis by deconjugating primary bile acids to secondary bile acids that act as signal mediators via the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5) to regulate lipid metabolism, glucose homeostasis, and inflammation, with an alteration of the bile acids composition by dysbiosis having the potential to increase cardiovascular risk [14].

Besides, the gut microbiota maintains the barrier function of the gut, preventing the translocation of bacterial endotoxins like lipopolysaccharide (LPS) into the circulation, but dysbiosis could impair the barrier to cause enhanced intestinal permeability (leaky gut) and endotoxemia that lead to systemic inflammation and oxidative stress by stimulating TLR4, promoting endothelial dysfunction and atherosclerosis [15].

### *2.2 The Gut-Heart Axis in Myocardial Infarction*

The gut-heart axis is a two-way intricate interaction between the heart and the gut that plays a key function in the management of the inflammatory response to MI. As mentioned earlier, with MI the organism responds with a systemic inflammatory response by secreting cytokines with pro-inflammatory effects, such as IL-6 and TNF-$\alpha$, that are necessary to clear the necrotic tissue and start the repairing process [1,2]. A disproportionate or persistent inflammatory response, however, will lead to more tissue damage, adverse cardiac remodeling, and impaired cardiac function, thus to the necessity to closely regulate the inflammatory response.

The gut microbiota plays a key function in regulating the post-MI inflammatory response by a myriad of complex mechanisms. Dysbiosis or disturbance of the composition of the intestinal microbial flora compromises the intestinal barrier integrity and leads to increased intestinal permeability or leaky gut [16]. This allows bacterial endotoxins such as LPS to translocate into the circulation and LPS stimulates toll-like receptor 4 (TLR4) on immune cells to induce secretion of the inflammatory cytokines and perpetuate systemic inflammation, exacerbating cardiac damage and impairing the recovery of MI [17]. The gut microbiota also regulates the production of SCFAs such as acetate, propionate, and butyrate by fermentation of the dietary fiber. SCFAs have profound anti-inflammatory effects by the binding to G-protein-coupled receptors (GPCRs) such as GPR41 and GPR43 on the immune and endothelial cells [18]. This effect inhibits the NF-$\kappa$B pathway, thereby downregulating the expression of inflammatory cytokines. This action protects the heart from damage, maintains endothelial function, and preserves the integrity of the intestinal barrier, further preventing systemic inflammation [18]. The gut microbiota also regulates the production of TMAO, an injurious cardiovascular metabolite, by degrading nutrients such as choline, L-carnitine, and phosphatidylcholine to TMA, and TMA is oxidized to form TMAO in the liver, and excessive TMAO exacerbates inflammation, endothelial damage, and atherosclerosis by mechanisms such as inducing the NLRP3 inflammasome to trigger the secretion of inflammatory cytokines and disrupting the reverse cholesterol transport, with consequent plaque instability and adverse cardiac remodelling [19,20]. The pivotal function of the gut

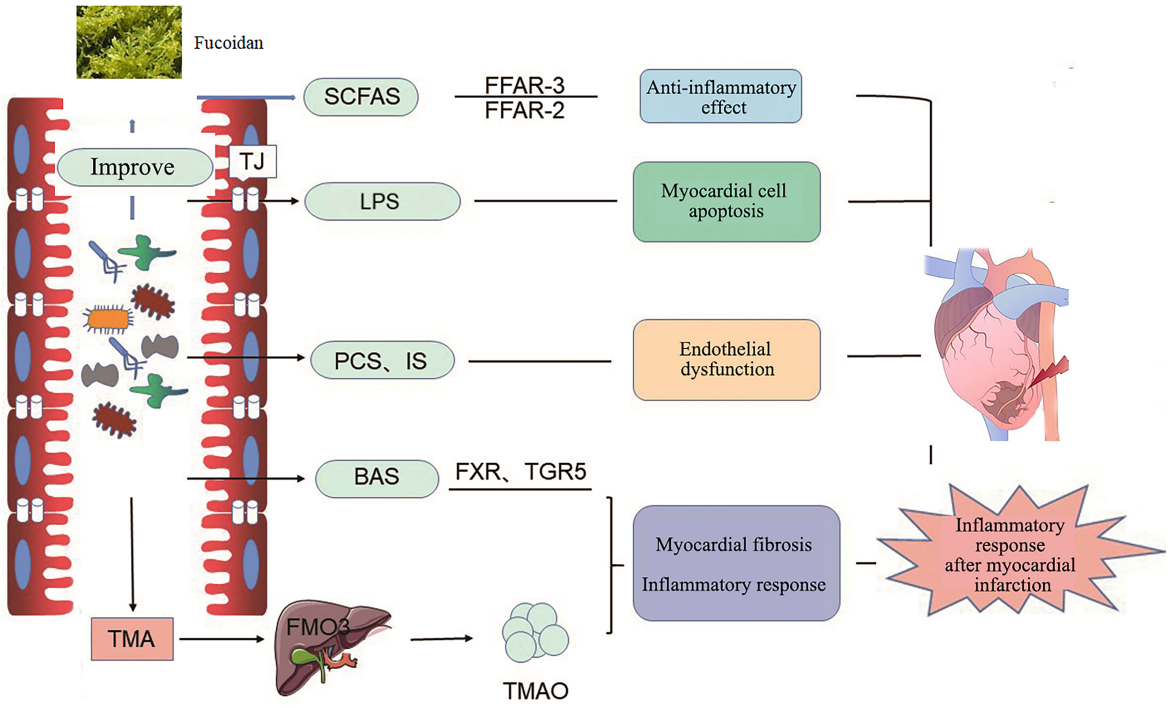


**Fig. 1. The inflammatory response to, and resolution of, myocardial infarction is controlled by the gut microbiota, and Fucoidan promote the return of the inflammatory response by improving the gut microbiota.** SCFAs, Short-chain fatty acids; FFAR-3, Free fatty acid receptor 3; FFAR-2, Free fatty acid receptor 2; LPS, Lipopolysaccharide; PCS, p-cresol sulfate; IS, Indoxyl sulfate; BAS, Bile acid synthesis; FXR, Farnesoid X receptor; TGR5, G-protein-coupled bile acid receptor 1; TMA, Trimethylamine; FMO3, Flavin-containing monooxygenase 3; TMAO, Trimethylamine-N-oxide; TJ, tight junctions.

microbiota in the modulation of the inflammatory response and consequences of myocardial infarction is summarized in Fig. 1.

## 3. Fucoidan and the Impact on Gut Microbiota

Fucoidan, derived from marine algae, represents a class of bioactive polysaccharides that have garnered significant attention for their potential health benefits, particularly in modulating the gut microbiota. These complex, sulfated polysaccharides can influence the gut environment by interacting with the resident microbial communities, thereby promoting a healthier microbial balance. Fucoidan has been shown to enrich beneficial bacteria such as Bifidobacterium and Lactobacillus, which are known for their probiotic properties, while simultaneously suppressing the growth of pathogenic bacteria, thus enhancing the overall diversity and functionality of the gut microbiota [21].

The impact of fucoidan on the gut microbiota is multifaceted. Studies have demonstrated that fucoidan can significantly increase the abundance of beneficial microbial taxa, including Akkermansia muciniphila and Faecalibacterium prausnitzii, which are associated with anti-inflammatory effects and improved metabolic health [22]. A study published in the journal Nutrition found that Fucoidan can ameliorate high-fat diet-induced dyslipidemia in rats by modulating the gut microbiota and bile acid metabolism [23]. This shift in microbial composition is crucial, as it can enhance the gut barrier function and reduce the risk of metabolic disorders. Beyond its microbiological benefits, fucoidan also enriches the gut environment with bioactive molecules. These include SCFAs such as acetate, propionate, and butyrate, which are produced through the fermentation of fucoidan by gut bacteria [24]. SCFAs play a vital role in maintaining gut health by strengthening the intestinal barrier, reducing inflammation, and modulating the immune response. For example, butyrate, a key SCFA, has been shown to enhance the expression of tight junction proteins, thereby reinforcing the integrity of the gut barrier and preventing the translocation of bacterial endotoxins into the bloodstream [25].

Fucoidan also exhibits potent antioxidant and anti-inflammatory properties. These effects are partly mediated through the modulation of gut microbiota and the production of bioactive metabolites. Fucoidan can induce the production of polyphenols and bioactive peptides, which act as antioxidants, neutralizing free radicals and reducing oxidative stress [26]. Additionally, these bioactive compounds can selectively promote the growth of beneficial bacteria while inhibiting the proliferation of pathogenic strains, thereby contributing to a healthier gut microbiota. Further-

more, fucoidan has been shown to regulate the production of harmful metabolites such as TMAO, a known risk factor for cardiovascular disease [27]. A recent study published in the journal Carbohydr Polym in 2025 demonstrated that fucoidan supplementation effectively reduced TMAO levels, accompanied by decreased systemic inflammation and improved cardiovascular health [28]. This finding underscores the potential of fucoidan as a therapeutic agent for preventing metabolic and cardiovascular diseases.

Fucoidan exerts a profound impact on the gut microbiota by promoting the growth of beneficial bacteria, enhancing the production of SCFAs, and reducing inflammation and oxidative stress. These multifaceted benefits highlight the potential of fucoidan as a valuable dietary component for maintaining gut health and preventing systemic diseases.

## 4. Anti-Inflammatory Mechanisms of Fucoidan

### *4.1 Regulation of Pro-Inflammatory Cytokines*

One of the primary mechanisms through which fucoidan exerts its anti-inflammatory effects is by modulating the production of pro-inflammatory cytokines. In conditions such as MI and chronic inflammatory diseases, there is a significant increase in the secretion of pro-inflammatory cytokines like IL-6 and TNF-$\alpha$, which contribute to tissue damage and adverse cardiac remodeling [29,30]. Fucoidan has been shown to inhibit the release of these cytokines by interfering with key signaling pathways, including NF-$\kappa$B and mitogen-activated protein kinase (MAPK). For instance, fucoidan suppresses the phosphorylation of the NF-$\kappa$B inhibitory protein, I$\kappa$B$\alpha$, thereby preventing the nuclear translocation of NF-$\kappa$B and the subsequent transcription of pro-inflammatory genes. These effects have been demonstrated in various experimental conditions, such as *in vitro* models using lipopolysaccharide (LPS)-induced inflammation in macrophages, as well as *in vivo* studies involving animal models of myocardial infarction. Additionally, fucoidan has been shown to inhibit the MAPK pathway, which plays a crucial role in the production of inflammatory mediators. This inhibition helps reduce the overall inflammatory response, making fucoidan a promising therapeutic agent for managing inflammation in both acute and chronic conditions [31,32]. Additionally, fucoidan has been found to inhibit the MAPK pathway, which plays a crucial role in the production of inflammatory mediators [33].

Fucoidan's anti-inflammatory effects are not limited to acute conditions like MI but also extend to chronic inflammatory diseases. A 2023 study demonstrated that fucoidan supplementation significantly reduced serum levels of TNF-$\alpha$ and IL-6 in patients with type 2 diabetes, a condition characterized by chronic low-grade inflammation [34]. Furthermore, fucoidan's ability to modulate the gut microbiota and enhance the production of SCFAs like butyrate, propionate, and acetate contributes to its anti-inflammatory properties. These SCFAs are known to inhibit NF-$\kappa$B activation and reduce the expression of pro-inflammatory cytokines [35,36]. The synergistic interaction between fucoidan and SCFAs enhances its overall anti-inflammatory efficacy, making it a promising therapeutic agent for managing inflammation in both acute and chronic conditions.

### *4.2 Enhancement of Short-Chain Fatty Acid Production*

Fucoidan has been shown to promote the production of SCFAs, which are crucial for maintaining gut health and regulating systemic inflammation. SCFAs, including acetate, propionate, and butyrate, are produced through the fermentation of dietary fibers by gut microbiota, particularly by bacteria such as Lactobacillus and Bifidobacterium [37,38]. These SCFAs play a pivotal role in modulating inflammation by inhibiting the activation of NF-$\kappa$B and MAPK pathways, thereby reducing the production of pro-inflammatory cytokines like IL-6 and TNF-$\alpha$ [39,40]. A 2024 study demonstrated that fucoidan supplementation significantly increased fecal levels of butyrate and propionate in a mouse model of atherosclerosis, leading to reduced systemic inflammation and improved lipid profiles [41].

In addition to their anti-inflammatory effects, SCFAs also enhance the integrity of the intestinal barrier by promoting the expression of tight junction proteins such as occludin and zonula occludens-1 (ZO-1). This prevents the translocation of bacterial endotoxins like lipopolysaccharide (LPS) into the bloodstream, which can trigger systemic inflammation [42]. Fucoidan's ability to modulate the gut microbiota and increase SCFA production has been linked to its cardiovascular protective effects. Butyrate, one of the key SCFAs, has been shown to improve endothelial function and reduce blood pressure by stimulating the production of nitric oxide (NO) and suppressing oxidative stress [43]. Similarly, propionate has been associated with reduced cholesterol synthesis and improved insulin sensitivity, both of which are beneficial for cardiovascular health [44].

### *4.3 Modulation of NF-$\kappa$B and MAPK Signaling Pathways*

The NF-$\kappa$B and MAPK signaling pathways are central to the regulation of inflammation, particularly in conditions like MI and chronic inflammatory diseases. In MI, ischemia triggers the activation of these pathways, leading to the secretion of pro-inflammatory cytokines such as IL-6 and TNF-$\alpha$, which exacerbate tissue damage and contribute to adverse cardiac remodeling [45]. NF-$\kappa$B activation involves the degradation of its inhibitory protein, I$\kappa$B$\alpha$, followed by the nuclear translocation of the NF-$\kappa$B dimer (p65/p50), which induces the transcription of pro-inflammatory genes [46]. Similarly, the MAPK pathway, which includes the ERK, JNK, and p38 subfamilies, is activated by upstream kinases and plays a crucial role in the production of inflammatory mediators [47].

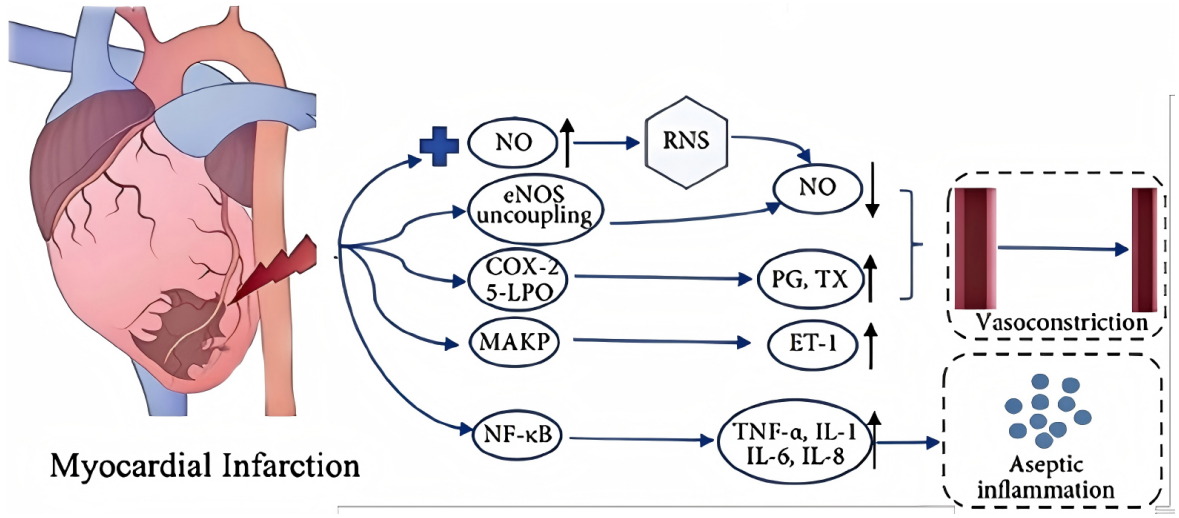


**Fig. 2. The injury of myocardial cells during myocardial infarction.** NO, Nitric Oxide; eNOS, Endothelial Nitric Oxide Synthase; COX-2, Cyclooxygenase-2; 5-LPO, 5-Lipoxygenase; MAKP, Mitogen-Activated Protein Kinase; NF-$\kappa$B, Nuclear Factor Kappa B; RNS, Reactive Nitrogen Species; PG, Prostaglandins; TX, Thromboxane; ET-1, Endothelin-1; TNF-$\alpha$, Tumor Necrosis Factor Alpha; IL-1, Interleukin-1; IL-6, Interleukin-6; IL-8, Interleukin-8.

Fucoidan has been shown to inhibit both the NF-$\kappa$B and MAPK pathways, thereby reducing the production of pro-inflammatory cytokines. Polyphenols and bioactive peptides present in fucoidan interfere with the phosphorylation of I$\kappa$B$\alpha$ and MAPK proteins, preventing the nuclear translocation of NF-$\kappa$B and the activation of downstream inflammatory genes [48]. A 2024 study demonstrated that fucoidan significantly reduced the phosphorylation of I$\kappa$B$\alpha$ and ERK1/2 in an LPS-induced inflammatory model, leading to a marked decrease in TNF-$\alpha$ and IL-6 levels [49]. Additionally, fucoidan's ability to modulate oxidative stress and enhance the activity of antioxidant enzymes further contributes to its anti-inflammatory effects by suppressing the activation of the MAPK pathway [50].

Clinical trials have further validated the therapeutic potential of fucoidan in modulating these signaling pathways. A 2025 randomized controlled trial involving patients with metabolic syndrome showed that regular consumption of fucoidan-rich foods significantly reduced serum levels of TNF-$\alpha$ and IL-6, leading to improved cardiovascular outcomes [51]. Another study in 2025 highlighted the synergistic effects of fucoidan and probiotics in suppressing NF-$\kappa$B and MAPK activation in a colitis model, demonstrating its broad anti-inflammatory potential [52]. These findings underscore the importance of fucoidan as a natural anti-inflammatory agent capable of modulating key signaling pathways to reduce inflammation and protect against tissue damage in various disease conditions.

## 5. Cardioprotective Effects of Fucoidan

### *5.1 Protection of Cardiomyocytes*

Cardiomyocytes, the primary functional cells of the heart, are highly susceptible to damage following MI. Pro-inflammatory cytokines such as IL-6 and TNF-$\alpha$, which are released in response to MI-induced inflammation, significantly increase cardiomyocyte death and trigger adverse cardiac remodeling and heart failure [53,54]. Fig. 2 illustrates the damage to myocardial cells in myocardial infarction. Fucoidan, a sulfated polysaccharide derived from marine algae, has demonstrated significant cardioprotective effects by modulating the inflammatory response and shielding cardiomyocytes from damage [29,55,56]. Fucoidan can inhibit the activation of NF-$\kappa$B and MAPK signaling pathways, thereby reducing the secretion of inflammatory cytokines such as IL-6 and TNF-$\alpha$ [57]. In a 2024 study, fucoidan was shown to significantly alleviate systemic inflammation in a murine model of atherosclerosis by downregulating NF-$\kappa$B activation, thereby mitigating cytokine-induced damage to cardiomyocytes [58]. Additionally, fucoidan contains bioactive compounds that can suppress the MAPK pathway, reducing the inflammatory response and decreasing cardiomyocyte apoptosis [54].

Fucoidan also protects cardiomyocytes through its antioxidant properties. Oxidative stress, characterized by the overproduction of reactive oxygen species (ROS), is a key factor in cardiomyocyte loss following MI. Fucoidan is rich in antioxidants such as polyphenols, which neutralize ROS and protect cardiomyocytes from oxidative damage [59]. Polyphenols found in fucoidan enhance the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby reducing oxidative stress [60]. A 2024 study on fucoidan demonstrated that polyphenols significantly reduced oxidative stress indicators in an LPS-induced model of inflammation, leading to improved cardiomyocyte survival [61]. Furthermore, the bioactive compounds in fucoidan work synergistically to

enhance its cardioprotective effects. For example, a study showed that the combined action of polyphenols and other bioactive components in fucoidan was more effective in suppressing IL-6 and TNF-$\alpha$ than either component alone, highlighting the synergistic action of fucoidan's bioactive constituents [62]. This synergy not only reduces inflammation but also enhances the antioxidant capacity of fucoidan, providing comprehensive protection to cardiomyocytes.

### *5.2 Regulation of Immune Responses*

The immune response to MI is a complex process that involves the activation of innate and adaptive immune cells. The immune response, although it plays a function in the tissue repair process, could also cause exacerbation of the tissue damage and cardiac remodeling by being overactivated. As mentioned above, Fucoidan have a vital function of modulating the immune response by modulating the gut microbiota as well as the secretion of SCFAs. SCFAs such as butyrate, propionate, and acetate promote the differentiation of regulatory T cells (Tregs), which have the important function of dampening excessive immune responses as well as tissue injury. In a 2024 published study, it was demonstrated that butyrate supplementation elevated the Treg differentiation in a mouse model of MI, leading to reduced inflammation and improved cardiac performance [63]. SCFAs also have the capacity to modulate the function of innate immune cells such as macrophages by polarizing the macrophages away from the pro-inflammatory (M1) to the anti-inflammatory (M2) phenotype as well as preventing the secretion of the pro-inflammatory cytokines IL-6 and TNF-$\alpha$ [64].

Fucoidan also contains bioactive molecules such as polyphenols that modulate immunity by controlling the activity of immune cells. A study demonstrated that fucoidan effectively suppressed the activation of dendritic cells and macrophages, thereby reducing the secretion of pro-inflammatory cytokines and enhancing the balance of the immune response [65]. Additionally, fucoidan can inhibit the activation of the NF-$\kappa$B and MAPK signaling pathways, which are central to the production of inflammatory mediators [63,64]. Collectively, these components of fucoidan help to modulate the immune response by both preventing excessive inflammation and promoting tissue repair.

## 6. Challenges and Future Directions

One of the primary challenges in the clinical application of fucoidan is the variability in its efficacy due to differences in its source, extraction methods, and processing conditions. This variability complicates the standardization of fucoidan for therapeutic use. Different species of brown algae (such as Laminaria japonica, Sargassum spp., and Undaria pinnatifida) exhibit significant differences in the backbone structure, branching patterns, and monosaccharide composition of their fucoidan, which directly impact its immunomodulatory and anti-inflammatory activities. Seasonal variation in the harvest time can also lead to fluctuations in molecular weight and the degree of sulfation, further contributing to inconsistencies in biological activity. Moreover, standardized protocols for the extraction and purification of fucoidan have yet to be established. Different studies employ diverse extraction methods—such as acid hydrolysis, enzymatic digestion, and ultrasound-assisted techniques—which vary greatly in their ability to preserve or degrade key functional groups within fucoidan molecule. These methodological inconsistencies affect structural integrity and biological function, resulting in products with variable molecular weights, purities, and sulfate content. Consequently, such variability undermines the reproducibility and comparability of research outcomes, limiting the controllability and scalability of fucoidan in clinical trials and pharmaceutical development.

Additionally, the optimal dosage of fucoidan required to initiate cardioprotective effects, particularly in promoting the resolution of post-MI inflammatory responses and protecting against cardiac injury, remains poorly defined. At present, research on the application of fucoidan in cardiovascular diseases remains largely confined to animal studies and *in vitro* models, and there is no clear consensus regarding the optimal dosage required to exert cardioprotective effects in humans. In particular, key aspects such as the resolution of post-myocardial infarction inflammation, suppression of immune overactivation, and prevention of myocardial fibrosis and remodeling lack systematic investigation in terms of fucoidan's effective dosage, administration frequency, and duration. Existing literature reports a wide range of doses—from a few milligrams to several hundred milligrams per day—with various administration routes including oral intake, intraperitoneal injection, and localized delivery, but no standardized guidelines have been established. These dosage inconsistencies likely correlate with differences in molecular weight, degree of sulfation, purity, and the source or method of fucoidan extraction, further complicating the identification of an effective dosing window. Moreover, fucoidan exerts bidirectional immunomodulatory effects: under certain conditions, it suppresses the release of pro-inflammatory cytokines, whereas in others, it may activate innate immune responses. This dose-dependent nature makes it a critical factor influencing both the safety and efficacy of treatment. High doses may trigger nonspecific immune activation or coagulation abnormalities, while insufficient doses may fail to deliver adequate anti-inflammatory benefits. Therefore, establishing a clear dose–response curve for fucoidan in the context of post-MI inflammation—along with identifying its therapeutic threshold and toxicity ceiling—is fundamental for its clinical application. The lack of high-quality dose-escalation clinical trials and comprehensive pharmacodynamic modeling further hampers its progression as a viable therapeutic agent in cardiology. Future studies should aim

**Table 1. The mechanisms of fucoidan that have the potential to improve the post-myocardial infarction inflammatory.**

| Mechanism | Effect | Description | Key Compounds/Components | References |
|---|---|---|---|---|
| Regulation of Gut Microbiota | Improvement of gut microbiota imbalance | Fucoidan increases the abundance of beneficial bacteria and reduces the abundance of harmful bacteria, enhancing gut barrier function and reducing the translocation of endotoxins | SCFAs, Probiotics | [21,22,23] |
| Enhancement of SCFA Production | Anti-inflammatory effects | Fucoidan promotes the production of SCFAs through fermentation, which inhibit the NF-$\kappa$B and MAPK signaling pathways, reducing the production of pro-inflammatory cytokines | SCFAs | [24,39,40,41] |
| Inhibition of Inflammatory Signaling Pathways | Reduction of pro-inflammatory cytokine secretion | Fucoidan inhibits the activation of NF-$\kappa$B and MAPK signaling pathways, reducing the secretion of pro-inflammatory cytokines and alleviating post-MI inflammatory responses | Fucoidan | [31,32,33,48] |
| Antioxidant Effects | Reduction of oxidative stress | Fucoidan is rich in antioxidants that neutralize free radicals, reduce oxidative stress, and protect cardiomyocytes | Polyphenols, Antioxidant enzymes | [26,59,60,61] |
| Modulation of Immune Responses | Balancing immune responses | Fucoidan modulates immune responses by regulating the gut microbiota and SCFA production, promoting the differentiation of regulatory T cells and inhibiting the secretion of pro-inflammatory cytokines, thereby reducing post-MI inflammation | SCFAs, Polyphenols | [63,64,65] |
| Protection of Cardiomyocytes | Reduction of cardiomyocyte damage | Fucoidan protects cardiomyocytes by inhibiting the NF-$\kappa$B and MAPK signaling pathways, reducing the secretion of inflammatory cytokines, and alleviating oxidative damage and apoptosis of cardiomyocytes | Fucoidan, Polyphenols | [29,57,58,62] |

NF-$\kappa$B, nuclear factor-kappa B; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; SCFAs, Short-chain Fatty Acids.

to develop dose-optimization models based on relevant biomarkers such as IL-6, TNF-$\alpha$, and hsCRP, while incorporating individual variability and disease stage. This will help formulate more precise and controllable fucoidan-based therapeutic strategies, thereby advancing its transition from experimental research to standardized clinical use.

Another area of potential improvement is the enhancement of fucoidan's bioactivity through the addition of specific probiotics or prebiotics. As a marine-derived sulfated polysaccharide, fucoidan exhibits extremely low absorption in the upper gastrointestinal tract. The majority of it reaches the colon in its intact form, where it undergoes fermentation and metabolism by gut microbiota. Studies have shown that fucoidan can serve as a selective substrate for modulating the gut microbial ecosystem, but its effectiveness is highly dependent on the composition of the host's microbiota. When combined with specific probiotics—such as Bifidobacterium, Lactobacillus, or Akkermansia muciniphila—the metabolic efficiency of fucoidan can be enhanced by enriching microbial populations capable of degrading complex polysaccharides. This microbial remodeling contributes to increased production of SCFAs, including butyrate, acetate, and propionate, which are well recognized for their anti-inflammatory, gut barrier-protective, and cardioprotective functions. For example, butyrate has been shown to inhibit HDACs, reduce oxidative stress, and modulate immune cell activity—effects that are particularly critical in the context of post-myocardial infarction repair. Moreover, the co-administration of fucoidan with functional prebiotics—such as inulin, galactooligosaccharides, or resistant starch—may produce synergistic effects. These combinations not only facilitate the degradation and absorption of fucoidan but also stimulate gut microbes to generate a range of secondary bioactive metabolites (e.g., polyphenol derivatives and bile acid conjugates), which exert physiological regulatory effects throughout the body. This approach aligns with the emerging trends in precision nutrition and microbiome-targeted therapy, offering the potential for more individualized and effective therapeutic interventions. Through the synergistic interaction between probiotics, prebiotics, and fucoidan, it may be possible to develop the next generation of functional formulations that enhance bioavailability, improve targeting efficiency, and reduce inter-individual variability in treatment outcomes.

To fully harness the cardiovascular protective potential of fucoidan, targeted research and technological advancements are needed to address these challenges. The development of highly advanced delivery systems would provide a platform for optimizing the therapeutic effects of fucoidan in clinical applications, particularly in modulating the inflammatory response following myocardial infarction.

## 7. Conclusion

In summary, fucoidan has shown significant potential in modulating post-myocardial infarction inflammatory responses through its interactions with the gut microbiota. By enhancing the abundance of beneficial bacteria, promoting the production of short-chain fatty acids, and inhibiting inflammatory signaling pathways, fucoidan may offer a novel therapeutic strategy for mitigating cardiac damage and improving recovery after MI. The multifaceted benefits of fucoidan, including its anti-inflammatory and antioxidant properties, further support its role in cardiovascular protection.

However, several challenges remain in translating these findings into clinical practice. Variability in fucoidan composition due to differences in source, extraction methods, and processing conditions complicates standardization. Additionally, optimal dosing strategies for fucoidan in humans are yet to be established, particularly for post-MI inflammation. The mechanisms of fucoidan that have the potential to improve the post-myocardial infarction inflammatory response are presented in Table 1 (Ref. [21,22,23,24,26,29,31,32,33,39,40,41,48,57,58,59,60,61,62,63,64,65]).

## Author Contributions

YZ and YL drafted the manuscript, YZ, YL and MK collected and sorted references, and YY designed and prepared the figures and tables. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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