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The Role of Omega-3 Fatty Acids and Gut Microbiota in Atherosclerosis Prevention: A Focus on Functional Food Innovation

Anum Tauqir[1], Ayesha Umer[2], Uzair Rehman[3], Mudasser Munawar[3], Ahsan Junaid[3], Hamna Batool[4], Noor Ul Ain[5], Zarish Noreen[6]

[1]Department of Nutrition and Dietetics, University of Management and Technology, Lahore, Punjab, Pakistan.
[2]Aquatic Diagnostic and Research Center, Bahria University, Karachi Campus, Sindh, Pakistan.
[3]Department of Food Science and Technology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Punjab, Pakistan.
[4]Department of Food Engineering, University of Agriculture, Faisalabad, Punjab, Pakistan.
[5]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Punjab, Pakistan.
[6]Department of Biological Sciences, International Islamic University, Islamabad, Pakistan.

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Correspondence to: Anum Tauqir, Department of Nutrition and Dietetics, University of Management and Technology, Lahore, Punjab, Pakistan.
Email: anum.tauqir58@gmail.com

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ABSTRACT

The leading cause of death worldwide is cardiovascular diseases (CVDs), which are mostly caused by atherosclerosis. This review examines the potential of omega-3 fatty acids as dietary modulators of the gut-heart axis and emphasizes the growing role of gut microbiota dysbiosis in CVD pathogenesis. Synopsis of the content: We present the powerful bioactive lipids known as omega-3 fatty acids (EPA, DHA, and ALA), which have been shown to have positive effects on inflammation and lipid metabolism. We describe their recently found ability to suppress pro-atherogenic metabolites such as trimethylamine-N-oxide (TMAO), improve the synthesis of beneficial short-chain fatty acids (SCFAs), and correct gut dysbiosis. Innovations in functional foods that combine omega-3s with probiotics and prebiotics for specific cardiovascular prevention are also covered in the review. omega-3-enriched functional foods have great potential as a microbiota-targeted, non-pharmacological approach to reducing atherosclerotic risk and fostering long-term cardiovascular health.

INTRODUCTION

With an estimated 17.9 million deaths per year and the top cause of death globally, cardiovascular diseases (CVDs) pose a serious threat to global health (1). The main pathological basis for the majority of CVDs, including coronary artery disease and stroke, is atherosclerosis, a chronic inflammatory disease of the arterial wall marked by the buildup of lipids, immune cells, and fibrous elements into plaques (2). For many years, the treatment of atherosclerosis has centered on reducing traditional risk factors like diabetes, smoking, high blood pressure, and hyperlipidemia. Despite the effectiveness of these initiatives, there is still a residual risk of cardiovascular disease, which has led to the search for new pathophysiological pathways and treatment targets.

The vast ecosystem of trillions of microorganisms that live in the gastrointestinal tract, known as the human gut microbiota, has become a crucial factor in host physiology and disease in recent years. Gut microbes and their metabolites have a significant impact on cardiovascular health, according to the "gut-heart axis" theory, which has gained significant traction and clarified a complex, two-way communication network (3). By controlling host lipid and cholesterol metabolism, modifying systemic inflammation, and generating bioactive metabolites that can either prevent or worsen vascular dysfunction, this axis produces its effects.

Because of their strong cardioprotective effects, omega-3 polyunsaturated fatty acids (PUFAs), in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have long been regarded as important dietary components. Their well-established mechanisms include boosting endothelial function, improving plasma lipid profiles by lowering triglycerides, and having strong anti-inflammatory and antioxidant effects (4). The advantages of omega-3 PUFAs, however, might go beyond these direct host effects, according to mounting data. According to recent preclinical and clinical

research, omega-3 fatty acids are potent gut microbiome modulators that can reduce the synthesis of pro-atherogenic metabolites like trimethylamine-N-oxide (TMAO), improve microbial diversity, and repair dysbiosis (5).

This review's main goal is to summarize the growing body of research that shows omega-3 fatty acids are an essential component of gut health and cardiovascular protection. We suggest that their advantageous remodeling of the gut microbiota and its metabolic output accounts for a sizable amount of their atheroprotective effects. Our goal is to present a thorough overview of the mechanisms relating to the prevention of atherosclerosis, gut microbial composition, and omega-3 intake. Additionally, by examining how functional food innovation can provide targeted, microbiota-centric nutrition for cardiovascular health a promising non-pharmacological approach to addressing the global burden of atherosclerosis we will highlight the translational potential of this knowledge.

Gut Microbiota and Atherosclerosis: Mechanistic Insights

Structure and Function of a Healthy Gut Microbiota

Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria are the four main bacterial phyla that dominate the complex and generally stable microbial community found in the human gut in a healthy state (6). The gut microbiota provides the host with essential services, so this symbiotic relationship is not passive. It facilitates the digestion of complex carbohydrates and dietary fibers that are otherwise indigestible by human enzymes. The synthesis of short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, is a major advantageous result of this fermentation (7). In addition to providing energy, SCFAs are essential for preserving the integrity of the gut barrier, controlling the activity of immune cells, and affecting systemic metabolism. Additionally, the gut microbiota produces some vitamins (like vitamin K and B vitamins), aids in defense against colonization by pathogenic organisms, and is crucial for the growth and education of the host immune system (8).

Dysbiosis and its Role in Cardiovascular Disease

A negative change in the gut microbiota's composition and function is called dysbiosis, and it is frequently typified by an increase in pathobionts (potentially harmful microbes), a decrease in overall diversity, and the extinction of beneficial species. Numerous factors, such as recurrent antibiotic use, ongoing psychological stress, and most importantly poor dietary patterns that are high in saturated fats, refined sugars, and low in dietary fiber, can cause this state (9). Dysbiosis's effects are essential to the pathophysiology of atherosclerosis. Increased intestinal permeability, or "leaky gut," is a defining feature of dysbiosis. This allows bacterial products, such as lipopolysaccharide (LPS), a strong endotoxin found in the cell wall of Gram-negative bacteria, to move into the portal circulation. Endotoxemia, a chronic condition of low-grade systemic inflammation, is brought on by this. It accelerates the development and instability of atherosclerotic plaques, activates innate immune pathways, and encourages endothelial dysfunction (10).

Microbial Metabolites: Direct Mediators of Atherogenesis

The production of a diverse range of metabolites by the gut microbiota has a profound impact on host physiology:

The TMAO Pathway

One of the gut-heart pathways that has been studied the most is the TMAO pathway. Certain gut microbes (such as those from the Clostridia and Desulfovibrio genera) convert dietary nutrients like choline and L-carnitine, which are found in abundance in red meat, eggs, and some fish, into trimethylamine (TMA). Following absorption, TMA is taken to the liver, where the enzyme flavin monooxygenase 3 (FMO3) converts it to trimethylamine-N-oxide (TMAO) (11). In large clinical cohorts, elevated plasma TMAO levels have been strongly associated with increased cardiovascular risk. By encouraging the formation of "foam cells" from cholesterol accumulation in macrophages, increasing platelet hyperreactivity and thrombosis, and causing vascular inflammation, TMAO contributes to atherosclerosis (12).

Short-Chain Fatty Acids (SCFAs)

SCFAs are generally regarded as protective, in contrast to TMAO. Colocytes primarily use butyrate as an energy source, which strengthens the intestinal barrier. Propionate can prevent the liver from synthesizing cholesterol, and both propionate and acetate enter the bloodstream and have anti-inflammatory and anti-proliferative effects on immune cells (7). One common characteristic of dysbiosis linked to CVD is a decrease in SCFA-producing bacteria.

Bile Acid Metabolism

Primary bile acids produced in the liver are biochemically changed into secondary bile acids by the gut microbiota. In addition to facilitating lipid absorption, this process produces signaling molecules that trigger host receptors, particularly the G protein-coupled bile acid receptor 1 (TGR5) and the farnesoid X receptor (FXR) (13). These signaling pathways, which are essential for controlling the metabolism of glucose, fats, and energy as well as inflammatory reactions, can be disrupted by dysbiosis, which can change the bile acid pool.

The Immunometabolic Link

The host's innate immune system receives a continuous low-grade stimulus from dysbiosis. Toll-like receptors (TLRs), especially TLR4, on immune and endothelial cells can be activated by microbial substances such as LPS. The production of important cytokines in atherogenesis, such as IL-6, TNF-α, and IL-1β, is increased as a result of this activation, which also sets off downstream pro-inflammatory signaling cascades like the NF-κB and NLRP3 inflammasome pathways (14). By encouraging the recruitment of monocytes, their development into macrophages, and the ultimate development of atherosclerotic plaques, these cytokines intensify the inflammatory response within the vascular wall. C-reactive protein (CRP), a systemic indicator of this inflammation, contributes to the risk of CVD and is a biomarker of it, generating a vicious cycle that accelerates the course of the disease.

Dietary Omega-3 Fatty Acids: Sources and Biological Roles

Omega-3 polyunsaturated fatty acids (PUFAs) are vital lipids that are necessary for human health but cannot be produced in large enough amounts from scratch, so they must be obtained through diet or supplements. Although their cardioprotective benefits are widely known, a better comprehension of their origins and complex biological functions is essential to understanding how they function within the gut-heart axis.

Classification and Chemistry

The primary omega-3 PUFAs of nutritional and physiological importance are:

Alpha-linolenic acid (ALA; C18:3, n-3): A fatty acid with three double bonds and an 18-carbon chain. It is a metabolic precursor to the longer-chain derivatives and the fundamental omega-3.

Eicosapentaenoic acid (EPA; C20:5, n-3): A fatty acid with five double bonds and a 20-carbon chain. An essential precursor to a group of powerful signaling molecules called eicosanoids is EPA.

Known for its function in neuronal structure and function, **docosahexaenoic acid** (DHA; C22:6, n-3) is a 22-carbon chain fatty acid with six double bonds that is also essential for reducing inflammation.

The "n-3" designation indicates the position of the first double bond from the methyl end of the fatty acid chain, a structural feature that dictates their biochemical behavior distinct from omega-6 fatty acids.

Dietary Sources

The two main categories of dietary sources of omega-3s plant and marine offer distinct profiles of these vital fats.

Marine Sources: These are the direct suppliers of pre-formed EPA and DHA.

Fatty Fish: The best natural sources are cold-water fatty fish like anchovies, sardines, mackerel, salmon, and herring.

Fish oils: A popular type of supplement, these oils are extracted from the tissues of these fish.

Krill Oil: Made from Antarctic krill, this oil mainly contains phospholipids of EPA and DHA, which may affect its bioavailability (15).

Microalgae: In the marine food chain, some types of algae are the main sources of EPA and DHA. Algal oils are becoming more and more popular in fortification as a sustainable, vegan-friendly source of these long-chain PUFAs (16).

Plant Sources: These provide ALA, which requires enzymatic conversion to EPA and DHA.

Seeds and Oils: Two of the best sources of ALA are flaxseeds (linseeds) and flaxseed oil. Hemp seeds, chia seeds, and their oils are also important sources.

Nuts: A significant source of ALA is found in walnuts and walnut oil.

Leafy Greens and Legumes: Vegetables like spinach and soybeans contain lower concentrations of ALA.

Biological and Molecular Effects

The varied and potent molecular and cellular mechanisms of action of EPA and DHA are the foundation of their well-established cardioprotective reputation.

Regulation of Lipid Metabolism

The nuclear transcription factor Peroxisome Proliferator-Activated Receptor-alpha (PPAR-α) is strongly activated by omega-3 polyunsaturated fatty acids, especially EPA. One of the most reliable clinical effects of PPAR-α is a significant decrease in circulating triglyceride levels, which is achieved by increasing the β-oxidation of fatty acids in the liver and decreasing the synthesis and secretion of very-low-density lipoprotein (VLDL) particles (17). They might also affect how VLDL is converted to LDL, which could lower the quantity of dense, tiny LDL particles which are very atherogenic.

-inflammatory Action

Their biological role is based on this. Arachidonic acid (AA), an omega-6 fatty acid, and omega-3 polyunsaturated fatty acids compete with each other for inclusion in phospholipids found in cell membranes as well as for the enzymes lipoxygenase (LOX) and cyclooxygenase (COX). As a result of this competition, less inflammatory (such as series-3 prostaglandins) or anti-inflammatory mediators are produced instead of pro-inflammatory eicosanoids derived from AA (such as series-2 prostaglandins and series-4 leukotrienes). Additionally, the production of Specialized Pro-Resolving Mediators (SPMs), such as resolvins, protectins, and maresins, which actively coordinate the resolution of inflammation, is facilitated by EPA and DHA (18). Additionally, they suppress the transcription and release of cytokines like IL-6 and TNF-α by directly blocking the activation of important pro-inflammatory signaling pathways, including NF-κB and the NLRP3 inflammasome (19).

Improvement in Endothelial Function

One of the main targets of omega-3 action is the endothelium, which is the inner lining of blood vessels. By increasing the synthesis of the powerful vasodilator nitric oxide (NO) and decreasing the synthesis of vasoconstrictors such as endothelin-1, DHA and EPA enhance endothelial function. Blood flow and vascular reactivity are enhanced as a result (20).

Modulation of Membrane Fluidity and Signaling

The highly unsaturated structures of EPA and DHA enhance membrane fluidity when they are incorporated into cell membranes. This physical alteration can modify intracellular signaling cascades in immune cells, platelets, and cardiomyocytes by changing the function of membrane-bound proteins such as receptors, ion channels, and signaling platforms. Their anti-arrhythmic and anti-thrombotic properties are based on this (21).

Recommended Intake and Bioavailability Issues

Intake recommendations have been established by international health bodies in recognition of the health benefits. For adults' cardiovascular health, the American Heart Association and the World Health Organization (WHO) recommend a daily minimum intake of 250–500 mg of combined EPA and DHA (22).

However, these suggestions are complicated by a number of factors:

Bioavailability
The way omega-3s are absorbed depends on how they are consumed. When taken without a meal that contains fat, ethyl ester forms which are frequently found in concentrated supplements may have a lower bioavailability than the natural triglyceride or phospholipid forms found in whole fish and krill oil because they require pancreatic lipase for hydrolysis (23).

The ALA Conversion Challenge
Although ALA can undergo a sequence of desaturation and elongation reactions to produce EPA and DHA, this process is extremely inefficient in humans, with conversion rates to EPA estimated to be less than 10% and to DHA at less than 5% (24). Age, sex, genetic polymorphisms, and a high dietary intake of omega-6 fatty acids which compete for the same enzymes all have an impact on this inefficiency. Therefore, the most dependable method of increasing body levels of pre-formed EPA and DHA and obtaining therapeutic benefits is through direct consumption of these substances from marine or algal sources.

Interplay Between Omega-3 Fatty Acids and Gut Microbiota
A vibrant area of nutritional research is the relationship between omega-3 fatty acids and gut microbiology, which demonstrates how these fatty acids function as prebiotic-like regulators of the microbial environment.

Omega-3 Influence on Microbial Diversity
Studies on both humans and animals consistently show that taking omega-3 supplements can drastically alter the gut microbiota. This is characterized by a decrease in the abundance of pro-inflammatory taxa from the Enterobacteriaceae family and an increase in beneficial genera like Lactobacillus, Bifidobacterium, Akkermansia (which is known for its mucin-degrading and barrier-strengthening properties), and Roseburia (which produces butyrate) (25).

Mechanisms of Microbiota Modulation
Through a number of direct and indirect mechanisms, omega-3 fatty acids alter the gut environment.

Production of Anti-inflammatory Lipid Mediators
Omega-3s produce SPMs like resolvins locally in the gut, which actively reduce intestinal inflammation and improve the conditions for the growth of good bacteria (22).

Modulation of Bile Acid Composition
Omega-3s change the chemical composition of the gut by affecting the bile acid profile of the host. The community structure can be shaped by these modifications, which can selectively inhibit or promote the growth of specific bacterial species due to the antimicrobial properties of bile acids (26).

Enhancement of the Mucosal Barrier
It has been demonstrated that omega-3 fatty acids increase the expression of tight junction proteins such as occludin and Zonula Occludens-1 (ZO-1). By strengthening the intestinal barrier, this lessens the translocation of LPS and the ensuing systemic inflammation, which may have an adverse effect on the composition of microorganisms (27).

Effects on Microbial Metabolites
The microbial community's metabolic output is directly impacted by omega-3 remodeling:

TMAO Suppression
Consuming omega-3 is linked to a reduction in microorganisms that encode the CutC/D enzymes, which are essential for the synthesis of TMA from choline and carnitine. This, in turn, lowers the substrate for the synthesis of TMAO (28).

SCFA Enhancement
Higher fecal concentrations of butyrate and propionate, which support an anti-inflammatory tone and better metabolic health, are the result of omega-3s supporting SCFA-producing companies such as Lachnospiraceae (25).

Influence on Host Immunity
One of the main points of contact between the microbiota and the host immune system is the gut-associated lymphoid tissue (GALT). Through their integration into immune cell membranes and their function in the synthesis of SPM, omega-3 fatty acids aid in the regulation of GALT, fostering an anti-inflammatory and tolerogenic state that reduces systemic inflammatory responses associated with atherosclerosis (29).

Omega-3 Mediated Modulation of Gut-Derived Metabolites in Atherosclerosis Prevention
Through important metabolic pathways, the advantageous alterations in the gut microbiota brought about by omega-3 fatty acids combine to directly prevent atherogenic effects. The precise ways that omega-3 fatty acids alter gut-derived metabolites to stop atherosclerosis are described in this section.

Direct and Indirect Suppression of the TMAO Pathway
Omega-3s use a multifaceted strategy to prevent TMAO-induced atherosclerosis. They primarily limit the production of the precursor TMA from dietary choline and L-carnitine by decreasing the number of TMA-producing bacteria in the gut (such as *Clostridiaceae* and *Desulfovibrionaceae*) (30). Additionally, there is growing evidence that the hepatic enzyme FMO3, which converts TMA to TMAO, may be downregulated as a result of the anti-inflammatory properties of EPA and DHA. Reduced foam cell formation, decreased platelet aggregation, and attenuated vascular inflammation are all directly correlated with lower plasma TMAO levels, which are the consequence of this dual action, which lowers substrate production and may limit its conversion (31).

Enhancement of SCFA Production and Signaling
Omega-3s increase the colonic production of butyrate, propionate, and acetate by stimulating the growth of bacteria that produce SCFAs, including Lachnospiraceae, Bifidobacterium, and Roseburia (25). Following their absorption into the bloodstream, these SCFAs cause different cell types' G-protein coupled receptors (GPR41 and GPR43) to become active. Improved lipid metabolism, increased secretion of gut hormones such as glucagon-like

peptide-1 (GLP-1) and peptide YY (PYY), which support satiety and metabolic health, and direct anti-inflammatory effects on immune cells are all results of activating these receptors (32). One of the main causes of systemic inflammation in atherosclerosis is butyrate, which is essential for preserving the integrity of the gut barrier and preventing the translocation of pro-inflammatory LPS into the bloodstream (33).

Modulation of Bile Acid Signaling and Metabolism

By directly influencing host synthesis and by modifying the microbial communities that convert primary bile acids into secondary bile acids, omega-3 fatty acids have an impact on the makeup of the bile acid pool. This change brought on by omega-3 promotes the synthesis of secondary bile acids, which are strong TGR5 receptor agonists. TGR5 activation on immune cells, including macrophages, reduces the production of pro-inflammatory cytokines and chemokines by blocking NF-κB-driven inflammation. This is a key mechanism by which omega-3s protect the vascular endothelium by causing systemic anti-inflammatory effects through microbial bile acid metabolism (26).

Integrated Anti-atherogenic Immune Modulation

A potent, systemic anti-atherogenic environment is produced by the combined effects of decreased TMAO, increased SCFAs, and altered bile acid signaling. Mechanistically, this is demonstrated by the downregulation of important inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Important early stages of atherogenesis, including monocyte adhesion to the activated endothelium and their subsequent differentiation into lipid-laden foam cells within the arterial intima, are prevented by this inhibition of the inflammatory cascade. Together, these effects stabilize pre-existing plaques and prevent the formation of new ones (34).

Functional Food Innovation for Atherosclerosis Prevention

The development of targeted, evidence-based functional foods has replaced general dietary recommendations in nutritional science as a result of the growing understanding of the gut-heart axis. Delivering bioactive substances, such as omega-3s, in forms that are palatable, stable, and efficient while blending in with everyday life is the goal of these innovations.

The Concept and Imperative of Functional Foods

Foods that offer a proven physiological advantage over basic nourishment, such as lowering the risk of chronic illness or improving general health, are referred to as functional foods. They offer a calculated, non-pharmacological method of lowering population-level risk in the context of atherosclerosis. Their growth depends on closing the gap between the established advantages of nutrients like omega-3s and the real-world difficulties of obtaining a steady and sufficient intake through diet alone (35).

Omega-3-Enriched Functional Foods: Formulations and Challenges

Omega-3 PUFAs have been successfully added to a variety of food matrices to improve their cardiovascular health profile.

- **Dairy Products:** Because of their fat content, which can help mask off-flavors and facilitate the absorption of omega-3s, yogurt, cheeses, and milk are common carriers.
- **Bakery and Cereal Products:** Stable plant-based ALA oils, such as flaxseed flour or microencapsulated omega-3 powders, can be used to fortify bread, muffins, and breakfast cereals.
- **Drinks:** Smoothies, fruit juices, and milk substitutes are being used more and more as delivery systems.
- **Spreads and Condiments:** Oils high in EPA, DHA, or ALA can be used to make salad dressings, mayonnaises, and margarines.

The main obstacle in this area is the long-chain PUFAs' intrinsic chemical instability. They are extremely prone to oxidation, which can result in rancidity, off flavors, and the creation of potentially hazardous compounds. To overcome this, advanced encapsulation technologies are needed, including:

Microencapsulation

To protect small droplets of omega-3 oil from oxygen, light, and moisture, they are coated with a protective wall material (such as proteins or carbohydrates) (36).

Nanoemulsions

producing incredibly fine oil-in-water mixtures that increase bioavailability and stability.

Liposomal Encapsulation

For improved protection and targeted delivery, omega-3s are encased in phospholipid bilayers that resemble cell membranes.

Synbiotic and Postbiotic Functional Foods: A Multi-Targeted Approach

The most cutting-edge functional foods for the gut-heart axis combine multiple ingredients in a synergistic way.

Synbiotics

These products combine omega-3s with prebiotics (like inulin and fructooligosaccharides) and/or probiotics (like particular strains of Lactobacillus or Bifidobacterium). The reasoning goes that probiotics directly introduce health-promoting microbes, prebiotics supply the fuel for good bacteria, and omega-3s produce an anti-inflammatory environment in the gut. Compared to any one element alone, this multifaceted strategy may have a bigger effect on host metabolism and microbial ecology (37).

Postbiotics

A very stable and secure substitute for live probiotics is provided by postbiotic formulations, a next-generation approach that uses inanimate microorganisms and/or their metabolic byproducts. For example, combining omega-3s with postbiotics made from bacteria that produce SCFA may directly send anti-inflammatory microbial signals to the host, guaranteeing a consistent and focused effect (38).

Industrial and Technological Advances
Innovation is also driving sustainability and efficiency.

Advanced Delivery Systems
In addition to encapsulation, technologies such as extrusion and spray chilling are enhancing the stability and durability of fortified goods.

Sustainable Sourcing
One important development is the move to omega-3s derived from algae. It offers EPA and DHA in a scalable, vegan, and ecologically friendly manner, avoiding issues related to overfishing and marine heavy metals (39).

Market and Regulatory Perspectives
Strong regulatory frameworks are necessary for these innovations to reach consumers. Certain health claims for omega-3s, such as "EPA and DHA contribute to the maintenance of normal blood cholesterol levels," have been approved by organizations like the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) (22). However, a high degree of scientific validation is needed for claims pertaining to altering the gut microbiota for cardiovascular benefits. Market acceptance and the impact on public health depend heavily on product safety and efficacy, consumer education regarding the gut-heart axis, and clear labeling.

Translational and Clinical Perspectives
It takes a critical evaluation of human evidence and the creation of individualized and useful implementation strategies to close the gap between compelling mechanisms and cutting-edge food technology and actual clinical application.

Evidence from Human Trials: Promise and Heterogeneity
The omega-3-gut-heart axis is supported by a number of studies on human interventions. In a randomized controlled trial, for example, omega-3 supplementation dramatically enhanced gut microbiota diversity and SCFA-producing bacterial abundance in middle-aged, healthy participants. Other studies have demonstrated that omega-3 consumption can correlate with changed plasma TMAO levels in addition to improving conventional risk markers (such as lowering triglycerides and CRP) (40).
The clinical data are not totally consistent, though. Study results frequently exhibit heterogeneity, which can be ascribed to various factors, including:

Baseline Status
Participants' dietary practices, gut microbiota composition, and starting omega-3 level all have a big impact on the response. Changes may be more noticeable in people with higher baseline dysbiosis (41).

Dose, Duration, and Form
Direct comparisons are made more difficult by the fact that the quantity, chemical form (triglyceride vs. ethyl ester), and duration of omega-3 administration differ between trials (23).

Study Population
Results vary depending on the subjects' health status (healthy vs. diabetic vs. established CVD patients) (42). To strengthen the body of evidence, large-scale, carefully monitored RCTs are still required to examine the effects of omega-3 fatty acids on hard cardiovascular endpoints as mediated by the microbiome.

The Dawn of Personalized Nutrition for the Gut-Heart Axis
This variable inter-individual response to omega-3 supplementation ushers in the era of precision nutrition and highlights the drawbacks of a one-size-fits-all strategy. Response to an omega-3 intervention may be predicted by an individual's distinct gut microbiota "enterotype," genetic polymorphisms in FMO3 or PUFA metabolic pathways, and overall dietary pattern (43). To optimize the cardiovascular benefits of omega-3 functional foods for each person, future dietary recommendations could be customized based on a combination of these factors.

Biomarkers for Monitoring Response and Efficacy
Strong biomarkers are required to track the effectiveness of interventions on the gut-heart axis in order to apply personalized nutrition and precisely evaluate the success of interventions in clinical trials. Among the promising applicants are:

- **Plasma TMAO:** As a readout of microbial metabolic activity and a direct pro-atherogenic metabolite (1).
- **Fecal SCFAs**: As an indicator of the metabolic output of beneficial microorganisms (7).
- **Plasma Oxylipin Profile:** The range of bioactive lipid mediators derived from omega-3s, such as hydroxy-EPAs and resolvins, offers a functional readout of their pro-resolving and anti-inflammatory properties in the host (44).
- **Inflammatory Cytokines:** Indicators of systemic inflammatory tone include inflammatory cytokines like IL-6, TNF-α, and hs-CRP (34).

Beyond standard lipid panels, incorporating these biomarkers into clinical practice and research will enable a more nuanced evaluation of an intervention's effectiveness.

Integration into Public Health and Dietary Guidelines
The evidence must be converted into practical recommendations for the greatest possible impact on public health. Future revisions to the national dietary guidelines for the prevention of cardiovascular disease should take into account:

1. **Emphasizing Direct EPA/DHA Intake:** stating unequivocally that eating fatty fish or sustainable algae sources is advised (45).
2. **Endorsing Fortified Foods:** recognizing the usefulness of functional foods enhanced with omega-3 that have been scientifically proven to be effective for people who are unable to meet dietary recommendations .(46)
3. **Promoting a Fiber-Rich, Plant-Based Diet:** promoting the use of prebiotic fibers to complement omega-3s by fostering a gut microbiota that produces SCFAs, thus establishing a comprehensive, microbiota-focused dietary pattern for cardiovascular health (47).

Omega-3 functional foods that target the gut-heart axis have the potential to become a key component of contemporary cardiovascular prevention strategies by

bringing together food technology, clinical science, and public health policy.

CONCLUSION

A fascinating story regarding the prevention of atherosclerosis is revealed by the complex interaction between the gut microbiota and dietary omega-3 fatty acids. In addition to their direct anti-inflammatory and hypolipidemic effects, omega-3 fatty acids are strong prebiotic-like modulators that alter the gut microbial community to a more diverse and beneficial state. This remodeling has systemic anti-inflammatory and anti-atherogenic effects by reducing the synthesis of pro-atherogenic metabolites like TMAO, increasing the synthesis of protective SCFAs, and modifying bile acid signaling.

A practical and long-term strategy for cardiovascular health is provided by the application of this science to innovative functional foods, such as omega-3 fortification, synbiotic formulations, and sophisticated delivery systems. Although there are still issues with clinical validation and tailored response, there is great potential for incorporating these foods into public health initiatives that are informed by precision nutrition and developing biomarkers. In the end, using omega-3 fatty acids to activate the gut-heart axis is a potent combination of food technology, microbiology, and nutrition that will usher in a new era of non-pharmacological cardiovascular disease prevention.

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