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Trimethylamine N-Oxide (TMAO): A Gut Microbiota-Derived Metabolite Linking Diet, Metabolism, and Cardiovascular Disease

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Abstract
Trimethylamine N-oxide (TMAO) is a metabolite of the gut microbiota that originates from dietary sources of nutrients such as choline, L-carnitine, and phosphatidylcholine. Microbial metabolism of these precursors yields trimethylamine (TMA) which is then oxidized to TMAO through hepatic flavin monooxygenase-3 (FMO3). Elevated circulating levels of TMAO have been linked to several cardiometabolic diseases including atherosclerosis, type 2 diabetes mellitus, obesity, non-alcoholic fatty liver disease (NAFLD), and chronic kidney disease. Suggested pathways linking TMAO to disease and disrupted cardiometabolic health include impaired cholesterol transport, increased platelet reactivity, endothelial dysfunction, and activation of pro-inflammatory pathways. Recently, studies have also implicated TMAO in cancer and metabolic syndrome. TMAO levels can be modulated by gut microbiota, and dietary interventions, prebiotics, probiotics, and synbiotics have been studied as food-based approaches to modulate TMAO levels. While strong associations have been made between TMAO and disease, precise mechanisms connecting TMAO to disease are unclear. Understanding these associations gives a necessity to review TMAO as a biomarker and therapeutic target in cardiometabolic disease and health.

Keywords: Trimethylamine N-oxide (TMAO), Gut microbiota, Cardiovascular disease, Metabolism, Probiotics

Introduction
Trimethylamine N-oxide (TMAO), a dietary compound with formula (CH3)3NO, is an amine oxide. An oxidized form of trimethylamine (TMA) is referred to as TMAO. TMAO possesses the ability to affect the structure and functionality of a broad diversity of physiologically important substances [1]. TMAO is involved in stabilizing the nucleic acid and folded protein state. TMAO inhibits protein denaturation and the reversal of heat and pressure effects, based on thermodynamic studies on its action on proteins. Several mechanisms are used to explain TMAO's folding propensity, based on the literature [1, 2]. The purpose of this review was to present the present state of knowledge regarding TMAO, biochemical properties, metabolic processes, and nutrient metabolism which serve as precursors to TMAO. The significance of the metabolism of TMAO and its role in human health are also emphasized. We presented and discussed the possible interactions between TMAO and intestinal microbiota. Care was not only taken to the possible role of intestinal microbiota-derived production of TMAO from the metabolism of nutrients, which in humans has been linked with a heightened risk of major adverse disorders. Next we showed the possible role of TMAO in the pathogenesis of different diseases, and the possible mechanisms that could ex-plain their connection. Lastly, we compared the existing analytical methods that are employed in the determination of TMAO in biological fluids [1-3].
TMAO is a low-molecular-weight, organic, gut microbiota-derived metabolite and is an emerging new potentially significant cause of enhanced atherosclerosis and cardiovascular risk Circulating TMAO levels rise after gut microbial metabolism of dietary L-carnitine and phosphatidylcholine-enriched foods, such as red meat, eggs, dairy foods, ubiquitous nutrients of the Western diet. Recently we described a new association between plasma levels of

TMAO and the Mediterranean diet in healthy normal-weight adults, with a distinct gender difference in this association [3]. The metabolic process of TMAO involves digestion of gut microbiota-derived amines with the generation of trimethylamine (TMA), which is further catabolized to TMAO through flavin-monooxygenase-3 (FMO3) in the liver. Much research has been done on the relationship between gut microbiota and metabolites produced by microbes and food makeup. There is a molecular link between TMAO, inflammatory pathways, atherosclerosis, type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVD), as numerous research have shown. In mice and men, atherosclerosis risks are specifically associated with levels of TMAO and its metabolites, betaine and choline, in the blood. Among the pro-atherosclerotic effects of TMAO proposed are the inhibition of the reverse cholesterol transport, albeit this effect was described in animal models only and the facilitation of human platelet hyperresponsiveness and thrombosis activity [3, 4]. Showed that in humans there is a dose-dependent positive correlation between TMAO circulating levels and elevated cardiovascular risk and mortality. However, in this metanalysis the population samples were not split based on the BMI classes. Showed that among patients with T2DM increased circulating levels of TMAO were significantly correlated with increased overall mortality by 2.07- to 2.7-fold, also after BMI adjustment. Recently, the close relationship between gut microbiota and either obesity and diseases related to obesity in humans on the one hand, and the relationship between the TMAO pathway and cardio-metabolic disorders on the other, implied that the TMAO pathway is also mechanistically involved in obesity pathogenesis [4]. The plasma TMAO levels were associated with obesity characteristics in the various inbred strains of mice on a high-fat diet and implied that the TMAO-forming pathway is associated with obesity and energy metabolism, although as yet, scientific evidence to establish this link in humans has not been reported. TMAO was positively correlated with BMI, insulin resistance, visceral fat mass, and liver fat content. It had positive correlations of the circulating levels of TMAO and two of its dietary precursors, choline, and betaine, with the presence and severity of NAFLD, the hepatic component of the MetS in a large hospital- and community-based sample of Chinese adults [4, 5].

Trimethylamine n-oxide (TMAO) synthesis and metabolism

The dietary components of TMA are taken up instantaneously and converted to TMA by numerous enzymes. Intestinal bacteria of the colon are responsible for its production largely from nutritional substrates of the metabolism of phosphatidylcholine/choline, carnitine, betaine, dimethylglycine, and ergothioneine [1, 2]. TMA is metabolized in the colon to methylamine, dimethylamine (DMA), and ammonia but is also taken up into the bloodstream and converted to TMAO by flavin monooxygenases of the liver (FMO1 and FMO3) [6]. The production of TMA and TMAO is preceded by choline and carnitine, which are more prevalent in a diet rich in these nutritional substrates. A common amine oxide produced by the oxidation of trimethylamine (TMA), an intermediate byproduct of the microbial metabolic pathway, is trimethylamine N-oxide (TMAO). Choline and L-carnitine from food can be the main sources of TMA, which intestinal bacteria can produce and enter into the bloodstream through the hepatic portal. Hepatic enzymes called flavin monooxygenases 3 (FMO3) further oxidize TMA in the host liver, producing TMAO as the final product that is incapable of further metabolism. The kidney can eliminate most of the TMAO in the urine unaltered in less than 24 hours. There has been recent focus given to trimethylamine-N-oxide (TMAO) as a potential cardiovascular disease (CVD) marker for diagnosis [2, 6]. Recent studies have indicated that elevated risk of CVD is associated with rising plasma concentrations of TMAO. Increased risk of myocardial infarction, stroke, and death was associated with higher levels of circulating TMAO, which were found to be present in various cohorts of cardiac patients with stable heart failure. It was found that in patients with chronic renal disease, plasma TMAO levels can independently forecast coronary atherosclerosis and mortality [7]. In addition, diabetes and reduced glucose tolerance were associated with increased TMAO levels. In recent years, TMAO has been associated with a higher risk of colorectal and prostate cancer. Even though there is definite correlation of TMAO with many chronic disorders, the precise mechanism by which TMAO causes development and progression of different diseases is not yet understood. Some of the mechanisms proposed to date include alterations of the host sterol/lipid biosynthetic pathway leading to alterations of the transport and excretion of cholesterol, alterations of platelet responsiveness, and activation of profibrotic pathways [6, 7]. Based on recent studies, leukocyte adhesion was enhanced in vivo and the nuclear factor-kappa B signal cascade and mitogen-activated protein kinase were activated. All of these results suggest the potential that TMAO induces vascular and endothelial inflammation, injury, and fibrotic process, all of which may contribute to atherogenesis. It is not yet known, therefore, how TMAO is involved in the initiation and progression of atherosclerotic vascular disease [5-7].

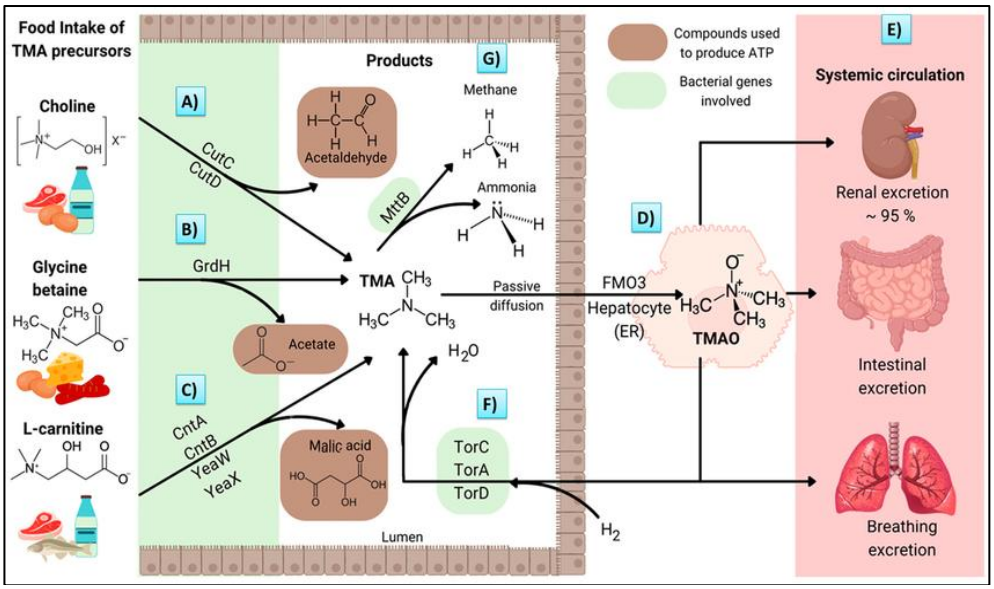

Fig 1: Illustration of the biosynthesis and metabolism of TMAO and the associated genes

Bacterial genes cntA and cntB produce trimethylamine (TMA), a precursor to TMAO. While cntA codes for a choline monooxygenase, the latter codes for a reductase that is dependent on NAD (P). Both enzymes break down and synthesize TMA and malic acid using carnitine as a substrate [8]. Furthermore, there are other genes that are closely related to cntA and cntB, like yeaW and yeaX, which code for a reductase and a monooxygenase, respectively. Together with the yeaX reductase, the YeaW monooxygenase synthesizes TMA using -butyrobetaine as an intermediary. Its functional domain is nearly identical to that of the cntA monooxygenase [8, 9].

Glycine betaine is the substrate in a third pathway for the production of TMA. Glycine betaine is reduced to acetate and TMA by a glycine betaine reductase, which is encoded by the grdH gene. The acetate molecule is then oxidized to supply electrons for the reduction of betaine. The gut microbiota produces a sizable amount of TMA, which passively diffuses through the enterocytes and into the portal circulation. After flavin-containing monooxygenase 3 (FMO3) reaches the liver, around 95% of TMA is changed into TMAO. There is still another pathway involving bacteria and TMAO. Under anaerobic conditions, TMAO is an electron acceptor for some bacteria species (e.g., Escherichia coli) thatcolonize the human intestine [10, 11].

The Developing Field of Cardiovascular Research: Atherosclerosis and TMAO

Early research that generated hypotheses identified novel compounds and the pathways that connect them that may be linked to cardiovascular risk using untargeted metabolomic analyses of plasma samples. Several metabolites whose levels in plasma were consistently linked to the risks of CVD were found through an iterative process of case-control studies that used an initial learning cohort, a second independent validation cohort, and a third, larger independent validation cohort (n = 1,876 subjects) (25). Three metabolites were identified by structural validation as being associated with the metabolism of phosphatidylcholine (PC; lecithin): choline (m/z 104), betaine (m/z 116), and TMAO (m/z 76) (25). Choline is reported to directly oxidize to betaine [12].

One recognized byproduct of choline's direct oxidation is betaine [10, 11]. Trimethylamine (TMA), an intermediate produced by bacteria's metabolism of choline, and flavin monooxygenase 3 (FMO3) in the liver were originally thought to be the sources of TMAO (28–31). PC is the main dietary source of choline for omnivores (32–34), and it has been demonstrated that consuming PC directly raises TMAO, betaine, and choline levels. Furthermore, our research revealed that the largest positive link between CVD risk and plasma levels of TMAO [8, 10]. The largest quantities of choline and L-carnitine are frequently found in foods high in cholesterol and lipids, such as red meat, liver, and egg yolk. Accordingly, our preliminary metabolomics studies indicated that plasma levels of three metabolites of dietary PC and gut microbiota might be associated to CVD in humans [12]. The association between eating eggs and cardiovascular risks has produced mixed findings, despite the fact that multiple large-scale epidemiologic studies have connected eating red meat with increased mortality and CVD risks [13]. A higher risk of CVD phenotypes is linked to plasma levels of all three metabolites (choline, betaine, and TMAO) found in the original metabolomics study in subjects presenting for cardiac risk evaluation (n = 1,876) [13]. Subsequent analyses in larger cohorts showed that the prognostic value was primarily limited to the formation of TMAO, particularly from choline and L-carnitine [7, 13]. In a different follow-up trial with more than 4,000 participants getting elective coronary angiography, higher TMAO levels were predictive of significant adverse cardiac events like mortality, myocardial infarction (MI), and stroke over a three-year span.In particular, patients with TMAO levels in the upper quartile (as opposed to the lowest quartile) had a lower overall event-free survival and a significant, 2.5-fold higher risk of suffering a major adverse cardiac event (MI, stroke, or death), regardless of conventional cardiovascular risk factors, renal function, or medication use [13, 14].

It has been shown that people with coronary heart disease (CHD) have higher plasma TMAO levels than healthy individuals, and that this difference is significantly greater in those who develop type-2 diabetes, which raises the risk of CVD. A prospective research of 593 individuals who had previously suffered their first ischemic stroke revealed a correlation between higher TMAO levels and an increased

chance of developing CVD issues in the future. Toru *et al*. conducted a cross-sectional study in which they examined 972 samples of patients with acute heart failure and came to the conclusion that plasma levels of TMAO were closely linked to renal dysfunction in patients with acute heart failure and helped predict risk for in-hospital death [13, 14, 15].
In a similar vein, Mafune *et al*. examined 227 individuals who had cardiovascular surgery and found that those in the top quartile for plasma TMAO levels had a noticeably greater number of infarcted coronary arteries. Additionally, the PREDIMED cohort found a strong correlation between elevated risk of major cardiovascular events and plasma TMAO(16).
The processes by which TMAO may cause the establishment of an aortic lesion have been assessed in animal research. FXR activation, which led to a decrease in the expression of cholesterol 7-alpha hydroxylase, was responsible for the observed increased aortic lesion formation in male apo E knockout mice given 0.3% TMAO for eight weeks. By boosting the expression of two scavenger receptors on the cell surface, cluster of differentiation 36 and scavenger receptor A, TMAO has been demonstrated in cell experiments to encourage the absorption of cholesterol in macrophages [16]. The activation of NLRP3 inflammasomes in mouse cell cultures exposed with TMAO suggests that TMAO has a role in endothelial damage, which is one of the initial stages in the development of atherosclerosis.
All of these research in humans, animal models, and cells either show a link between elevated TMAO levels and changes in metabolism (in the case of human studies) or they show how elevated TMAO concentrations may raise the risk of CVD (in the case of animal and cell studies [15, 16].

Diet and Gut Health Prebiotics and Probiotics Help Lower TMAO

The gut hosts trillions of microorganisms consisting of fungi, parasites, viruses, and bacteria. The microbiota represents an invisible organ of the human system creating homeostasis or disease in a person. Under normal conditions, such interactions are mostly symbiotic and affect a host's nutrition, metabolism, energy, and immunity. Current methodologies have provided insights into the function of the gut in a number of processes like absorption, distribution of nutrients and extraction of nutrients, synthesis of vitamins, immunomodulation, and protection against pathogens [2, 3, 5]. The composition of the microbiota may differ among individuals of the same ethnicity, age, or lifestyle because there is an intricate relationship between traditional genetic and environmental determinants. More than 50 phyla of bacteria exist in the gut, but there are two dominant phyla that control the gut microbiome: the Gram-positive Firmicutes (e.g., Enterococcus and Lactobacillus) and the Gram-negative Bacteroidetes (e.g., Bacteroides). The other phyla exist in varying quantities and comprise Actinobacteria (Bifidobacterium), Proteobacteria, and Verrucomicrobia. In total, several factors including the host's physiological conditions (e.g., age and stress), feeding habits, environmental conditions (e.g., use of drugs particularly antibiotic therapy), and infections of the intestine may modify the composition and diversity in intestinal microorganisms causing an environment of dysbiosis [5, 17-18]. This condition has been linked to the pathogenesis of both intestinal and extraintestinal disorders like irritable bowel syndrome, metabolic syndrome, obesity, diabetes, and cardiovascular system disorders. Reduced Bacteroides abundance; increased Lactobacillus, Enterobacteriaceae, and Streptococcus spp. abundance; increased Firmicutes to Bacteroidetes ratio have been linked to cardiovascular disease (CVD). All of them are most likely to increase the intestinal permeability with elevated systemic levels of bacterial products resulting in low-grade chronic inflammation [17]. This inflammation can trigger the development of atherosclerosis and has also been theorized to modify plasma lipid and lipoprotein concentrations. In spite of intensive studies in human and in animal models, the precise protective microorganisms depleted in dysbiotic cases and the exact molecular mechanisms responsible for disease are not known due to the complicated interplay between genetic and nongenetic factors. Evidence is found that the gut microbiome is implicated in the pathogenesis of CVD as studies reveal itsassociation with fluctuations in body mass index and blood lipids levels, irrespective of age, sex, and host genetics(17,18).Lowering of levels of cholesterol can be done with dietary modification and exercise, but only lipid-lowering medications are needed in specific cases where modification of lifestyle is not feasible or adequate to achieve targeted desired blood cholesterol level. It is worth noting that nonpharmacologic management should, whenever possible, be concomitant with lipid-lowering therapy because it optimizes a patient's result. Improvement in lifestyle can decrease LDLc by 5–15% and can result in significant CVD risk reduction. Notably, determinants of plasma lipids and atherosclerosis including intake of dietary fatty acids, carbohydrates, and dietary fibers as well as smoking, obesity and physical activity level, are also linked to alterations in the gut microbial ecosystem. Gut microbes are responsible for the biosynthesis of a variety of compounds involved in normal human physiological processes or eliciting disease [8]. Studies in the last decade have identified a number of important microbial metabolites including secondary bile acids, trimethylamine-N-oxide (TMAO) and short chain fatty acids (SCFAs) that could play a role in the development and pathogenesis of atherosclerosis. While these metabolites are excellently researched, the mechanisms by which they act to cause CVD are not well understood. That modulation of the production of these metabolites through a change in the microbial population through diet might be a non-pharmacological therapy for CVD is an exciting possibility [19].
The use of synbiotics, prebiotics, and probiotics has attracted significant attention as food supplements to shield the host from enteral issues. Probiotics add extra external bacteria in the intestinal tract whereas prebiotics enhance the rate of growth of one or more of such microorganisms in the host. Both these uses may be blended (i.e., synbiotics) to enhance the probiotic microorganism viability [19-20]. Therefore, the potential to modulate lipid profiles through the modulation of microbial communities to regulate SCFA and TMAO production through dietary interventions can be utilized as a therapeutic agent for enhancing human health and reducing hypercholesterolemia. Yet, it remains unclear which gut microbiota play the most significant roles in CVD, and the mechanisms in detail need to be explained investigation. Prebiotics are dietary non-digestible ingredients that may be fermented by gut microflora and induce the growth of advantageous bacteria that inhabit the

gut [20]. Prebiotics and probiotics both have the capability of modulating the gut microbiome, with resultant beneficial effects on the host. The beneficial impact of resveratrol (RSV), a natural polyphenol with prebiotic effects, on intestinal health, particularly on its capacity to induce a decrease in TMAO levels in vivo. RSV occurs naturally in grapes, berries, and other nutritional components, and is reported to be useful in the management of numerous metabolic disorders, such as atherosclerosis but its bioavailability is low. Evidence explained that phenolic phytochemicals of low bioavailability can,act by remodeling the gut microbiota. Based on the link between TMAO levels, gut microbiota, bile acid (BA) metabolism, and atherosclerosis, Chen *et al*. investigated the impact of RSV on TMAO-mediated atherosclerosis and the aforementioned factors in C57BL/6J and ApoE/mice. They were able to establish that RSV attenuated TMAO-induced atherosclerosis through the reduction of TMAO concentrations and amplification of hepatic BA neosynthesis via remodeling the gut microbiota. Furthermore, they were able to demonstrate that RSV-induced BA neosynthesis was partly mediated through downregulation of the enterohepatic farnesoid X receptor–fibroblast growth factor 15 (FXR/FGF15) axis [107-20].

In India, fermented milk beverages were recognized already 800–300 years B.C., and in Turkey in the 8th century. In Central Russia in the 12th century, a milk beverage called "ajran" was used, and "tarho" was taken in Hungary during the 14th century [5]. A special interest in lactic acid fermentation was demonstrated at the start of the 20th century by Russian scientist and immunologist at the Pasteur Institute in Paris, Nobel laureate in medicine for work on immunology (in 1907), Ilia Miecznikow. The following is a citation from his book "Studies on Optimism": "with different foods being fermented with lactic acid and eaten raw (sour milk, kefir, sauerkraut, pickles) human beings exposed humongous quantities of reproducing lactic acid bacteria to their alimentary canals Probiotic products contain one or several chosen microbial strains. Human probiotic microorganisms consist predominantly of the following geni: Lactobacillus, Bifidobacterium, and Lactococus, Streptococcus, Enterococcus.". In addition, Gram-positive bacteria belonging to the Bacillus genus and some yeast strains of the Saccharomyces genus are most widely used in probiotic preparations [6-8]. Probiotics are regulated by the residing general food law, stipulating that they must be safe for human and animal health [2, 1]. In the USA, ingesta used for the purpose of consumption must have the GRAS status, which is controlled by the FDA (Food and Drug Administration). EFSA coined the term of QPS (Qualified Presumption of Safety) in Europe. The concept of QPS includes certain other conditions of safety evaluation of bacterial supplements, such as the background on safe use and lack of the risk of acquired antibiotic resistance. probiotic microorganisms present in medicinal products and used as food additives. Probiotics can be beneficial for the cure of inflammatory enteral diseases, such as ulcerative colitis, Crohn's disease, and non-specific ileitis [20, 21]. The pathology of those diseases is not fully understood, but it is clear that they are linked to recurrent and chronic infections or inflammations of the intestine. Clinical trials have proven that probiotics induce the remission of ulcerative colitis, yet no beneficial effect on Crohn's disease has been noted. Many studies evaluated the utilization of probiotics in the cure of lactose intolerance, irritable bowel syndrome, and the prevention of colorectal cancer and peptic ulcers. Given their function in the inhibition of certain bacterial enzymes, probiotics can decrease the risk of colorectal carcinoma in animals. In humans, though, the same effect has not yet been approved in clinical trials [22]. A beneficial action on the urogenital system (prevention and treatment of Urinary Tract Infections (UTIs) and bacterial vaginitis) is a fine example of the advantages of using probiotics. There was a trial to administer probiotics to pregnant women and neonates in an effort to avert allergic diseases like atopic dermatitis.

Animal studies showed that orally taken Lactobacillus acidophilus causes expression of m-opioid and cannabinoid receptors by intestinal cells and modulate analgesic acts in the intestine, and that the effect found is similar to the effect of morphine. Yet, the effect has not been proven in humans. There are numerous accounts of using probiotics in the treatment of diarrhoea [8]. The use of Saccharomyces boulardii yeast in patients with acute, watery diarrhoea led to the cure and diminished frequency of that kind of complaint in two consecutive months. The effectiveness of probiotic strains in the treatment of nosocomial, non-nosocomial, and viral diarrhoeas has also been established. It appears that probiotics can enhance the level of IgA antibodies, which results in the halt of a viral infection. Antibiotic-associated diarrhoea (AAD) is a frequent side effect of the majority of antibiotics and Clostridium difficile disease (CDD), which also is triggered by antibiotics, and is a major cause of nosocomial diarrhoea and colitis outbreaks [023]. Probiotics for these two diseases are still controversial in use. Many types of different probiotics have the potential to be good therapies for these two diseases. Three types of probiotics (Saccharomyces boulardii, Lactobacillus rhamnosus GG, and mixtures of probiotics) using meta-analyses significantly decreased the occurrence of antibiotic-associated diarrhoea. S. boulardii alone was effective for CDD. Experiments conducted at a foster home in Helsinki (Finland) showed that the routine supplementation of Lactobacillus rhamnosus GG in the probiotic form led to a decreased count of respiratory tract infections. Other studies proved that the introduction of a diet low in fermented foods induced a reduction of congenital immunological response, as well as a drastic reduction of stool Lactobacillus level and of the stool content of short-chain fatty acids [23, 24].

Prebiotics of different types will promote the growth of various natural gut bacteria. Prebiotics have great scope for altering the gut microbiota, but such alterations take place at the strain and species levels and are difficult to predict in advance [24]. Moreover, gut environment, particularly pH, significantly affects the outcome of interspecies competition. Both for reasons of efficacy and of safety, prebiotic development aimed at benefiting human health must consider the highly individual species profiles that can occur Fruit, vegetables, cereals, and other edible plants are sources of carbohydrates that form potential prebiotics. The following can be cited as such potential souces: tomatoes, artichokes, bananas, asparagus, berries, garlic, onions, chicory, green vegetables, legumes, as well such as oats, linseed, barley, and wheat. Certain artificially synthesized prebiotics include, among others:lactulose, galactooligosaccharides, fructooligosaccharides, maltooligosaccharides, cyclodextrins, andlactosaccharose [6,

[8]. Lactulose accounts for a major proportion of manufactured oligosaccharides (up to 40%). Fructans, e.g., inulin and oligofructose, are thought to be the most utilized and efficacious with respect to many species of probiotics [8]. Research on colorectal carcinoma revealed that the illness arises less frequently in individuals frequently consuming vegetables and fruits. This action is owed predominantly to inulin and oligofructose. Amongst the benefits of those prebiotics, it is also possible to point out the lowering of the blood LDL (low-density lipoprotein) level, immunological system stimulation, higher absorbability of calcium, keeping correct intestinal pH value, low caloric content, and easing of symptoms of peptic ulcers and vaginal mycosis [24]. Other impacts of inulin and oligofructose on the health of humans are prevention of carcinogenesis, as well as the assistance in lactose intolerance or dental caries treatment.

Conclusion

Trimethylamine N-oxide (TMAO) has emerged as a crucial gut microbiota–derived metabolite that plays a significant role in human health and disease. Elevated TMAO levels are strongly associated with cardiometabolic disorders such as atherosclerosis, diabetes, obesity, non-alcoholic fatty liver disease, chronic kidney disease, and even certain cancers. Despite clear correlations, the exact molecular mechanisms through which TMAO contributes to disease progression remain only partially understood. Current evidence suggests that disruptions in cholesterol metabolism, endothelial dysfunction, platelet hyperactivity, and inflammatory pathways may collectively mediate these effects.

The modulation of gut microbiota through dietary interventions, prebiotics, probiotics, and synbiotics represents a promising non-pharmacological strategy to regulate TMAO levels and reduce disease risk. However, further research is essential to precisely identify the microbial species and molecular pathways involved, as well as to establish TMAO as a reliable biomarker and therapeutic target. Ultimately, a deeper understanding of the gut microbiota–TMAO axis could pave the way for novel diagnostic and therapeutic approaches in cardiometabolic health management.

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