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REVIEW ARTICLE

A Review on Molecular Mechanisms Linking Gut Dysbiosis to Chronic Metabolic, Cardiovascular, and Renal Disorders

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Abstract: The human gastrointestinal tract serves as a dense reservoir of microbiome whose metabolic outputs act as critical molecular bridges between the external environment and host internal physiology. Commensal mutualism preserves epithelial barrier function, coordinates immune tolerance, and regulates host energy harvesting. Similarly, compositional and functional gut dysbiosis disrupts barrier integrity, instigating pathobiont outgrowth, localized tissue destruction, and pathologic translocation of bioactive molecular intermediates. Structural disruptions in apical junctional complexes permit mucosal penetration of pathogen-associated molecular patterns, notably lipopolysaccharides, into systemic circulation. This microbially derived metabolic endotoxemia triggers chronic, low-grade systemic inflammation through toll-like receptor 4 signaling cascades across distal organ systems. Pathological shifts in microbial catabolism alter systemic concentrations of key regulatory metabolites. The selective depletion of beneficial short-chain fatty acids impairs host metabolic homeostasis, attenuates free fatty acid receptor 2 and 3 activation, and downregulates histone deacetylase inhibition. Parallel aberrant metabolic activity accelerates production of toxic intermediates, including trimethylamine, which undergoes hepatic conversion to pro-atherogenic trimethylamine N-oxide, alongside the excessive accumulation of protein-derived uremic toxins such as indoxyl sulfate and p-cresyl sulfate. These biochemical intermediates accelerate the pathophysiology of type 2 diabetes mellitus, systemic hypertension, atherosclerosis, and chronic kidney disease through oxidative stress, vascular endothelial dysfunction, and profibrotic signaling. Restoring microbially mediated metabolic equilibrium via dietary modulations, targeted postbiotic or probiotic supplementation, microbial enzymatic inhibition, and fecal microbiota transplantation could be a pivotal frontier in precision medicine.

Keywords: Gut microbiota; Dysbiosis; Microbial metabolites; Metabolic endotoxemia; Systemic inflammation.

1. Introduction

The adult human gastrointestinal tract hosts a diverse ecological reservoir comprising bacteria, archaea, fungi, protozoa, and viruses [1]. This microbial flora has coevolved with mammalian hosts to establish an obligate symbiotic relationship that regulates basal metabolic reactions, nutrient assimilation, xenobiotic processing, epithelial barrier preservation, and the structural maturation of both innate and adaptive immune lineages [2, 3]. Under physiological equilibrium, the gut microbiota maintains mutualistic homeostasis, excluding exogenous pathogens and calibrating host metabolic networks through continuous biochemical dialogue [4, 5].

Perturbations in microbial ecological balance—termed dysbiosis—are characterized by the depletion of commensal diversity, loss of obligate beneficial anaerobes, and the opportunistic expansion of facultative anaerobic pathobionts [6, 7]. A significant body of clinical and experimental literature indicates that gut dysbiosis is closely linked with the etiology and accelerated progression of chronic non-communicable diseases [8-10]. Alterations in microbiota structural configurations and their corresponding catalytic outputs are implicated in type 2 diabetes mellitus, metabolic dysfunction-associated steatohepatitis, atherosclerosis, arterial hypertension, and chronic kidney disease [11-14].

Deciphering the mechanistic continuum between localized intestinal dysbiosis and systemic conditions requires clarifying the biochemical intermediates generated by microbial catabolism. Rather than acting strictly as an isolated localized organ, the gut microbiota behaves as an active endocrine factory, converting non-digestible dietary substrates and endogenous host secretions into small-molecule metabolites [15, 16]. These biochemical mediators—ranging from regulatory short-chain fatty acids to hazardous metabolic toxins like trimethylamine N-oxide and indoxyl sulfate—cross impaired mucosal barriers and enter the portal and systemic circulation, where they engage specific host receptors and remodel epigenomic programs [17-19]. This manuscript examines the molecular mechanisms governing microbial metabolite biosynthesis, mucosal barrier disruption, and the biochemical cascades

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through which gut dysbiosis promotes systemic inflammation, metabolic derangements, cardiovascular remodeling, and progressive renal decline.

The human gastrointestinal tract harbors approximately 3.8×10^{13} microbial cells, establishing an absolute microbial-to-host cellular ratio approaching 1:1, with the dense bacterial aggregate situated predominantly within the colon [2, 3]. In contrast to this vast cellular biomass, overall taxonomic richness comprises an estimated 500 to 1,000 distinct microbial species per individual, drawn from a global human pan-microbiota cataloging thousands of distinct taxa [4, 5]. The non-redundant collective microbial gene pool, termed the gut microbiome, encompasses more than 3.3 million distinct genes, surpassing the coding capacity of the host eukaryotic genome by over 100-fold and equipping the host with extensive metabolic machinery for polysaccharide degradation, lipid regulation, and enzymatic biosynthesis [6, 7].

At the phylum level, the taxonomic architecture of the healthy adult intestinal tract is overwhelmingly dominated by two bacterial lineages: Bacillota (formerly Firmicutes) and Bacteroidota (formerly Bacteroidetes), which together constitute 70% to 90% of the total microbial population [6-8]. The remaining population is distributed among Actinomycetota (primarily *Bifidobacterium*), Pseudomonadota (including *Escherichia* and other Enterobacteriaceae), Verrucomicrobiota (dominated by the mucin-degrading specialist *Akkermansia muciniphila*), and minor proportions of Fusobacteriota, along with methanogenic archaea such as *Methanobrevibacter smithii* [8, 9].

Within Bacillota, prominent anaerobic genera such as *Faecalibacterium*, *Roseburia*, *Eubacterium*, *Coprococcus*, *Ruminococcus*, and *Blautia* specialize in carbohydrate fermentation and terminal butyrate biosynthesis [10, 11]. The Bacteroidota phylum is anchored by *Bacteroides* and *Prevotella*, which deploy expanded arrays of polysaccharide utilization loci to digest complex plant xylans, host-derived glycans, and pectins [12, 13].

Colonization commences dynamically during birth. The pioneer intestinal ecosystem of vaginally delivered infants reflects maternal vaginal and perianal inocula rich in *Lactobacillus* and *Bifidobacterium*, whereas infants delivered via Cesarean section exhibit primary colonization characterized by epidermal and nosocomial taxa, such as *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Klebsiella* [14, 15]. The pioneer microbial consortium rapidly diversifies during weaning and dietary transitions, transitioning toward an adult-like anaerobic consortium dominated by Bacteroidota and Bacillota by three to five years of age [16].

In healthy adults, daily microbial community composition oscillates in phase with host circadian cycles and feeding rhythms, stabilized by a functional core of conserved catalytic pathways [17]. In late senescence, however, this ecological resilience diminishes, characterized by reduced species richness, depletion of specialized butyrate-producing Bacillota, and the compensatory expansion of opportunistic Pseudomonadota [18, 19].

The intestinal mucosal interface forms an expansive biological filter that orchestrates a delicate balance: facilitating fluid and nutrient absorption while forming a tight physical and chemical barrier against luminal antigens, toxins, and pathobionts [20]. This functional separation is maintained by a specialized multilayered defense architecture comprising an overlying mucus barrier, a contiguous monolayer of intestinal epithelial cells, and a coordinated underlying lamina propria immune system [20, 21].

The physical cellular barrier consists of intestinal epithelial cells linked apically by junctional protein complexes (as shown in Figure 1). The most apical structures, tight junctions, act as gatekeepers for paracellular permeability, composed of transmembrane proteins including occludin, claudin family members (e.g., pore-sealing claudins 1, 3, 4, and 5; pore-forming claudin-2), and junctional adhesion molecules [21, 22]. These transmembrane assemblies are anchored to the perijunctional actomyosin cytoskeleton by peripheral intracellular scaffold proteins, predominantly zonula occludens-1, zonula occludens-2, and zonula occludens-3 [22, 23]. Beneath the tight junctions lie adherens junctions (composed of E-cadherin and catenin complexes) and desmosomes, which provide the structural rigidity and lateral cellular cohesion needed to endure shear stress [23].

Covering the apical brush border is a protective mucus hydrogel secreted by specialized goblet cells. In the colon, this barrier is organized into two distinct strata: an inner stratified mucus layer approximately 50 to 100 micrometers thick that remains largely sterile and imperious to bacterial penetration, and an outer non-attached layer that provides a nutritional niche for commensal taxa [24, 25]. Membrane-associated mucins (MUC1, MUC3, MUC17) create an apical protective brush border glycocalyx, while the gel-forming mucin MUC2 forms the main structural component of the polymeric mucus hydrogel [25]. Dispersed within this matrix are antimicrobial peptides (e.g., alpha-defensins, beta-defensins, RegIII-gamma) secreted by Paneth cells and enterocytes, alongside dimeric secretory immunoglobulin A produced by lamina propria plasma cells, neutralizing luminal pathobionts without triggering destructive inflammatory responses [26, 27].

Figure 1. Comparison of Intact Mucosal Homeostasis vs. Dysbiosis-Induced Tight Junction Breakdown and TLR4 Signaling

When local microenvironments undergo dysbiotic destabilization—triggered by low-fiber ultra-processed diets, chemical xenobiotics, alcohol ingestion, or chronic psychological stress—the mutualistic equilibrium deteriorates [28, 29]. Commensal communities deficient in fermentable dietary fiber are forced to consume host mucin O-glycans as alternative energy sources, degrading and thinning the inner protective mucus barrier [29, 30]. Pathobiont overgrowth generates cytotoxic metabolites, while proinflammatory cytokines (e.g., TNF-alpha, IFN-gamma, IL-1-beta) stimulate myosin light chain kinase activity, driving perijunctional actomyosin ring contraction, occludin internalisation, and claudin pore dysregulation [31, 32].

This deterioration in structural barrier integrity results in pathological intestinal hyperpermeability ("leaky gut"), facilitating the paracellular translocation of bacteria-derived immunogenic products into the lamina propria and mesenteric lymphatic vessels [33]. The primary driver of this systemic pathology is lipopolysaccharide (LPS), a major structural glycolipid located in the outer membrane of Gram-negative bacteria [34]. Translocated LPS enters the portal circulation and binds to circulating lipopolysaccharide-binding protein, which transfers monomeric LPS to cluster of differentiation 14 (CD14) and myeloid differentiation protein-2 (MD-2), forming a multimeric complex with toll-like receptor 4 on monocytes, macrophages, and endothelial surfaces [34, 35].

LPS-mediated dimerization of TLR4 activates two canonical intracellular cascades: the MyD88-dependent pathway, which recruits interleukin-1 receptor-associated kinases to activate the I-kappa-B kinase complex, releasing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa-B); and the TRIF-dependent pathway, driving interferon regulatory factor 3 phosphorylation [36, 37].

NF-kappa-B translocates into the nucleus, orchestrating the transcription of proinflammatory genes including TNF-alpha, IL-6, IL-1-beta, MCP-1, and inducible nitric oxide synthase [37]. This state of chronic low-grade inflammation, termed metabolic endotoxemia, suppresses insulin signaling, disrupts vascular endothelial relaxation, promotes ectopic lipid accumulation, and drives multi-organ dysfunction across cardiovascular, metabolic, and renal systems [38].

2. Biosynthesis and Signaling Mechanisms of Microbial Metabolites

Rather than acting merely as passive structural inhabitants of the lumen, gut commensals drive a metabolically active bioreactor. The small-molecule intermediates generated from dietary nutrients and endogenous host substrates diffuse through the mucosa, functioning as hormones, paracrine signals, and epigenetic modulators [39]. Three major metabolic axes mediate systemic pathological signaling (described in Figure 2): the fermentation of complex polysaccharides into short-chain fatty acids, the catabolism of quaternary amines into trimethylamine and trimethylamine N-oxide, and the proteolytic breakdown of aromatic amino acids into bioactive indoles and uremic toxins [40].

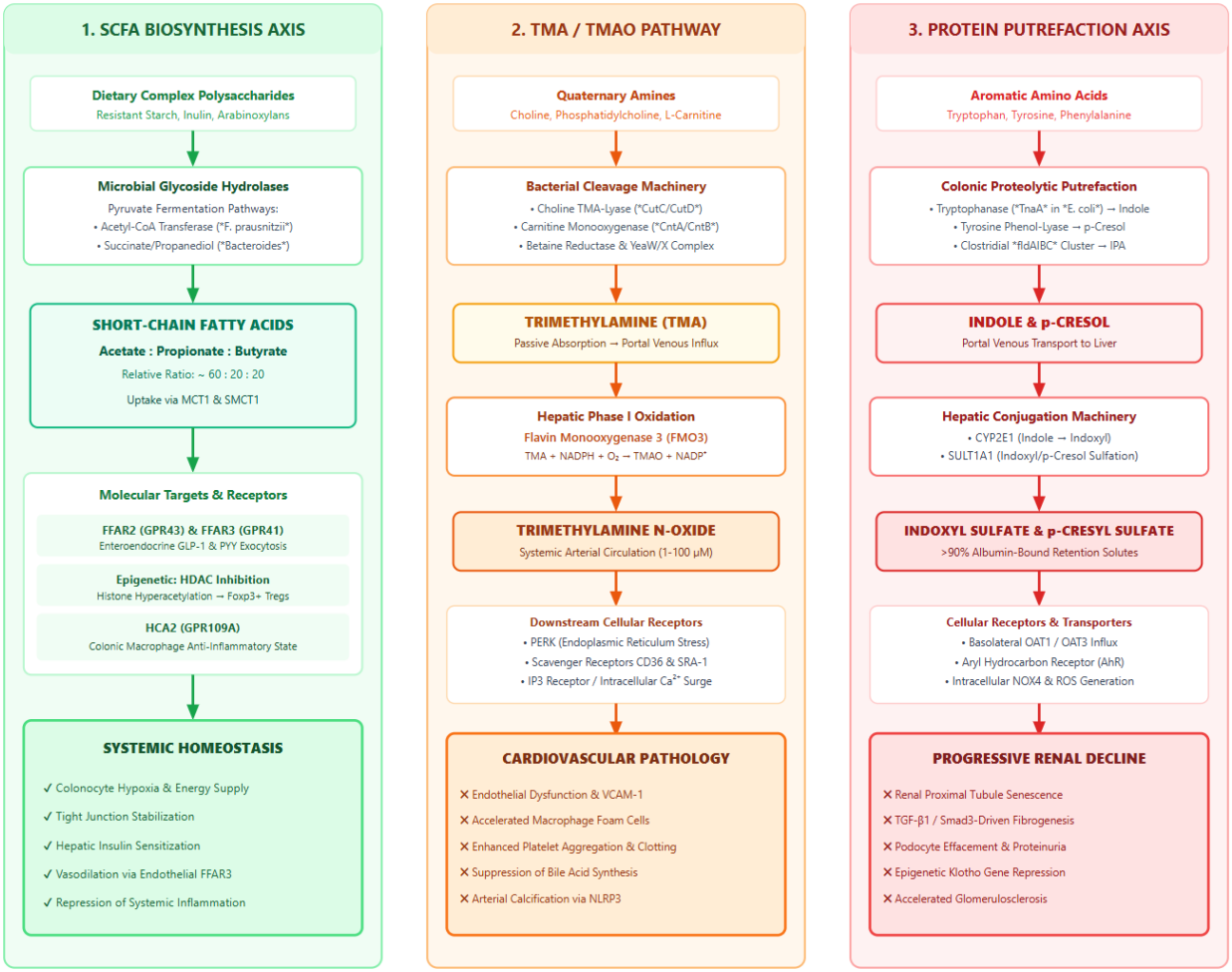

Figure 2. Enzymatic Transformations, Inter-Organ Transport, and Target Receptors of SCFAs, TMAO, and Uremic Toxins

2.1. Short-Chain Fatty Acids (SCFAs): Acetate, Propionate, and Butyrate

Short-chain fatty acids—primarily acetate, propionate, and butyrate, existing in a canonical molar ratio of approximately 60:20:20 in healthy human colonic lumens—represent the major end products of anaerobic microbial fermentation of non-digestible carbohydrates, including resistant starches, soluble plant non-starch polysaccharides, oligosaccharides, and host-derived glycans (described in Figure 3) [41, 42].

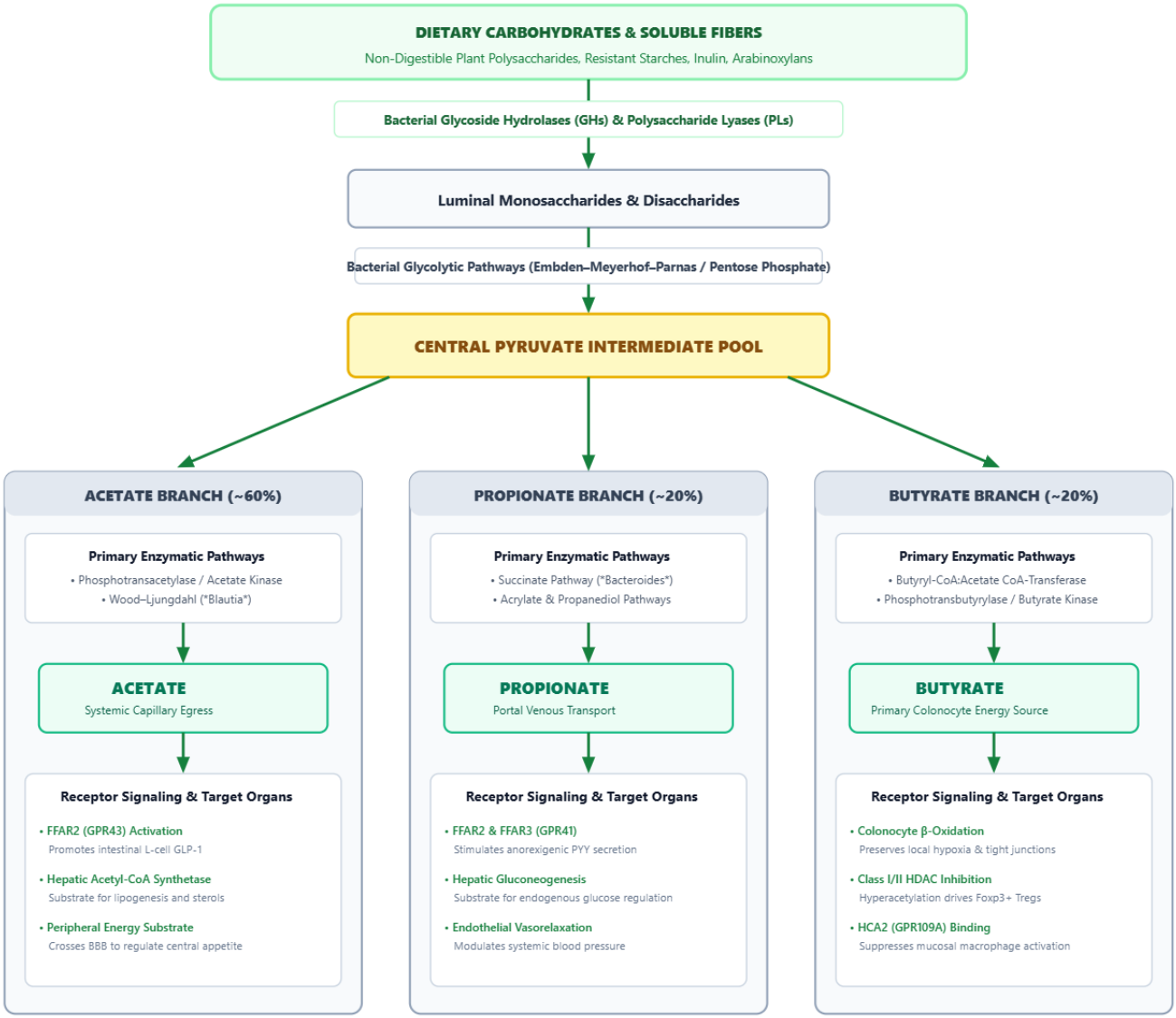

Figure 3. Microbial Fermentation of Dietary Polysaccharides to Short-Chain Fatty Acids

Acetate is synthesized through two distinct pathways: the dominant cleavage of pyruvate to acetyl-CoA via pyruvate-ferredoxin oxidoreductase, followed by conversion via phosphotransacetylase and acetate kinase, and the autotrophic Wood-Ljungdahl pathway utilized by acetogenic bacteria such as *Blautia hydrogenotrophica*, which fixes hydrogen and carbon dioxide directly into acetate [42, 43].

Propionate is generated through three distinct routes: the succinate pathway, predominantly utilized by Bacteroidota (*Bacteroides fragilis*) and certain Bacillota (*Veillonella*), wherein phosphoenolpyruvate is converted to succinate and subsequently decarboxylated; the acrylate pathway, employed by *Megasphaera elsdenii*, converting lactate to propionate; and the propanediol pathway, utilized by *Roseburia inulinivorans* to metabolize deoxy-hexoses like fucose and rhamnose [44, 45].

Butyrate is synthesized from two molecules of acetyl-CoA, which are condensed into acetoacetyl-CoA, reduced to beta-hydroxybutyryl-CoA, dehydrated to crotonyl-CoA, and reduced to butyryl-CoA [46]. The terminal formation of butyrate proceeds through two distinct enzymatic routes: the butyrate kinase pathway (utilizing phosphotransbutyrylase and butyrate kinase, found in *Coprococcus comes*), and the more prevalent butyryl-CoA:acetate CoA-transferase pathway (utilized by *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Eubacterium rectale*), which transfers the CoA moiety from butyryl-CoA onto external acetate, generating butyrate and acetyl-CoA [46, 47].

Upon synthesis, SCFAs are transported across colonocyte apical membranes via monocarboxylate transporter 1 (MCT1, encoded by *SLC16A1*) and sodium-coupled monocarboxylate transporter 1 (SMCT1, encoded by *SLC5A8*) [48]. Butyrate serves as the

primary metabolic fuel for colonic epithelial cells, undergoing mitochondrial beta-oxidation to supply up to 70% of their total energy demands, which maintains local epithelial hypoxia and preserves apical barrier integrity [49]. Unmetabolized propionate and acetate transit the mesenteric and portal circulation. Propionate undergoes hepatic uptake, serving as an allosteric substrate and regulator of hepatic gluconeogenesis and lipogenesis, while acetate reaches systemic circulation, crossing the blood-brain barrier and entering peripheral tissues to serve as a substrate for acetyl-CoA synthetase [50].

At the cellular level, SCFAs execute biological functions through two primary mechanisms: G-protein coupled receptor activation and epigenetic modification via histone deacetylase (HDAC) inhibition [51]. SCFAs bind to free fatty acid receptor 2 (FFAR2, or GPR43) and free fatty acid receptor 3 (FFAR3, or GPR41) [51, 52]. FFAR2 displays an affinity rank order of acetate = propionate > butyrate, coupling to both Gi/o and Gq/11 alpha subunits to suppress cAMP production, mobilize intracellular calcium, promote the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from enteroendocrine L-cells, and direct neutrophil chemotaxis [52, 53]. Conversely, FFAR3 preferentially responds to propionate and butyrate > acetate, coupling solely to Gi/o proteins to regulate vascular tone and sympathetic ganglionic signaling [53]. A third SCFA receptor, hydroxycarboxylic acid receptor 2 (HCA2, or GPR109A), is activated by butyrate, suppressing colonic macrophage activation and inhibiting adipocyte lipolysis [54].

Independently of membrane receptors, butyrate and propionate enter host cell nuclei where they act as direct endogenous inhibitors of Class I and Class II histone deacetylases (HDACs) [55]. By blocking HDAC catalytic pockets, butyrate prevents the removal of acetyl groups from the lysine tails of histone proteins H3 and H4 [55, 56]. This hyperacetylation opens chromatin architecture, facilitating the binding of RNA polymerase II and activating transcription factors such as forkhead box P3 (Foxp3) [56]. Within naive CD4+ T cells, this HDAC inhibition enhances Foxp3 expression, driving the peripheral differentiation of immunosuppressive regulatory T cells (Tregs) and suppressing the production of IL-17 and interferon-gamma, thereby preserving systemic immune self-tolerance [57].

2.2. Trimethylamine (TMA) and Trimethylamine N-Oxide (TMAO) Pathway

The microbial metabolism of quaternary amine-containing dietary compounds—principally phosphatidylcholine, free choline, L-carnitine, and betaine, which are abundant in red meat, egg yolks, high-fat dairy, and shellfish—is responsible for the downstream generation of pro-atherogenic trimethylamine N-oxide (illustrated in Figure 4) [58].

Figure 4. Quaternary Amine Cleavage and the Hepatic TMAO Axis

Because human digestive enzymes lack the ability to cleave the carbon-nitrogen bond in quaternary ammonium complexes, unabsorbed dietary precursors reach the dense microbial habitats of the distal ileum and cecum [58, 59]. There, specific bacterial enzymes catalyze carbon-nitrogen bond cleavage, releasing volatile trimethylamine gas [59].

Choline is cleaved into TMA and acetaldehyde via the bacterial choline TMA-lyase enzyme complex, encoded by the choline utilization (*Cut*) gene cluster [60]. The catalytic subunit CutC performs radical-mediated cleavage of the C-N bond, supported by the CutD activating protein, an S-adenosylmethionine-dependent enzyme [60, 61]. The CutC/D machinery is widely distributed across human gut microbes, notably within the Bacillota (e.g., *Clostridium*, *Ruminococcus*), Pseudomonadota (e.g., *Klebsiella pneumoniae*, *Escherichia coli*), and Actinomycetota phyla [61].

Similarly, L-carnitine undergoes enzymatic conversion to TMA through two distinct mechanisms: direct cleavage by the two-component rieske-type carnitine monooxygenase complex encoded by *CntA* and *CntB* (found in *Acinetobacter* and *Enterobacteriaceae*), or a sequential two-step pathway wherein L-carnitine is converted to gamma-butyrobetaine by the *bbx* gene cluster, followed by microbial cleavage to TMA via the oxygen-independent carnitine/gamma-butyrobetaine lyase *YeaW/YeaX* [62, 63].

Upon generation, hydrophobic TMA diffuses passively through the colonic mucosa into the mesenteric venous network and travels via the portal circulation to the liver [64]. In hepatocytes, TMA is oxidized by host flavin-containing monooxygenase enzymes, primarily flavin-containing monooxygenase 3 (FMO3), which catalyzes NADPH-dependent oxygen transfer to form trimethylamine N-oxide (TMAO) [64, 65]. TMAO is released into the systemic arterial circulation, where it reaches physiological concentrations between 1 and 5 micromolar in healthy individuals, but can exceed 100 micromolar in patients with severe renal failure or progressive atherosclerosis [65, 66].

TMAO disrupts host cardiovascular and metabolic physiology through multiple downstream mechanisms:

- In vascular endothelial cells, TMAO activates protein kinase C and reactive oxygen species pathways, triggering nuclear translocation of NF-kappa-B [67]. This upregulates vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which promotes trans-endothelial leukocyte recruitment and extravasation [67, 68].
- In macrophages, TMAO upregulates scavenger receptors CD36 and scavenger receptor A1, accelerating modified low-density lipoprotein uptake and promoting foam cell formation while simultaneously suppressing ATP-binding cassette transporter A1 (ABCA1)-dependent reverse cholesterol transport [69].
- In vascular smooth muscle cells, TMAO activates the nod-like receptor protein 3 (NLRP3) inflammasome and caspase-1, inducing inflammatory cell death and vascular calcification [70].
- In platelets, TMAO acts on intracellular storage pools to prime stimulus-dependent inositol 1,4,5-trisphosphate production, augmenting intracellular calcium mobilization, submaximal agonist sensitivity, and platelet aggregation, thereby accelerating arterial thrombus formation [71].

2.3. Tryptophan Catabolites and Protein-Derived Uremic Toxins

In the distal colon, the depletion of fermentable carbohydrates shifts microbial metabolism toward protein fermentation (proteolytic putrefaction) [72]. Anaerobic bacteria ferment dietary and host-derived proteins into aromatic amino acids: tryptophan, tyrosine, and phenylalanine [72, 73]. The microbial catabolism of these aromatic substrates generates diverse bioactive small molecules, including beneficial indole derivatives alongside precursors of cytotoxic uremic toxins [73].

Tryptophan catabolism proceeds along two divergent enzymatic axes. Approximately 90% of dietary tryptophan is utilized by the host kynurenine pathway, but the remainder is processed by colonic microbes [74]. Gut bacteria expressing the enzyme tryptophanase (TnaA)—such as *Escherichia coli*, *Proteus vulgaris*, *Bacteroides fragilis*, and *Clostridium* species—catalyze the hydrolytic beta-elimination of tryptophan, yielding indole alongside pyruvate and ammonia [75].

Indole is absorbed into the portal vein and transported to the liver, where it undergoes phase I oxidation by cytochrome P450 enzymes (predominantly CYP2E1 and CYP2A6) to produce 3-hydroxyindole (indoxyl) [76]. Subsequently, hepatic cytosolic sulfotransferase 1A1 (SULT1A1) sulfates this intermediate to generate indoxyl sulfate (IS), a potent, protein-bound uremic solute [76, 77].

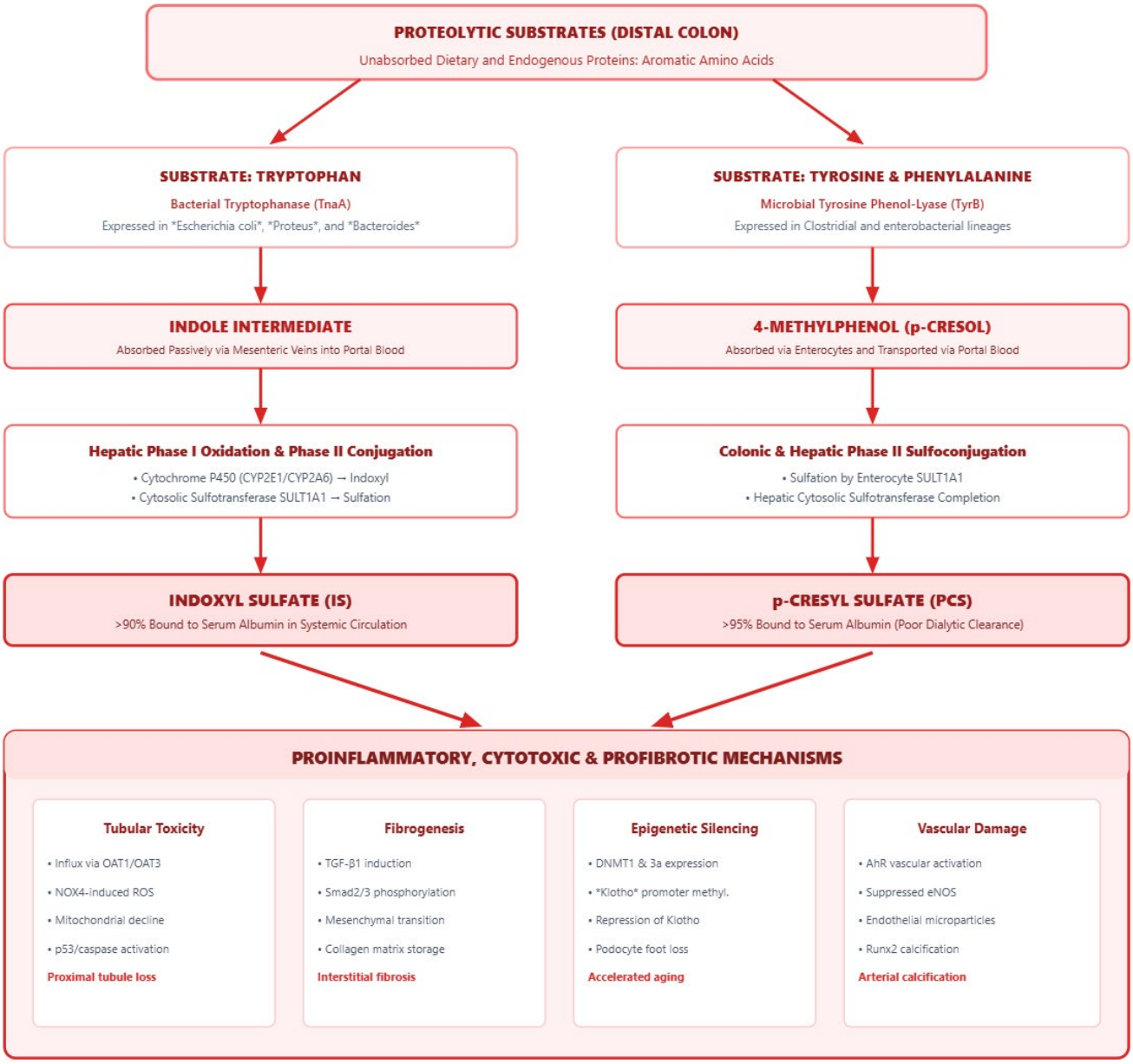

Figure 5. Colonic Proteolytic Putrefaction and Uremic Toxin Generation

Other commensals direct alternative tryptophan conversions that yield indole-3-propionic acid (IPA), indole-3-acetic acid (IAA), indole-3-aldehyde (IAld), and tryptamine [78]. The conversion of tryptophan to IPA is mediated by the phenyllactate dehydratase gene cluster (*fldAIBC*) in species such as *Clostridium sporogenes* and *Peptostreptococcus anaerobius* [78, 79]. IPA preserves homeostatic epithelial integrity by acting as an agonist for the pregnane X receptor (PXR) and the aryl hydrocarbon receptor (AhR), reinforcing tight junctional occludin and downregulating enterocyte proinflammatory signaling [79, 80].

Conversely, indoxyl sulfate exerts cytotoxic and pro-fibrotic effects. Pathologically elevated indoxyl sulfate enters renal tubular epithelial cells, podocytes, and vascular smooth muscle via organic anion transporters 1 and 3 (OAT1/OAT3) [81]. Within renal parenchyma, indoxyl sulfate activates the nuclear transcription factor AhR, inducing excessive production of reactive oxygen species via NADPH oxidase 4 (NOX4) [82]. This triggers the profibrotic transforming growth factor-beta 1 (TGF-beta 1) / Smad3 axis, promoting progressive tubulointerstitial fibrosis and glomerulosclerosis [82, 83]. In vascular tissue, indoxyl sulfate disrupts endothelial nitric oxide synthase (eNOS) phosphorylation, accelerates vascular calcification, and upregulates monocyte chemotactic protein-1 (MCP-1) [83].

Tyrosine and phenylalanine catabolism follows a similar pathogenic route. Colonic microbes expressing tyrosine phenol-lyases convert tyrosine into 4-methylphenol (p-cresol) [84]. During transcellular absorption across colonic enterocytes and within

hepatocytes, p-cresol is sulfated by cytosolic sulfotransferase SULT1A1 to form p-cresyl sulfate (PCS) [84, 85]. In circulation, p-cresyl sulfate is 90% to 95% bound to albumin, which restricts its clearance by glomerular filtration or standard hemodialysis [86]. p-Cresyl sulfate exerts direct toxic effects on vascular and renal tissues, activating leukocyte free radical production, inducing shedding of endothelial microparticles, disrupting mitochondrial membrane potential, and promoting renal tubular cell apoptosis [86, 87].

3. Pathophysiological Crossroads: Dysbiosis and Chronic Diseases

The dysregulation of intestinal mucosal permeability, coupled with pathological alterations in microbial metabolite profiles, drives systemic inflammation and multiorgan dysfunction [88]. Chronic metabolic, cardiovascular, and renal conditions share core dysbiotic signatures, characterized by a reduction in obligate butyrate-producing anaerobic bacteria, depletion of structural barrier integrity, and the sustained accumulation of pro-atherogenic, insulin-desensitizing, and cytotoxic metabolites [89].

3.1. Type 2 Diabetes Mellitus and Metabolic Syndrome

Type 2 diabetes mellitus (T2DM) and its precursor, metabolic syndrome, are characterized by peripheral insulin resistance, inadequate compensatory insulin secretion by pancreatic beta-cells, systemic low-grade inflammation, and hepatic gluconeogenic dysregulation (illustrated in Figure 6) [90]. Metagenomic sequencing demonstrates distinct taxonomic and functional shifts in the gut microbiota of patients with T2DM [91]. These profiles are characterized by the selective depletion of obligate butyrate-producing taxa within the Bacillota phylum—including *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, *Eubacterium rectale*, and *Subdoligranulum*—along with the opportunistic expansion of facultative anaerobes and pathobionts such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Eggerthella lenta* [91, 92].

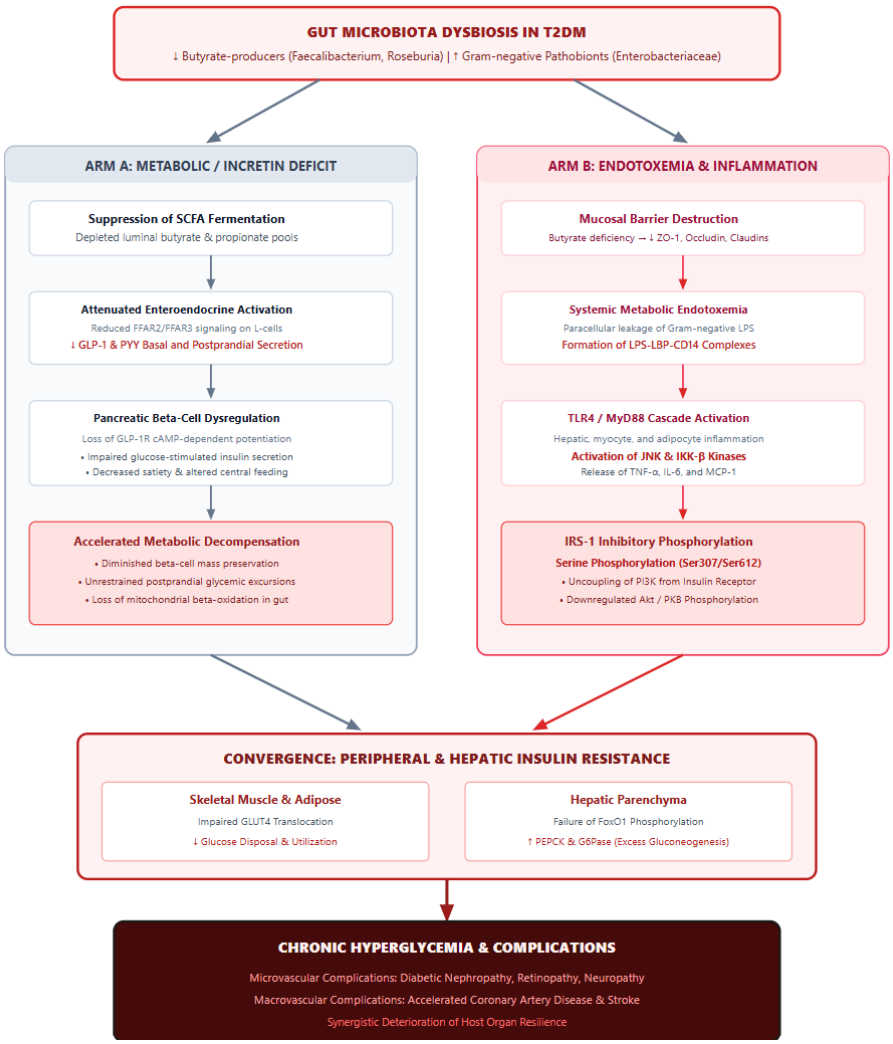

Figure 6. Molecular Mechanisms of Gut Dysbiosis in Type 2 Diabetes Mellitus

The loss of SCFA-producing bacteria directly impairs metabolic regulation. Butyrate and propionate activate FFAR2 and FFAR3 on enteroendocrine L-cells, triggering cyclic AMP and intracellular calcium cascades that stimulate the exocytosis of GLP-1 and PYY into the mesenteric capillaries [93]. GLP-1 binds to receptors on pancreatic beta-cells to augment glucose-dependent insulin secretion, while centrally suppressing gastric emptying and hypothalamic hunger signaling [93, 94].

Depletion of these microbial fermenters lowers luminal SCFA concentrations, impairing GLP-1 secretion and accelerating postprandial glycemic excursions [94]. Diminished colonic butyrate levels deprive colonocytes of their primary energy source, downregulating the synthesis of tight junction proteins (ZO-1, occludin, and claudin-1) and inducing mucosal hyperpermeability [95].

This barrier breakdown facilitates the translocation of luminal LPS into the portal venous circulation, establishing chronic metabolic endotoxemia [96]. Circulating LPS binds to the TLR4/MD-2 receptor complex on hepatocytes, skeletal myocytes, and adipocytes [96, 97].

TLR4 activation engages MyD88-dependent signaling, activating two serine/threonine kinase complexes: c-Jun N-terminal kinase (JNK) and inhibitor of kappa-B kinase beta (IKK-beta) [97]. Phosphorylated JNK and IKK-beta directly catalyze the inhibitory serine phosphorylation of insulin receptor substrate 1 (IRS-1) at sites Ser307 and Ser612, disrupting downstream tyrosine phosphorylation of IRS-1 by the activated insulin receptor kinase [98]. This blocks the recruitment of phosphatidylinositol 3-kinase (PI3K) and the subsequent phosphorylation of protein kinase B (Akt/PKB) [98, 99].

In skeletal muscle and adipose tissue, suppressed Akt activation prevents the translocation of glucose transporter 4 (GLUT4) storage vesicles to the plasma membrane, attenuating glucose uptake [99]. In hepatocytes, attenuated Akt signaling fails to phosphorylate and inhibit forkhead box protein O1 (FoxO1), leading to the unchecked transcription of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, which sustains unsuppressed hepatic gluconeogenesis despite elevated systemic insulin levels [100]. Elevated branched-chain amino acid (BCAA) synthesis by pathobionts such as *Prevotella copri* and *Bacteroides vulgatus* worsens mammalian target of rapamycin complex 1 (mTORC1) hyperactivation, exacerbating systemic insulin resistance [101].

3.2. Cardiovascular Disease: Atherosclerosis, Heart Failure, and Hypertension

Cardiovascular diseases, including atherosclerosis, heart failure, and arterial hypertension, are shaped by microbially derived metabolites and barrier breakdown [102]. Metagenomic evaluations reveal distinct functional dysbiosis in hypertensive and coronary artery disease cohorts, characterized by an elevated Bacillota-to-Bacteroidota ratio, loss of protective *Lactobacillus* and *Bifidobacterium* species, and the overrepresentation of TMA-generating taxa [103, 104].

In atherosclerosis, microbial TMA production acts as an independent risk factor for plaque development and rupture [105]. Upon hepatic conversion of TMA to TMAO by FMO3, circulating TMAO interacts with vascular endothelial cells to induce intracellular oxidative stress and activate the NF-kappa-B signaling pathway [105, 106]. Endothelial NF-kappa-B activation upregulates vascular adhesion molecules, facilitating monocyte arrest, adhesion, and trans-endothelial migration into the subendothelial intima [106].

Within the subendothelial space, TMAO upregulates the expression of macrophage scavenger receptors CD36 and SRA-1, accelerating the uptake of oxidized low-density lipoprotein (oxLDL) particles [107]. This unchecked intracellular lipid accumulation drives the transformation of vascular macrophages into lipid-laden foam cells, the hallmark of fatty streak formation [107, 108]. TMAO suppresses hepatic bile acid synthetic enzymes, specifically cholesterol 7-alpha-hydroxylase (CYP7A1) and sterol 27-hydroxylase (CYP27A1), while downregulating ATP-binding cassette transporters ABCA1 and ABCG1 in peripheral macrophages [108]. This disrupts reverse cholesterol transport, impairing cholesterol clearance from arterial walls (as shown in Figure 7) [109].

TMAO lowers the threshold for platelet activation by enhancing submaximal agonist-stimulated inositol 1,4,5-trisphosphate production and triggering release of intracellular calcium from the platelet endoplasmic reticulum [110]. This platelet hyperreactivity accelerates thrombus formation at sites of endothelial erosion or plaque rupture, increasing the risk of acute myocardial infarction and stroke [110, 111].

In arterial hypertension, dysbiosis-mediated vascular dysfunction centers on the disruption of counter-regulatory SCFA signaling and persistent vascular wall inflammation [112]. Commensal SCFAs regulate systemic vascular resistance through two distinct receptors: FFAR3, located in vascular endothelial and smooth muscle cells, which responds to propionate and butyrate to promote vasorelaxation via endothelial nitric oxide release; and olfactory receptor 78 (Olfr78, and its human ortholog OR51E2), expressed in the renal juxtaglomerular apparatus, which stimulates renin secretion, driving blood pressure elevation [113, 114]. In physiological states, the vasodilatory effect of FFAR3 balances the renin-releasing action of Olfr78 [114].

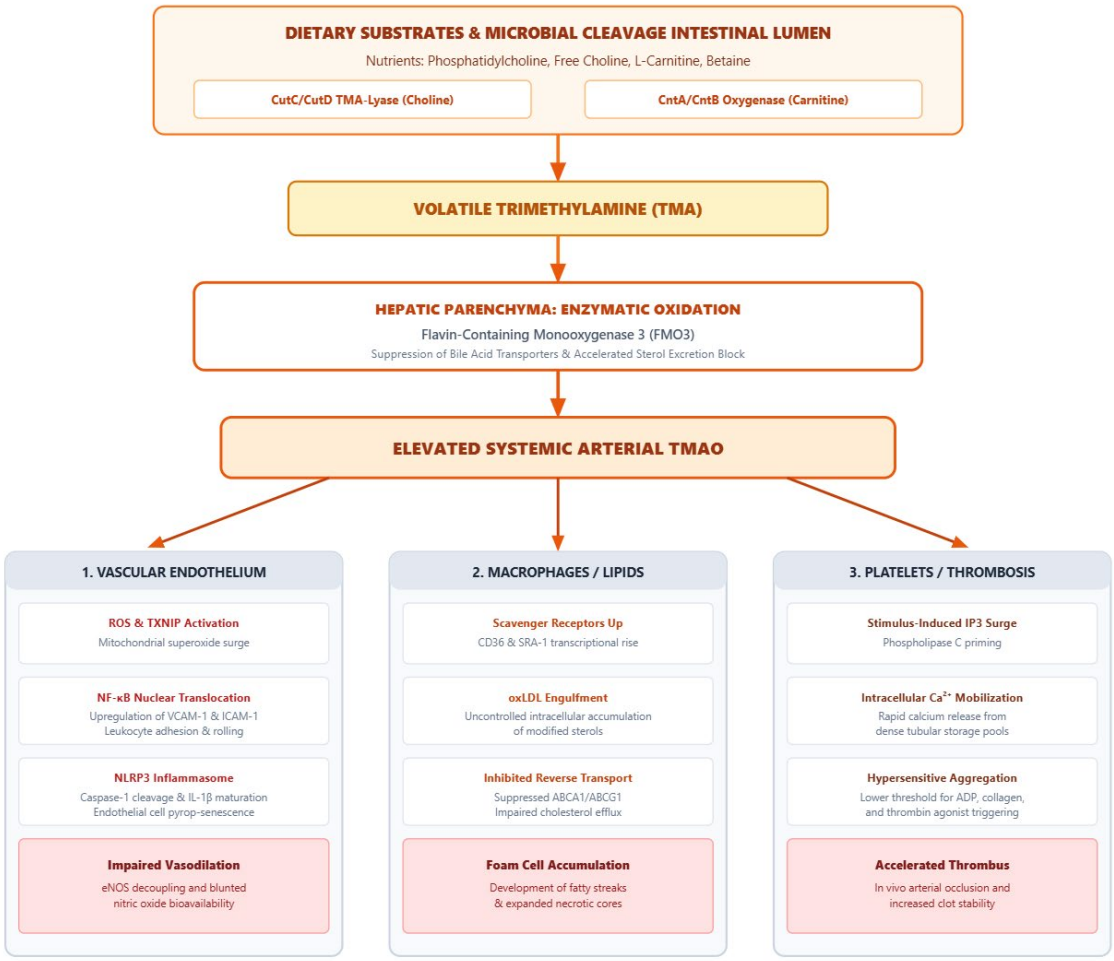

Figure 7. Microbial-Endothelial Signaling Axes in Cardiovascular Diseases

In hypertensive patients, loss of SCFA-producing taxa disrupts this equilibrium, leaving Olfr78 unopposed and impairing FFAR3-mediated vasodilation [114, 115]. High-salt intake selectively depletes *Lactobacillus murinus*, accelerating downstream Th17 cell expansion and IL-17A production, which blunts endothelial nitric oxide synthase phosphorylation, elevates vascular smooth muscle tone, and drives arterial wall stiffness [115, 116].

Heart failure introduces a self-reinforcing gut-cardiac loop: decreased cardiac output and systemic venous congestion induce intestinal microcirculatory hypoperfusion, bowel wall edema, and mucosal hypoxia [117]. The resulting disruption of tight junction complexes promotes the unchecked paracellular translocation of bacterial endotoxins into the systemic circulation [117, 118]. This circulating LPS activates myocardial TLR4 complexes, upregulating myocardial TNF-alpha, IL-1-beta, and IL-6 production, which induces cardiomyocyte apoptosis, myocardial fibrosis, and negative inotropic responses that accelerate progressive ventricular decompensation [118].

3.3. Chronic Kidney Disease and the Gut-Kidney Axis

The relationship between gut dysbiosis and chronic kidney disease (CKD) forms an interconnected feedback loop termed the "gut-kidney axis" [119]. Progressive nephron loss impairs the renal clearance of nitrogenous metabolic end products, leading to the passive accumulation of urea in the circulation and mucosal capillary beds (as shown in Figure 8) [119, 120].

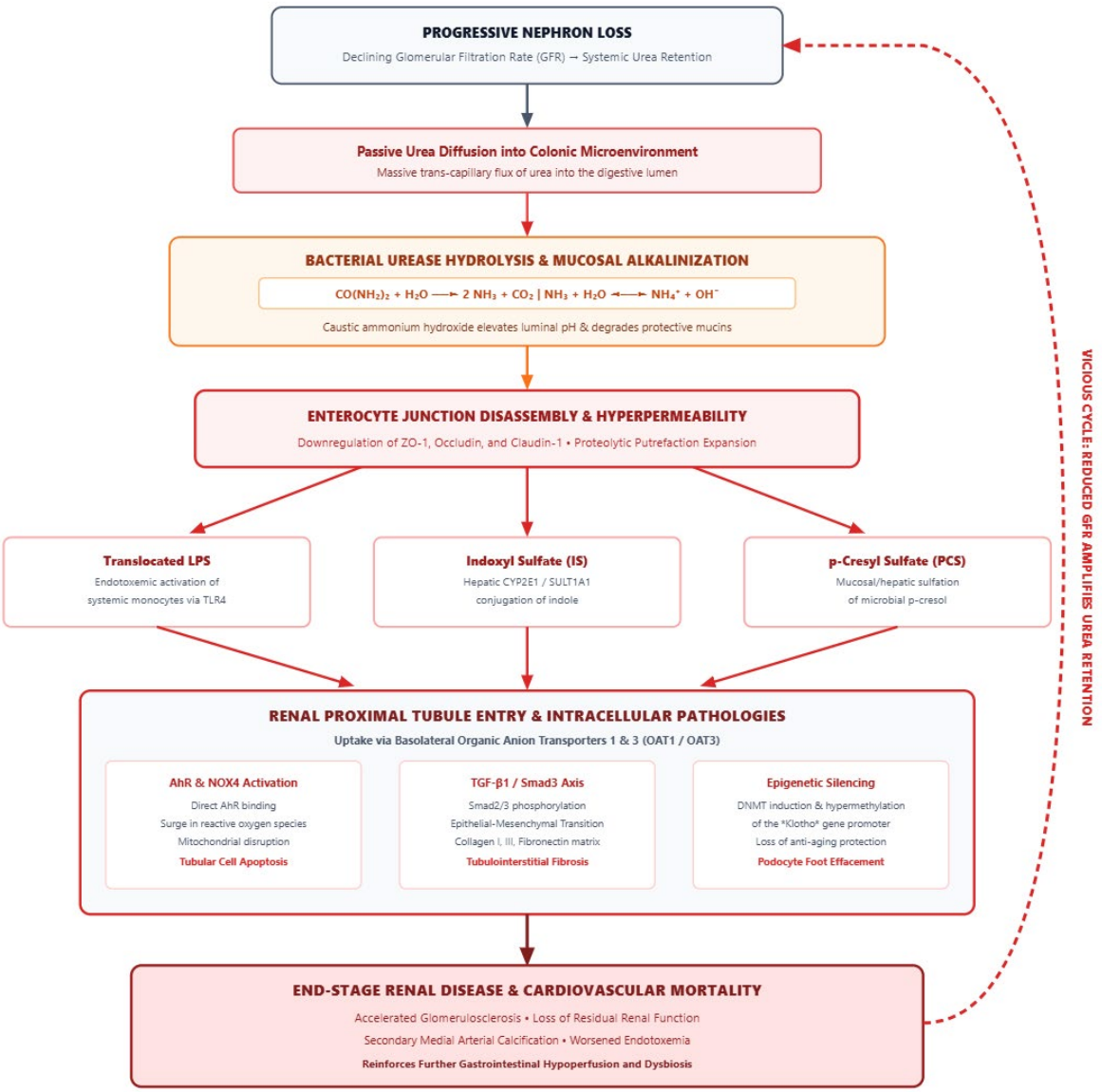

Figure 8. The Cyclic Entero-Renal Pathological Axis in Chronic Kidney Disease

Circulating urea diffuses across intestinal capillaries into the colonic lumen, where it undergoes catalytic hydrolysis by bacterial urease, an enzyme absent from eukaryotic genomes [120, 121]. Microbial species such as *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Helicobacter* hydrolyze luminal urea into ammonia and carbon dioxide [121]:

$$CO(NH_2)_2 + H_2O \xrightarrow{\text{urease}} 2\,NH_3 + CO_2$$

The generated ammonia rapidly hydrolyzes in mucosal water to form caustic ammonium hydroxide:

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

This accumulation of ammonium hydroxide elevates colonic luminal pH, disassembles the mucin matrix, and disrupts enterocyte tight junction complexes by downregulating occludin, claudin-1, and zonula occludens-1 [122, 123].

The resulting colonic microenvironment favors the expansion of proteolytic, urease-positive taxa within the Pseudomonadota phylum (including *Escherichia*, *Klebsiella*, and *Enterobacter*), while depleting saccharolytic, butyrate-synthesizing Bacillota (e.g., *Faecalibacterium prausnitzii*, *Roseburia*) and Verrucomicrobiota (*Akkermansia muciniphila*) [123, 124].

The expansion of proteolytic bacteria drives the putrefaction of aromatic amino acids, producing high amounts of indole, p-cresol, and phenylacetic acid [125]. Following portal absorption, phase I oxidation and phase II hepatic conjugation convert these precursors into the protein-bound uremic toxins indoxyl sulfate and p-cresyl sulfate [125, 126]. In healthy kidneys, these compounds are actively secreted into urine via basolateral organic anion transporters OAT1 and OAT3 located on renal proximal tubule cells [126]. In CKD, the loss of functional proximal tubular mass limits secretory capacity, driving systemic toxin accumulation [127].

Within renal tubular epithelial cells, intracellular indoxyl sulfate and p-cresyl sulfate activate NADPH oxidase 4 (NOX4), generating reactive oxygen species that induce mitochondrial dysfunction, activate p38 mitogen-activated protein kinase (MAPK), and stimulate the nuclear translocation of NF-kappa-B [127, 128]. This oxidative stress cascade upregulates TGF-beta 1 and induces the phosphorylation of Smad2/3, triggering tubular epithelial-mesenchymal transition and driving excess synthesis and extracellular deposition of collagen type I, collagen type III, and fibronectin [128, 129].

Simultaneously, indoxyl sulfate activates the intrarenal renin-angiotensin-aldosterone system and suppresses Klotho expression via DNA methyltransferase-dependent promoter hypermethylation [129, 130]. The loss of Klotho—a primary anti-senescence and anti-fibrotic protein—accelerates interstitial fibrosis, podocyte foot process effacement, and tubular cell apoptosis [130].

The translocated LPS and uremic toxins also activate the circulating immune system, sustaining chronic inflammation, accelerating vascular calcification, and worsening secondary cardiovascular mortality in chronic uremic cohorts [131, 132].

4. Impact of Pharmacotherapy and Polypharmacy on the Gut Ecosystem

The gut microbiota is sensitive to host pharmacological exposures. Numerous non-antibiotic drug classes exert off-target antibacterial and taxonomical effects, reshaping the composition and functional output of the intestinal ecosystem [133]. Polypharmacy—defined as the simultaneous administration of five or more therapeutic compounds—is common among individuals with complex chronic diseases, creating combined pharmacological pressures that amplify gut dysbiosis [133, 134]. Proton pump inhibitors (PPIs), prescribed to reduce gastric acid secretion, cause marked upstream changes in the downstream gastrointestinal microbiota [135]. By elevating gastric pH, PPIs diminish the acidic barrier that limits entry of oropharyngeal bacteria into the lower digestive tract [135, 136]. Consequently, PPI treatment leads to the distal colonization of oral-cavity taxa, including *Streptococcus*, *Rothia*, *Veillonella*, and *Micrococcaceae*, alongside the depletion of commensal *Bifidobacterium* and *Ruminococcaceae* [136]. This shift reduces community resistance to opportunistic pathogens, increasing susceptibility to *Clostridioides difficile* colitis and systemic enteric infections [137].

Cardiovascular agents, particularly statins and antihypertensives, also interact with the gut ecosystem [138]. HMG-CoA reductase inhibitors (statins) exhibit compound-specific interactions with the intestinal microbiota [138, 139]. Patients with coronary artery disease treated with atorvastatin demonstrate a reduction in the inflammatory Bact2 enterotype (an ecological state characterized by high *Bacteroides* abundance, low microbial cell densities, and depleted *Faecalibacterium*) and a restoration of butyrate-producing commensals [139]. Conversely, poor clinical lipid responses correlate with elevated baseline abundances of Proteobacteria and decreased community alpha diversity [140]. Antihypertensive therapies also exhibit reciprocal interactions: angiotensin II receptor blockers like candesartan help attenuate gut barrier permeability and restore local microbial diversity, whereas gut bacteria actively metabolize other cardiovascular drugs [141]. For example, the cardiac glycoside digoxin is inactivated by specific strains of *Eggerthella lenta* expressing the *cgr* (cardiac glycoside reductase) operon, which reduces the drug to inactive dihydrodigoxin and blunts its therapeutic efficacy [142].

Antidiabetic drugs demonstrate bidirectional interactions with the intestinal microbiota, which can contribute to their therapeutic mechanisms [143]. Metformin, the primary biguanide for T2DM, accumulates at millimolar concentrations in the intestinal lumen, where it shifts the microbiota by enriching *Akkermansia muciniphila*, *Bifidobacterium adolescentis*, and *Lactobacillus* species, alongside an elevated abundance of the *Escherichia* genus [143, 144]. Metformin promotes mucin secretion and goblet cell differentiation, counteracting barrier degradation and increasing microbial propionate and butyrate synthesis [144, 145]. These metformin-induced shifts in SCFA production and bile acid profiles partially mediate its glucose-lowering effects by activating intestinal AMPK and promoting GLP-1 secretion [145]. Conversely, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit protective cyclooxygenase-1 in the gastric and duodenal mucosa, inducing microvascular ischemia and mucosal ulceration, which accelerates local bacterial invasion and systemic LPS translocation [146, 147].

4.1. Comparison of Microbial Alterations and Metabolite Shifts Across Chronic Conditions

The following consolidated matrix details the characteristic microbial signatures, downstream metabolic alterations, signaling mechanisms, and end-organ conditions across major chronic non-communicable diseases (listed out in Table 1).

Table 1. Comprehensive Comparison of Microbial Alterations, Metabolite Dynamics, and Pathophysiological Pathways Across Chronic Diseases

Disease State	Taxonomic Dysbiosis	Altered Metabolites	Signaling Receptors & Pathways	Structural & Downstream Pathological Manifestations
Type 2 Diabetes Mellitus (T2DM)	↓ *Faecalibacterium prausnitzii*, *Roseburia*, *Akkermansia muciniphila* ↑ *Escherichia coli*, *Klebsiella pneumoniae*, *Prevotella copri*	↓ Butyrate, Propionate ↑ LPS (endotoxemia), BCAAs (leucine, isoleucine, valine)	↓ FFAR2 (GPR43), FFAR3 (GPR41), GLP-1R ↑ TLR4/MD-2 → MyD88 → JNK/IKK-β	Serine phosphorylation of IRS-1; impaired GLUT4 translocation; unchecked hepatic gluconeogenesis via FoxO1; chronic islet inflammation; systemic insulin resistance.
Atherosclerosis & Coronary Artery Disease	↓ *Bifidobacterium*, *Lactobacillus*, *Bacteroides fragilis* ↑ *Ruminococcus gnavus*, *Enterobacteriaceae*, *Eggerthella*	↑ Trimethylamine (TMA), TMAO, LPS ↓ Acetate, Butyrate	↑ Endothelial TLR4, NF- κ B, NLRP3 inflammasome ↓ Macrophage ABCA1/ABCG1 reverse cholesterol transport	Endothelial cell activation (upregulated VCAM-1, ICAM-1); macrophage CD36 and SRA-1 upregulation driving foam cell formation; arterial wall vascular calcification; plaque instability.
Arterial Hypertension	↓ *Lactobacillus murinus*, *Faecalibacterium* ↑ *Enterobacter*, *Prevotella*, Elevated Firmicutes/Bacteroidetes ratio	↓ Butyrate, Acetate ↑ LPS, Circulating IL-17A	↓ Vascular FFAR3 (vasodilatory NO release) ↑ Renal Olfr78 / OR51E2 (renin exocytosis)	Impaired vascular endothelial relaxation; unopposed renin release; arterial wall fibrosis and media hypertrophy; vascular stiffness.
Chronic Kidney Disease (CKD)	↓ *Faecalibacterium*, *Roseburia*, *Akkermansia*, *Prevotella* ↑ *Escherichia*, *Proteus*, *Enterobacter*, *Pseudomonas*	↑ Urea, Ammonia, Indoxyl Sulfate (IS), p-Cresyl Sulfate (PCS), TMAO ↓ Butyrate	↑ AhR, TLR4, NOX4, TGF-β1/Smad3 ↓ GPR109A, Intravascular eNOS, Renal Klotho expression	Urease-mediated mucosal alkalinization; enterocyte tight junction disassembly (ZO-1, occludin); renal proximal tubular epithelial apoptosis; progressive tubulointerstitial fibrosis; accelerated glomerulosclerosis.
Heart Failure	↓ *Faecalibacterium prausnitzii*, *Eubacterium rectale* ↑ *Candida*, *Campylobacter*, *Shigella*, *Streptococcus*	↑ Systemic LPS, TMAO, Uric acid ↓ Total SCFAs	↑ Myocardial TLR4, MyD88, NF- κ B, Caspase-1	Intestinal bowel wall edema; secondary mucosal hypoperfusion; chronic systemic endotoxemia; cardiomyocyte apoptosis; interstitial myocardial fibrosis; adverse ventricular remodeling.

5. Targeted Therapeutic Interventions and Microbiome Engineering

Recognizing microbial metabolites as mediators of chronic human disease has spurred the development of targeted therapeutic interventions (as shown in Figure 9). These strategies aim to suppress pathobiont overgrowth, restore the functional output of protective commensals, reinforce mucosal barrier integrity, and inhibit the enzymatic pathways generating toxic metabolites [148].

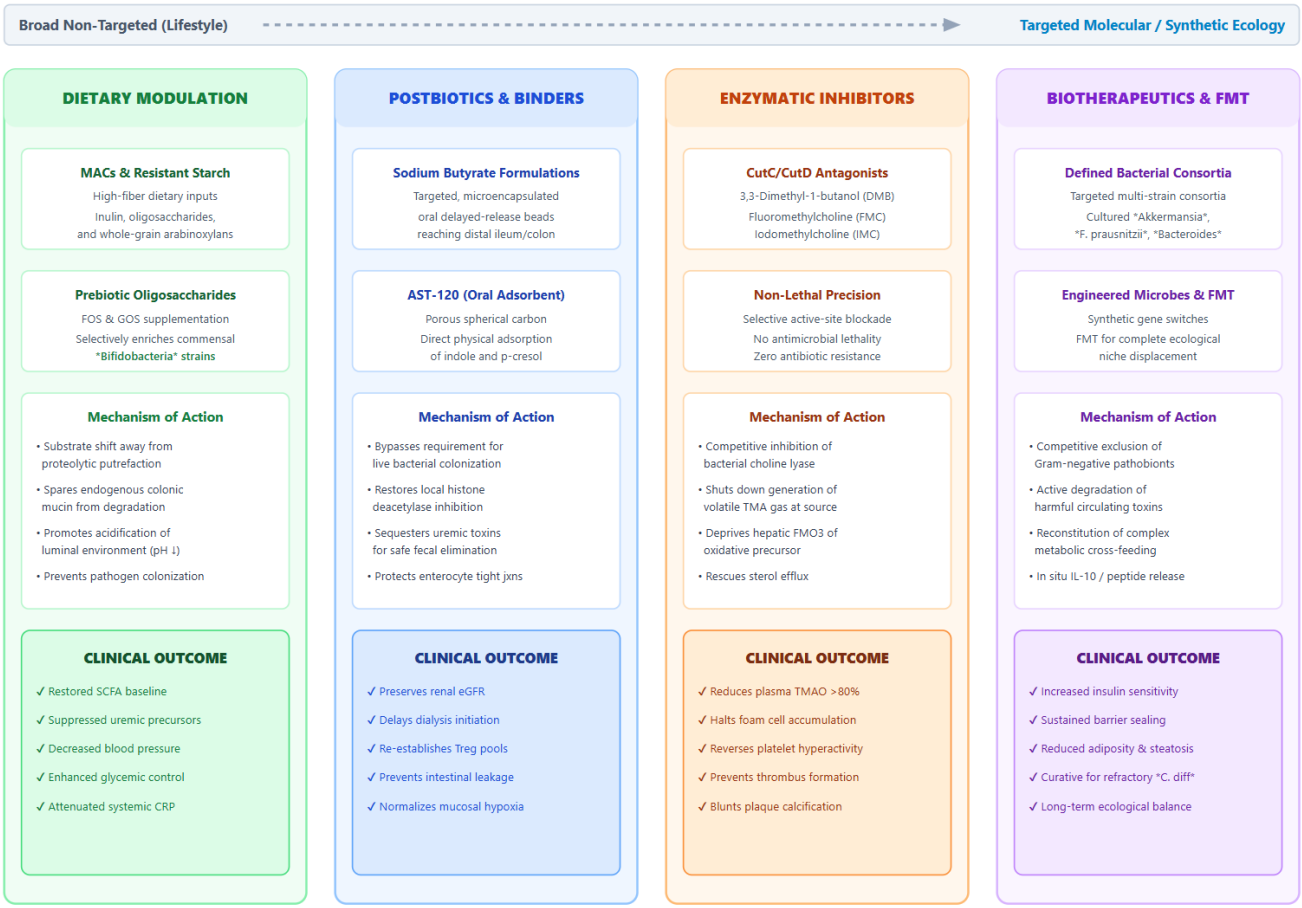

Figure 9. Targeted Therapeutic Treatment for Restoring Host-Microbe Metabolic Equilibrium

Dietary modulation remains an accessible approach for reshaping microbial metabolic output [149]. Diets rich in microbiota-accessible carbohydrates (MACs) and resistant starches supply the enzymatic substrates required for commensal saccharolytic fermentation, boosting SCFA production and reducing colonic proteolytic putrefaction [149, 150]. Conversely, the Western diet—rich in refined sugars, saturated fatty acids, and red meats, while deficient in plant fiber—starves saccharolytic species, forcing bacteria to degrade the host mucus layer and driving the biosynthesis of TMA, indoxyl sulfate, and p-cresyl sulfate [150]. Targeted postbiotic supplementation offers an alternative by delivering functional microbial metabolites directly to the host, bypassing the complexities of bacterial colonization [151]. Oral formulations of microencapsulated sodium butyrate restore colonic SCFA concentrations, increase tight junction protein expression, stimulate enterocyte oxygen consumption, and activate Foxp3-dependent regulatory T-cell differentiation in inflammatory disorders [151, 152]. Targeted small-molecule inhibitors of microbial enzymes represent another precision strategy [153]. To target the pro-atherogenic TMAO pathway without exerting selective pressure that drives antibiotic resistance, researchers have developed non-lethal structural choline analogs that selectively inhibit microbial choline TMA-lyase (CutC/D) [153, 154]. 3,3-Dimethyl-1-butanol (DMB) and fluoromethylcholine (FMC) selectively inhibit bacterial CutC/D activity in the intestinal lumen, suppressing TMA generation from dietary choline without affecting bacterial viability [154].

In pre-clinical models, small-molecule CutC/D inhibition significantly lowers circulating TMAO concentrations, reduces macrophage scavenger receptor expression, inhibits foam cell accumulation, and prevents diet-induced arterial thrombus formation [154, 155]. Similarly, targeting uremic toxins in CKD has led to the development of oral spherical carbonaceous adsorbents like AST-120 [156]. AST-120 binds microbially derived indole and p-cresol within the colonic lumen, preventing their absorption into the portal circulation and reducing systemic indoxyl sulfate and p-cresyl sulfate concentrations, which slows tubulointerstitial fibrosis and preserves residual renal function [156, 157]. Fecal microbiota transplantation (FMT) and defined live biotherapeutic consortia require systemic ecological interventions [158]. FMT involves transferring a processed microbial community from a healthy donor into a patient's intestinal tract, displacing dysbiotic communities and restoring mucosal barrier integrity [158, 159]. While FMT is established as a standard clinical treatment for recurrent and refractory *Clostridioides difficile* infections, clinical trials in metabolic syndrome, ulcerative colitis, and atherosclerosis demonstrate variable responses [159, 160]. This heterogeneity highlights the need to transition toward defined microbial consortia—standardized combinations of cultured, characterized bacterial strains such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Bacteroides uniformis* [160, 161]. Parallel advances in synthetic biology enable

the engineering of commensal strains (*Escherichia coli* Nissle 1917) equipped with synthetic gene circuits that degrade toxic metabolic intermediates, synthesize therapeutic anti-inflammatory peptides like IL-10, or sense mucosal inflammation in real time [161, 162].

6. Conclusion

The human gut microbiota functions as an active endocrine and metabolic organ that communicates continuously with distal host tissues through the generation of diverse bioactive metabolites. In homeostasis, mutualistic microbial consortia ferment non-digestible carbohydrates into short-chain fatty acids, which reinforce intestinal mucosal barriers, activate G-protein coupled receptors FFAR2 and FFAR3, inhibit histone deacetylases, and promote systemic immune tolerance. Conversely, compositional and functional dysbiosis disrupts this biochemical balance. The depletion of protective butyrate-producing taxa, coupled with the breakdown of apical junctional complexes and mucin matrices, enables the paracellular translocation of lipopolysaccharides into the systemic circulation, driving chronic metabolic endotoxemia and low-grade inflammation via TLR4-MyD88-NF-kappa-B signaling cascades. Simultaneously, the unchecked expansion of pathobionts accelerates the proteolytic catabolism of quaternary amines and aromatic amino acids, generating hazardous metabolites like trimethylamine N-oxide, indoxyl sulfate, and p-cresyl sulfate. These biochemical intermediates drive insulin resistance, endothelial dysfunction, accelerated atherosclerosis, arterial stiffness, and progressive tubulointerstitial renal fibrosis. Interventions that restore microbial metabolic balance—through targeted dietary fiber supplementation, postbiotic therapies, small-molecule enzymatic inhibition of CutC/D, oral uremic toxin adsorbents, and defined live biotherapeutic consortia—could be a promising frontier in modern medicine.

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