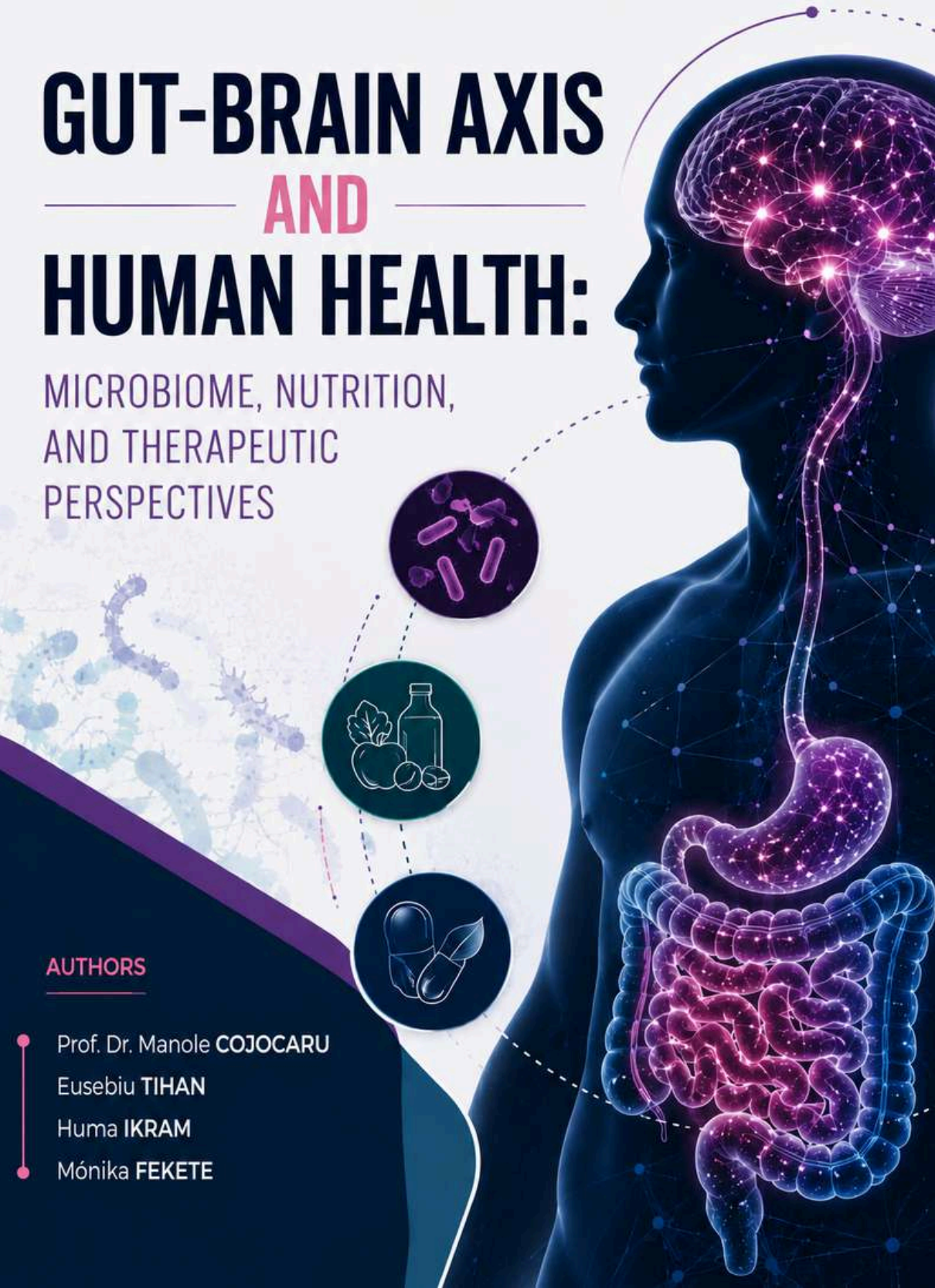
GUT-BRAIN AXIS AND HUMAN HEALTH:

MICROBIOME, NUTRITION, AND THERAPEUTIC PERSPECTIVES



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PREFACE

The growing recognition of the relationship between the gut microbiome, brain function, and overall health has transformed contemporary biomedical research. Increasing evidence suggests that the gut-brain axis plays a critical role in neurological, psychological, and metabolic processes, highlighting the importance of nutrition and microbial balance in maintaining health and preventing disease.

The chapters in this volume explore current developments in gut-brain axis research and their implications for human health. The discussion of substance use disorders examines the role of microbiota modulation and emerging therapeutic interventions in addressing complex neurobiological conditions. The exploration of the microbiome's influence on psychological wellbeing further highlights the intricate communication pathways linking the gastrointestinal system and the brain. In addition, the examination of modern dietary models, particularly the Mediterranean diet, demonstrates the importance of nutrition in promoting health and reducing the risk of chronic diseases.

By integrating perspectives from microbiology, neuroscience, nutrition science, and preventive medicine, this volume contributes to contemporary discussions on the biological mechanisms that connect diet, microbial ecosystems, and human health. It offers valuable insights for researchers, healthcare professionals, and students interested in emerging approaches to disease prevention and health promotion.

It is hoped that this book will encourage further interdisciplinary research and support a deeper understanding of the complex interactions between the gut microbiome, nutrition, and overall wellbeing.

Editorial Team
June 2026, Türkiye

CHAPTER 1
THE GUT-BRAIN AXIS IN SUBSTANCE USE DISORDERS: FROM MICROBIOTA MODULATION TO THERAPEUTIC INTERVENTIONS

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INTRODUCTION

The bidirectional communication network known as the gut-brain axis has emerged as one of the most dynamic and rapidly evolving fields in contemporary neuroscience. This intricate system connects the emotional and cognitive centers of the brain with peripheral intestinal functions through neural, endocrine, immune, and metabolic pathways. At the heart of this axis lies the gut microbiota, a complex ecosystem of trillions of microorganisms that collectively possess a genetic repertoire vastly exceeding that of the human genome (Wanyi et al., 2024). These microbial communities do not merely assist in digestion; they actively synthesize neurotransmitters, modulate neuroinflammation, and influence blood-brain barrier integrity. The vagus nerve serves as a primary anatomical conduit, transmitting microbial signals directly to brainstem nuclei and higher cortical regions. Understanding this axis has profound implications for psychiatric and neurological disorders, particularly those involving reward processing and behavioral control.

Substance use disorders represent a global health crisis characterized by compulsive drug seeking, loss of control over consumption, and persistent vulnerability to relapse. While decades of research have focused on neurochemical adaptations within the mesolimbic dopamine pathway, emerging evidence suggests that peripheral signals, particularly those originating from the gut microbiome, play an equally critical role in addiction pathophysiology (Volkow & Blanco, 2023). Preclinical studies demonstrate that manipulating the gut microbiota through antibiotics, probiotics, or fecal transplantation can profoundly alter behavioral responses to drugs of abuse including psychostimulants, opioids, and benzodiazepines. Clinical investigations reveal distinct microbial signatures in individuals with alcohol use disorder, opioid dependence, and stimulant addiction compared to healthy controls. These microbial alterations correlate with craving severity, cognitive impairment, and treatment outcomes, suggesting that the microbiome may serve as both a biomarker and a modifiable risk factor (Hofford & Kiraly, 2024).The recognition that gut microbes influence drug pharmacokinetics, neurotransmitter availability, and neuroimmune signaling has fundamentally expanded our understanding of addiction biology.

The therapeutic potential of targeting the gut-brain axis in substance use disorders represents an exciting frontier for clinical intervention. Conventional pharmacotherapies for addiction often demonstrate limited efficacy and significant adverse effects, driving the search for novel adjunctive strategies. Microbiome-directed interventions including probiotic supplementation, prebiotic fibers, dietary modifications, and fecal microbiota transplantation offer the promise of restoring healthy microbial ecosystems while simultaneously modulating addiction-related behaviors. Compounds such as N-acetylcysteine, already recognized for its antioxidant and glutamate-modulating properties, may exert additional benefits through direct effects on gut microbial composition and function (Fu et al., 2021). Dietary factors, particularly tryptophan availability and polyphenol content, influence both microbial diversity and central serotonin signaling, providing a nutritional avenue for intervention. This chapter will explore the mechanistic underpinnings of gut-brain communication in addiction, examine preclinical and clinical evidence linking microbiota to substance use disorders, and evaluate emerging therapeutic strategies that harness the microbiome for improved treatment outcomes. By integrating insights from neuroscience, microbiology, and pharmacology, we aim to present a comprehensive framework for understanding and targeting the gut-brain axis in addiction medicine.

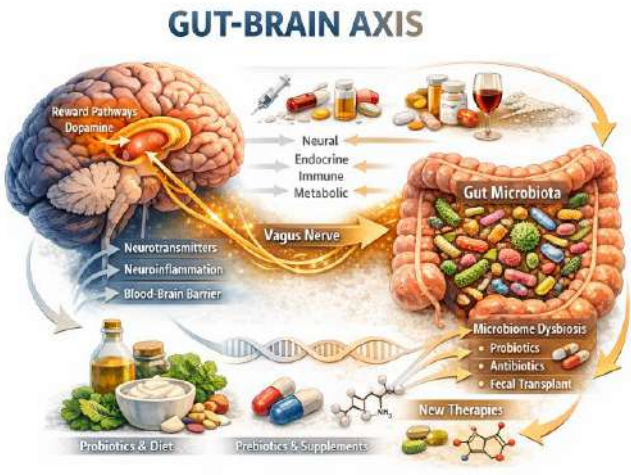

Figure 1. Gut-brain communication pathways explained

1. A BIDIRECTIONAL COMMUNICATION HIGHWAY

The concept of the gut-brain axis has evolved from a theoretical framework into a well-characterized physiological reality, representing one of the most significant paradigm shifts in modern neuroscience. This bidirectional communication highway connects the enteric nervous system, often termed the "second brain," with the central nervous system through an intricate network of neural, hormonal, and immunological pathways. The vagus nerve serves as the primary neural conduit, with approximately 80% of its fibers carrying afferent signals from the gut to the brainstem, enabling continuous monitoring of gastrointestinal status. Beyond this direct neural link, the axis encompasses spinal afferent pathways, the sympathetic and parasympathetic branches of the autonomic nervous system, and the hypothalamic-pituitary-adrenal axis, which together orchestrate integrated responses to internal and external stimuli (Zheng et al., 2023). These pathways do not operate in isolation but rather form a dynamic feedback loop wherein brain states influence gastrointestinal function, and gut-derived signals reciprocally modulate mood, cognition, and behavior. The recognition that this communication is fundamentally bidirectional has profound implications for understanding how peripheral events, particularly those involving the gut microbiota, can influence brain function and dysfunction.

The gastrointestinal tract houses an extraordinarily complex and dynamic microbial ecosystem that plays an indispensable role in gut-brain communication. This microbiota, comprising bacteria, archaea, fungi, and viruses, collectively possesses a genetic capacity that far exceeds that of the human host, enabling it to perform metabolic transformations that humans cannot accomplish independently. Through the production of neurotransmitters including gamma-aminobutyric acid, serotonin, dopamine, and norepinephrine, gut microbes can directly influence neurochemical signaling within the enteric nervous system and, via systemic circulation, within the brain itself. Short-chain fatty acids generated through microbial fermentation of dietary fiber serve as essential energy sources for colonocytes while simultaneously acting as signaling molecules that modulate microglial function and neuroinflammation (Ayivi-Tosuh et al., 2026).

The gut epithelium, reinforced by tight junctions and overlain with mucus, functions as a selective barrier that regulates microbial molecule translocation while preventing pathogenic invasion, a gatekeeping function that is itself influenced by stress and psychological states. This intricate relationship establishes the microbiota as a critical intermediary in gut-brain signaling, capable of translating dietary, environmental, and psychological inputs into neurochemical outputs that shape behavior.

The bidirectional nature of this axis ensures that perturbations at any point along the pathway can have cascading effects on both gastrointestinal and neurological function. Psychological stress activates the hypothalamic-pituitary-adrenal axis, releasing cortisol and other stress hormones that alter gut permeability, microbial composition, and intestinal motility, thereby modifying the very signals being transmitted to the brain. Conversely, dietary changes, antibiotic exposure, or infection can disrupt microbial homeostasis, leading to altered production of neuroactive metabolites and triggering inflammatory responses that compromise the blood-brain barrier and activate neuroinflammatory cascades. This bidirectional vulnerability has particular relevance for substance use disorders, wherein drugs of abuse simultaneously affect brain reward circuitry and gastrointestinal function, while stress-induced dysregulation of the axis contributes to craving and relapse vulnerability. The recognition that gut microbiota can influence drug metabolism and bioavailability adds another layer of complexity, suggesting that inter-individual differences in microbial composition may contribute to variable responses to both drugs of abuse and addiction pharmacotherapies (Sharan & Vellapandian, 2024). Understanding this bidirectional communication highway in its full complexity requires integrating knowledge from neuroscience, gastroenterology, immunology, and microbiology, a multidisciplinary approach that is yielding unprecedented insights into the pathophysiology of addiction and opening novel therapeutic avenues. The following sections will explore these mechanistic pathways in detail, examining how the gut-brain axis contributes to substance use disorders and how microbiome-directed interventions may offer new hope for treatment.

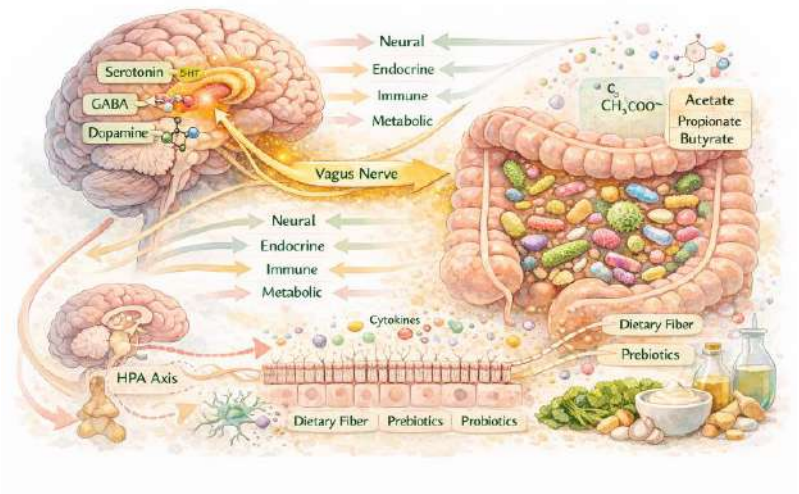

Figure 2. Gut-brain connections in balance

2. COMPOSITION, FUNCTION, AND DYNAMICS OF GUT MICROBIOTA

The human gut microbiota represents one of the most densely populated microbial ecosystems on Earth, housing approximately 10^14 microorganisms that collectively weigh 1-2 kilograms in the average adult. This complex community encompasses all three domains of life—bacteria, archaea, and eukarya—along with their associated viruses, predominantly bacteriophages, that together constitute the gut microbiome. Bacterial composition is dominated by two major phyla, Bacteroidetes and Firmicutes, which account for over 90% of the phylogenetic diversity, with Actinobacteria, Proteobacteria, and Verrucomicrobia representing smaller but functionally significant populations. Beyond taxonomic diversity exists immense functional redundancy, wherein phylogenetically distinct organisms perform similar metabolic transformations, contributing to ecosystem stability and resilience against perturbation (Colella et al., 2023). The collective genetic repertoire of these microorganisms, termed the microbiome, contains approximately 3.3 million non-redundant genes, vastly exceeding the 23,000 genes of the human host and enabling metabolic capabilities that humans cannot accomplish independently.

This genetic endowment varies considerably between individuals, with each person harboring a unique microbial signature shaped by factors ranging from birth mode and infant feeding to diet, medication exposure, and geographical location throughout the lifespan.

The functional contributions of the gut microbiota extend far beyond its traditional role in dietary digestion and nutrient extraction. Microbial metabolism of otherwise indigestible dietary fibers generates short-chain fatty acids including acetate, propionate, and butyrate, which serve as essential energy substrates for colonocytes while simultaneously functioning as signaling molecules that regulate host metabolism, immune function, and even gene expression through epigenetic modifications. Perhaps most remarkably for neuroscience, gut microbes possess the enzymatic machinery to synthesize and secrete a vast array of neuroactive compounds, including gamma-aminobutyric acid produced by Lactobacillus and Bifidobacterium species, serotonin derived from tryptophan metabolism by spore-forming bacteria, dopamine synthesized by Bacillus and Serratia strains, and norepinephrine produced by Escherichia and Saccharomyces species (Ma & Lee, 2025). The microbiota also plays a critical role in regulating tryptophan availability along the kynurenine pathway, thereby influencing peripheral and central serotonin synthesis while simultaneously modulating neuroinflammation through quinolinic acid production. Additionally, gut microbes metabolize primary bile acids into secondary bile acids that act as signaling molecules on nuclear receptors including the farnesoid X receptor and G-protein-coupled bile acid receptor TGR5, which influence brain function through both direct and indirect mechanisms. This extraordinary functional repertoire positions the gut microbiota as a veritable endocrine organ capable of influencing host physiology at nearly every level, from metabolism to mood.

The composition and function of the gut microbiota are inherently dynamic, exhibiting both resilience and plasticity in response to endogenous and exogenous challenges. Throughout the lifespan, microbial communities undergo predictable shifts, with dramatic diversification during infancy followed by relative stabilization in adulthood and characteristic changes associated with immune-senescence and physiological decline in aging.

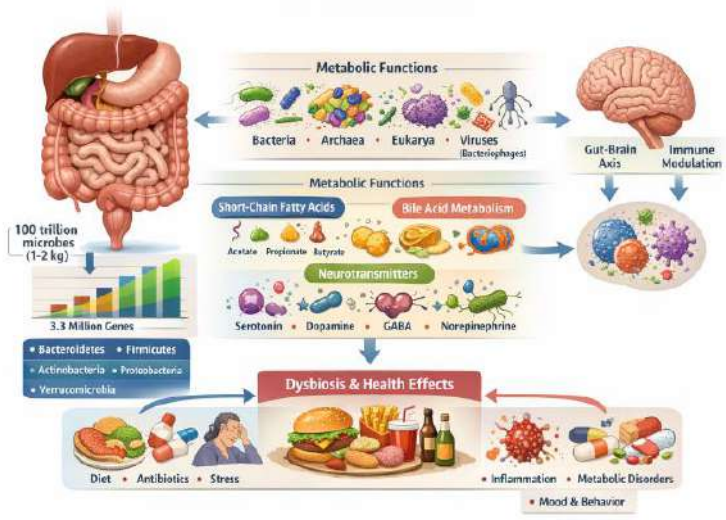

Figure 3. Gut microbiome and its function

Dietary patterns exert perhaps the most profound and rapidly reversible influence on microbial composition, with plant-based, fiber-rich diets promoting saccharolytic bacteria that produce beneficial short-chain fatty acids, while high-fat, high-sugar Western diets favor proteolytic organisms associated with inflammation and metabolic dysfunction. Antibiotic exposure represents a particularly disruptive force, capable of reducing taxonomic diversity by 30% or more within days, with recovery often incomplete and highly variable between individuals depending on the antibiotic class, treatment duration, and host factors. Psychological and physiological stressors activate sympathetic outflow and hypothalamic-pituitary-adrenal axis signaling, altering intestinal motility, mucus production, and luminal pH in ways that selectively favor or disadvantage specific microbial populations (Ma et al., 2026). For substance use disorders, these dynamics are particularly relevant, as drugs of abuse including opioids, psychostimulants, and alcohol directly alter microbial composition while simultaneously inducing stress responses and dietary changes that compound these effects, creating a vicious cycle wherein drug-induced dysbiosis may perpetuate drug-seeking behavior and increase relapse susceptibility.

Understanding these compositional and functional dynamics is essential for developing microbiome-targeted interventions that restore healthy microbial ecosystems and, through them, support recovery from addiction.

3. NEUROACTIVE MOLECULES FROM THE GUT

The discovery that gut microbes can synthesize and secrete molecules capable of influencing brain function has fundamentally transformed our understanding of the gut-brain axis. These neuroactive compounds, produced through microbial metabolic pathways that humans do not possess, represent a direct mechanism by which the microbiota can modulate neuronal activity, synaptic transmission, and ultimately behavior. Perhaps most striking is the capacity of gut bacteria to produce classical neurotransmitters traditionally associated with mammalian nervous systems, including gamma-aminobutyric acid, serotonin, dopamine, norepinephrine, and acetylcholine, each synthesized by specific bacterial strains through enzymatic processes distinct from but functionally analogous to those in neurons. Beyond direct neurotransmitter production, microbes generate an extensive repertoire of precursor molecules, neuromodulators, and signaling metabolites that influence neurotransmitter synthesis, release, and receptor sensitivity within the host nervous system. These microbial products gain access to the brain through multiple routes, including direct vagal nerve stimulation, absorption into the portal circulation with subsequent passage across the blood-brain barrier, and modulation of immune cell trafficking that carries microbial signals into the central nervous system (Loh et al., 2024).The realization that our gut microbiota functions as a distributed neurotransmitter factory operating continuously throughout life has profound implications for understanding individual differences in brain function and vulnerability to neuropsychiatric disorders including substance use disorders . This microbial neurochemistry operates beneath conscious awareness yet exerts measurable effects on mood, cognition, and behavior that are only beginning to be fully appreciated.

Among the most extensively characterized microbial neuroactive molecules are those targeting the GABAergic and serotonergic systems, both critically implicated in addiction pathophysiology.

Multiple Lactobacillus and Bifidobacterium species possess glutamate decarboxylase enzymes that convert glutamate to gamma-aminobutyric acid, the brain's primary inhibitory neurotransmitter, with animal studies demonstrating that probiotic administration can elevate central GABA concentrations and reduce anxiety-like and depression-like behaviors. Serotonin production by gut microbes is particularly significant given that approximately 95% of the body's serotonin resides in the gastrointestinal tract, where it regulates motility and secretion, but emerging evidence suggests microbial influences on tryptophan metabolism extend to central serotonin availability as well (Albani et al., 2025). Spore-forming bacteria, particularly Clostridial species, promote serotonin biosynthesis from tryptophan by stimulating enterochromaffin cells, while other microbes compete with the host for tryptophan, diverting this essential amino acid toward the kynurenine pathway and away from serotonin synthesis. The kynurenine pathway itself generates metabolites with opposing neuroactive properties, including kynurenic acid, which antagonizes NMDA receptors and may be neuroprotective, and quinolinic acid, which activates NMDA receptors and promotes neuroinflammation and excitotoxicity. This microbial influence over tryptophan fate has direct implications for substance use disorders, as serotonin signaling modulates impulse control and reward sensitivity, while kynurenine pathway metabolites influence the neuroinflammatory state that contributes to drug-induced neurotoxicity and cognitive impairment. The gut microbiota thus serves as a critical regulator of the delicate balance between neuroprotective and neurotoxic pathways that influence addiction vulnerability and recovery.

Short-chain fatty acids and other microbial metabolites represent an additional class of neuroactive molecules with increasingly recognized roles in brain function and dysfunction. Acetate, propionate, and butyrate, produced through bacterial fermentation of dietary fiber, are not merely energy substrates but potent signaling molecules that influence brain function through multiple mechanisms. Butyrate functions as a histone deacetylase inhibitor, promoting gene expression changes that enhance brain-derived neurotrophic factor production, synaptic plasticity, and cognitive function, effects with potential relevance for restoring drug-induced deficits in neuroplasticity.

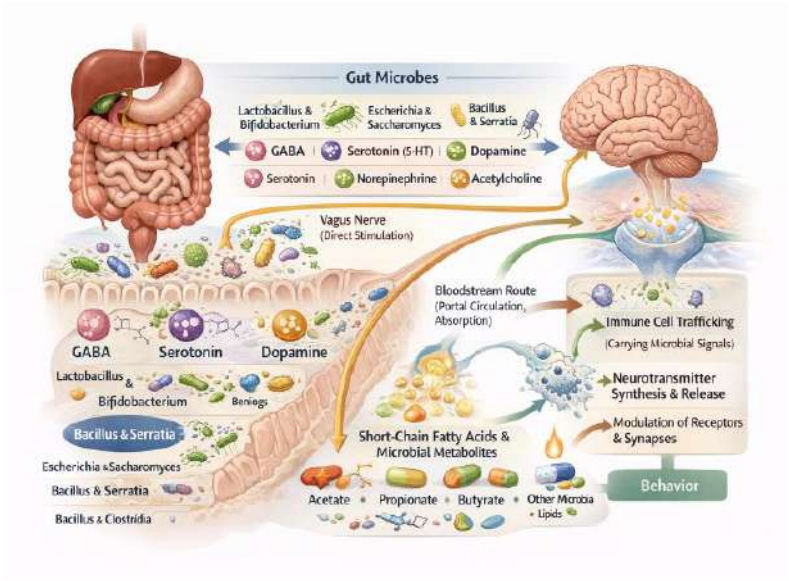

Figure 4. Gut microbes and brain interaction infographic

These short-chain fatty acids also activate free fatty acid receptors expressed on enteroendocrine cells, triggering release of peptide YY and glucagon-like peptide-1 that signal via vagal afferents to influence appetite, stress responses, and reward processing. Beyond short-chain fatty acids, gut microbes generate secondary bile acids, branched-chain amino acids, and phenolic compounds that cross the blood-brain barrier and modulate neurotransmitter systems, neuroinflammation, and mitochondrial function (Cho et al., 2026). Microbial production of bioactive lipids including endocannabinoid-like compounds adds another dimension, suggesting the microbiota may influence the very receptor systems targeted by drugs of abuse. Collectively, this expanding catalog of microbial neuroactive molecules reveals that the gut microbiome participates actively and continuously in brain function, not merely as a passive bystander but as an integral component of the neurochemical environment that shapes behavior, cognition, and vulnerability to substance use disorders. Understanding these microbial contributions opens unprecedented opportunities for therapeutic interventions that modulate the gut's neurochemical output to support addiction treatment and recovery.

4. THE GUT MICROBIOTA IN REWARD CIRCUITRY

The mesolimbic dopamine pathway, originating in the ventral tegmental area and projecting to the nucleus accumbens, prefrontal cortex, and other limbic structures, represents the core neural circuitry underlying reward processing and the reinforcing effects of drugs of abuse. Emerging evidence positions the gut microbiota as a previously unrecognized modulator of this circuitry, capable of influencing dopaminergic signaling, reward sensitivity, and ultimately vulnerability to substance use disorders through multiple convergent mechanisms. Preclinical studies demonstrate that germ-free animals, entirely lacking gut microbiota, exhibit exaggerated dopamine release in response to psychostimulants including amphetamine and cocaine, along with altered dopamine receptor expression and blunted behavioral responses compared to conventionally colonized controls. Fecal microbiota transplantation from animals with high versus low addiction vulnerability can transfer behavioral phenotypes, suggesting that microbial composition itself may influence susceptibility to drug-seeking behavior (Reynolds & Flores, 2021). The mechanisms underlying these effects involve microbial production of neuroactive metabolites that directly or indirectly modulate dopamine neuron activity, including short-chain fatty acids that influence microglial function and neuroinflammation within reward circuitry. Additionally, gut microbes influence the expression of dopamine transporters and receptors through epigenetic modifications, potentially altering the sensitivity of reward circuits to both natural reinforcers and drugs of abuse. Understanding how the microbiota shapes reward circuitry function has profound implications for identifying individuals at heightened risk for substance use disorders and developing preventive interventions.

Individual differences in addiction vulnerability arise from complex interactions between genetic predisposition, environmental exposures, and developmental factors, with the gut microbiota emerging as a critical mediator of these influences. Early-life disruption of the microbiota through cesarean section delivery, antibiotic exposure, or formula feeding has been associated with long-lasting alterations in reward-related behaviors and increased sensitivity to psychostimulants in animal models, effects that persist into adulthood even after microbial communities normalize.

Stress exposure, a well-established risk factor for substance use disorders, simultaneously activates hypothalamic-pituitary-adrenal axis signaling and disrupts gut microbial composition, with the resulting dysbiosis contributing to stress-induced potentiation of drug-seeking behavior through mechanisms involving altered dopamine signaling and neuroinflammation. Sex differences in addiction vulnerability may also involve the gut microbiota, as male and female animals exhibit distinct microbial compositions, and gonadectomy alters the microbiome in ways that influence behavioral responses to drugs of abuse (Borrego-Ruiz & Borrego, 2025). The composition of the gut microbiota influences the metabolism and bioavailability of drugs themselves, with certain microbial enzymes capable of transforming prodrugs into active metabolites or inactivating therapeutic compounds, thereby modifying the effective dose reaching brain reward circuitry. Dietary factors that shape microbial composition, including fiber content, fat composition, and polyphenol availability, may therefore influence addiction vulnerability through both direct effects on reward circuitry and indirect effects on drug pharmacokinetics. These findings position the gut microbiota as a critical interface through which environmental and developmental factors translate into individual differences in reward circuitry function and addiction susceptibility.

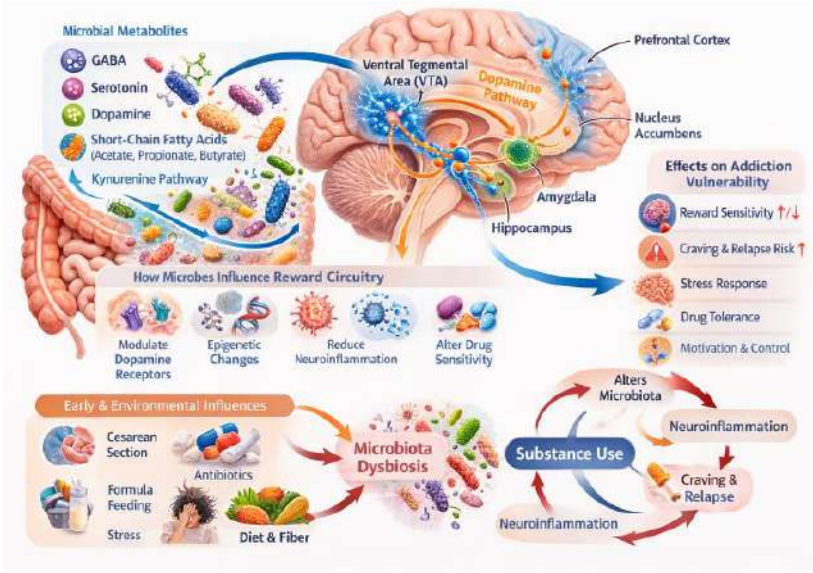

Figure 5. Gut-brain reward pathway and addiction cycle

The relationship between gut microbiota and reward circuitry is bidirectional and dynamic, with drugs of abuse themselves exerting profound effects on microbial composition that may contribute to addiction pathophysiology. Acute and chronic administration of psychostimulants including amphetamine, cocaine, and methamphetamine alters gut microbial diversity and composition in animal models, favoring pro-inflammatory organisms while depleting short-chain fatty acid producers. Opioids dramatically disrupt the gut microbiota through both direct antimicrobial effects and opioid receptor-mediated changes in gastrointestinal motility and secretion, creating a state of profound dysbiosis that persists even after drug cessation and may contribute to opioid-induced hyperalgesia, tolerance, and withdrawal severity. Alcohol consumption similarly alters microbial composition, increasing intestinal permeability and promoting translocation of bacterial products that trigger systemic inflammation and neuroinflammation within reward circuitry, effects that contribute to alcohol craving and relapse vulnerability (Lucerne et al., 2021). Benzodiazepines and other GABAergic drugs influence microbial composition through mechanisms that remain poorly understood but may involve direct antimicrobial effects and drug-induced changes in gastrointestinal physiology. This drug-induced dysbiosis creates a vicious cycle wherein substance use disrupts the microbiota, the resulting microbial alterations exacerbate drug-seeking behavior through effects on reward circuitry and stress responsiveness, and the perpetuation of substance use further degrades microbial communities. Breaking this cycle through microbiome-directed interventions, including probiotic supplementation, dietary modification, and fecal microbiota transplantation, represents a promising but underexplored approach to reducing addiction vulnerability and supporting sustained recovery. Understanding the reciprocal relationships between gut microbiota and reward circuitry function is therefore essential for developing comprehensive models of addiction pathophysiology and identifying novel therapeutic targets.

5. PRECLINICAL EVIDENCE

The establishment of causal relationships between gut microbiota composition and substance use disorder phenotypes has been critically advanced through carefully designed preclinical animal models. Germ-free animals, raised in sterile isolators entirely devoid of microbial colonization, provide the most reductionist approach for examining microbiota-dependent effects on drug-related behaviors, revealing that the absence of gut microbes fundamentally alters behavioral and neurochemical responses to psychostimulants, opioids, and alcohol. These studies consistently demonstrate that germ-free mice exhibit exaggerated dopamine release in response to amphetamine and cocaine, along with altered conditioned place preference and locomotor sensitization compared to conventionally colonized controls, effects that are partially reversed by microbial colonization. Antibiotic depletion models offer a complementary approach, enabling investigation of microbiota contributions in adult animals with otherwise normal developmental histories, with studies showing that broad-spectrum antibiotic administration sufficient to reduce bacterial diversity by 30-50% significantly attenuates drug-seeking behavior and reward sensitivity (Lucerne et al., 2021). The specificity of antibiotic effects has been confirmed through recovery experiments wherein behavioral alterations normalize following antibiotic cessation or, more definitively, through fecal microbiota transplantation from untreated donors that restores both microbial composition and drug response phenotypes. These model systems have proven particularly valuable for dissecting the temporal dynamics of microbiota-drug interactions, revealing that microbial influences on reward circuitry operate continuously rather than representing fixed developmental programming effects. The translational relevance of these preclinical approaches is increasingly recognized, with mechanistic insights from animal models informing the design of human studies investigating microbiota-targeted interventions for substance use disorders. Specific drug classes have been systematically investigated using preclinical models to elucidate how gut microbiota modulates their behavioral and neurochemical effects.

Psychostimulant studies demonstrate that microbiota depletion through antibiotics attenuates amphetamine-induced conditioned place preference and locomotor sensitization while reducing drug-evoked dopamine release in the nucleus accumbens, effects associated with altered expression of dopamine transporters and D1 receptors. Opioid research reveals that morphine treatment profoundly disrupts gut microbial composition, reducing beneficial Lactobacillus and Bifidobacterium species while promoting pathobiont expansion, and that this dysbiosis contributes to opioid tolerance, analgesic tolerance, and withdrawal severity through mechanisms involving toll-like receptor signaling and neuroinflammation. Alcohol studies have established bidirectional relationships wherein chronic ethanol consumption induces dysbiosis characterized by reduced short-chain fatty acid producers and increased Gram-negative bacteria, while microbiota depletion prior to alcohol exposure attenuates ethanol preference, consumption, and withdrawal severity (Veseli et al., 2025). Nicotine research demonstrates that smoking cessation alters gut microbial composition and that probiotic administration can reduce nicotine craving and withdrawal symptoms in animal models. Benzodiazepine studies reveal that midazolam and lorazepam administration alters gut microbial diversity and that microbiota status influences the reinforcing effects of these drugs through mechanisms involving GABAergic and serotonergic signaling. Collectively, these preclinical investigations establish that drug-microbiota interactions are not epiphenomenal but functionally significant, with microbial status actively shaping behavioral and neurochemical responses to virtually all classes of abused substances.

Fecal microbiota transplantation has emerged as a powerful tool for establishing causal relationships between specific microbial configurations and addiction-related phenotypes in preclinical models. In this paradigm, microbiota from donor animals with distinct behavioral characteristics or treatment histories is transferred to recipient animals, typically following antibiotic depletion, enabling assessment of whether microbial communities alone can transmit behavioral phenotypes.

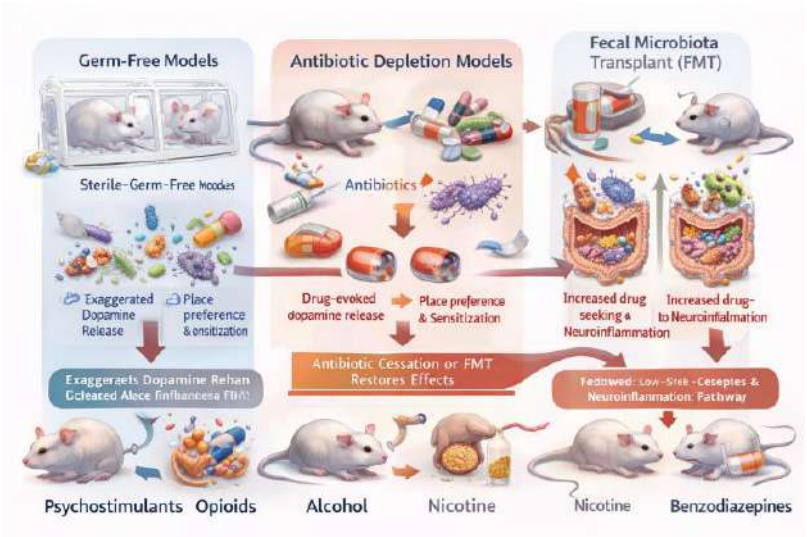

Figure 6. Gut microbiota and substance abuse models

Studies demonstrate that transplantation of microbiota from alcohol-preferring rat strains confers increased ethanol consumption and preference to previously low-drinking recipients, implicating microbial factors in genetically determined alcohol preference.

Similarly, transplantation of microbiota from cocaine-treated donors recapitulates aspects of cocaine-induced behavioral sensitization and neuroinflammation in antibiotic-treated recipients, suggesting that drug-induced dysbiosis itself contributes to addiction pathophysiology. Our ongoing work extends these findings to psychostimulants and benzodiazepines, with preliminary evidence that microbiota from amphetamine-exposed and midazolam-exposed animals transfers specific behavioral and neurochemical phenotypes to naive recipients (D'Onofrio et al., 2026). Probiotic and prebiotic intervention studies provide complementary evidence, demonstrating that oral administration of specific Lactobacillus and Bifidobacterium strains attenuates drug-seeking behavior, normalizes dopamine signaling, and reduces neuroinflammation in animal models of substance use disorders.

The convergence of evidence from germ-free, antibiotic-treated, and transplantation models establishes that the gut microbiota is not merely a passive bystander in addiction but an active participant whose modulation offers promising therapeutic avenues. These preclinical foundations provide the mechanistic rationale for translating microbiome-directed interventions to human substance use disorder populations, with the ultimate goal of developing adjunctive therapies that restore healthy microbial ecosystems and, through them, support addiction recovery.

6. CLINICAL EVIDENCE

Cross-sectional studies comparing individuals with substance use disorders to healthy controls have consistently revealed distinct microbial signatures associated with addiction. Alcohol use disorder represents the most extensively studied condition, with multiple investigations demonstrating reduced microbial diversity, depletion of short-chain fatty acid-producing bacteria including Faecalibacterium and Roseburia, and overgrowth of potentially pathogenic Gram-negative organisms such as Proteobacteria and Fusobacteria. These microbial alterations correlate with clinical parameters including craving severity, duration of alcohol consumption, and liver enzyme abnormalities, suggesting that dysbiosis reflects both the direct effects of alcohol and the systemic consequences of chronic drinking. Opioid use disorder studies similarly reveal profound microbial disruption, with decreased abundance of Bifidobacterium and Lactobacillus species and increased colonization by opportunistic pathogens, alterations that persist during methadone maintenance therapy and may contribute to opioid-induced constipation, immune dysfunction, and craving. Psychostimulant research in human populations remains more limited but emerging evidence suggests cocaine and methamphetamine use are associated with distinct microbial profiles characterized by reduced anti-inflammatory organisms and increased taxa capable of metabolizing these drugs (Chen et al., 2025). Cannabis studies present a more complex picture, with some evidence suggesting cannabidiol and tetrahydrocannabinol exert antimicrobial effects that may contribute to microbial alterations observed in chronic users.

The consistency of findings across multiple substance classes supports the conclusion that substance use disorders are associated with reproducible alterations in gut microbial composition, although whether these changes represent causal factors, consequential effects, or both remains an active area of investigation.

Longitudinal studies and treatment outcome investigations provide crucial insights into the temporal dynamics of microbiome-addiction relationships and the potential for microbial restoration to support recovery. Prospective studies following individuals through detoxification and early abstinence reveal that some microbial alterations partially normalize with cessation of substance use, although recovery is often incomplete and highly variable between individuals. Alcohol-dependent patients who remain abstinent for several weeks show gradual increases in microbial diversity and short-chain fatty acid producers, with the extent of recovery predicting reductions in craving and improved cognitive function. Opioid-dependent individuals transitioning to buprenorphine or methadone maintenance exhibit persistent dysbiosis despite reduced illicit opioid use, suggesting that medication-assisted treatment itself may influence microbial composition and that adjunctive microbiome-targeted interventions may be necessary for full restoration. Studies examining relapse predictors reveal that baseline microbial composition, particularly the abundance of specific short-chain fatty acid-producing taxa, may identify individuals at heightened risk for return to drinking or drug use during early recovery (Wang et al., 2025). The gut-liver-brain axis has received particular attention in alcohol research, with evidence that microbial translocation and endotoxemia resulting from alcohol-induced intestinal permeability predict both liver disease progression and neuroinflammation-related cognitive impairment.These clinical findings align with preclinical evidence and support the conceptualization of gut microbiota as both a biomarker of addiction severity and a modifiable therapeutic target with potential to improve treatment outcomes. Mechanistic human studies employing probiotic, prebiotic, and dietary interventions are beginning to establish proof-of-concept for microbiome-directed therapies in addiction treatment.

Randomized controlled trials of probiotic supplementation in alcohol-dependent patients demonstrate that administration of Lactobacillus and Bifidobacterium strains reduces liver enzyme elevations, improves intestinal barrier function as measured by circulating endotoxin levels, and may attenuate alcohol craving and consumption. Prebiotic fiber supplementation in individuals with alcohol use disorder increases fecal short-chain fatty acid concentrations, reduces inflammatory markers including C-reactive protein and interleukin-6, and is associated with modest improvements in mood and anxiety symptoms that often co-occur with addiction. Dietary intervention studies reveal that adoption of Mediterranean-style or high-fiber diets during early recovery from alcohol dependence is associated with more rapid restoration of microbial diversity and greater reductions in craving compared to standard dietary advice. Emerging research in opioid-dependent populations suggests that probiotic administration may alleviate opioid-induced constipation, a common and distressing side effect that contributes to medication non-adherence and reduced quality of life (Sarita et al., 2025). Neuroimaging studies incorporating microbiome measures provide preliminary evidence that microbial composition correlates with resting-state functional connectivity within reward circuitry and prefrontal control regions, suggesting a neural mechanism linking gut bacteria to addiction-related behaviors in humans. While the clinical evidence base remains less developed than preclinical findings, the convergence of observational and interventional human studies supports the translational potential of microbiome-targeted approaches and justifies continued investigation of their efficacy as adjunctive treatments for substance use disorders. The integration of microbiome assessments into addiction treatment research and clinical practice promises to advance personalized medicine approaches and ultimately improve outcomes for individuals struggling with substance use disorders.

Figure 7. Gut microbiota and substance use disorders

7. MECHANISTIC PATHWAYS: HOW THE MICROBIOME MODULATES DRUG RESPONSES

The gut microbiota exerts profound influence over drug responses through direct metabolic transformations that alter drug pharmacokinetics and bioavailability. Microbial enzymes expressed by gut bacteria possess catalytic capabilities that rival those of the liver, enabling them to perform oxidation, reduction, hydrolysis, and conjugation reactions that activate prodrugs, inactivate active compounds, or generate toxic metabolites with implications for both therapeutic efficacy and adverse effects. The reactivation of the chemotherapeutic agent irinotecan by bacterial beta-glucuronidases exemplifies this phenomenon, but similar mechanisms apply to drugs of abuse, with evidence that microbial enzymes can metabolize psychostimulants, opioids, and benzodiazepines in ways that modify their pharmacological activity. The enterohepatic circulation, wherein drugs and their metabolites are secreted into bile, modified by gut bacteria, and reabsorbed into systemic circulation, represents a particularly significant pathway through which microbiota prolong drug exposure and influence central nervous system concentrations.

Inter-individual variability in microbial composition translates into variable drug metabolism, potentially explaining differences in drug response, side effect profiles, and addiction liability that cannot be accounted for by host genetics alone (Flowers et al., 2020). Beyond direct metabolism, gut microbes influence drug absorption by modulating intestinal permeability, gastric emptying, and expression of drug transporters including P-glycoprotein, thereby affecting the rate and extent to which orally administered drugs reach systemic circulation. Individual differences in substance use disorder phenotypes and for optimizing pharmacotherapeutic approaches to addiction treatment.

Gut microbes modulate neurochemical signaling within reward circuitry through the production of neurotransmitter precursors, metabolites, and neuromodulators that influence drug responses at the synaptic level. The microbial influence over tryptophan metabolism along the kynurenine pathway determines the availability of this essential amino acid for serotonin synthesis, thereby modulating serotonergic tone in brain regions that regulate impulse control, mood, and reward sensitivity. Microbial production of short-chain fatty acids, particularly butyrate, functions as a histone deacetylase inhibitor that promotes epigenetic modifications enhancing brain-derived neurotrophic factor expression and synaptic plasticity, effects that may counteract drug-induced neurotoxicity and support recovery. Certain bacterial strains synthesize or stimulate host production of dopamine and norepinephrine precursors that influence catecholamine availability within the nucleus accumbens and prefrontal cortex, potentially modulating the reinforcing effects of psychostimulants (Kim et al., 2026). Microbial metabolites activate free fatty acid receptors and other G-protein-coupled receptors expressed on enteroendocrine cells, triggering release of gut peptides that signal via vagal afferents to influence dopamine neuron firing and drug-seeking behavior. The gut microbiota also influences expression and function of neurotransmitter transporters and receptors through both direct and indirect mechanisms, with animal studies demonstrating that microbiota status alters dopamine transporter density and D1 receptor expression in reward-related brain regions.

These neurochemical effects operate continuously and bidirectionally, with drugs of abuse simultaneously altering microbial composition and the resulting neuroactive output feeding back to influence drug responses in an ongoing cycle.

Neuroinflammatory pathways represent a third major mechanism through which the gut microbiota modulates drug responses and addiction-related behaviors. Intestinal barrier disruption, induced by stress, drugs of abuse, or dysbiosis itself, permits translocation of bacterial products including lipopolysaccharide and peptidoglycan into systemic circulation, triggering activation of toll-like receptor signaling and production of pro-inflammatory cytokines that access the brain. Once within the central nervous system, these inflammatory mediators activate microglia, the brain's resident immune cells, promoting a neuroinflammatory state that alters neurotransmitter metabolism, synaptic function, and neuronal survival. Chronic alcohol consumption exemplifies this pathway, with alcohol-induced intestinal hyperpermeability enabling bacterial lipopolysaccharide translocation that activates hepatic Kupffer cells and brain microglia, contributing to both liver disease and alcohol-related neurotoxicity and cognitive impairment. Opioid-induced dysbiosis similarly promotes intestinal barrier disruption and microbial translocation, with resulting neuroinflammation contributing to analgesic tolerance, opioid-induced hyperalgesia, and withdrawal severity (Li et al., 2025). Psychostimulants including amphetamine and methamphetamine activate neuroinflammatory pathways through both direct effects on glial cells and indirect effects involving gut-derived inflammatory signals, with evidence that microbiota composition influences the magnitude of drug-induced neuroinflammation. The convergence of these mechanistic pathways—pharmacokinetic, neurochemical, and neuroinflammatory—positions the gut microbiota as a central integrator of drug responses whose modulation offers unprecedented opportunities for therapeutic intervention in substance use disorders.

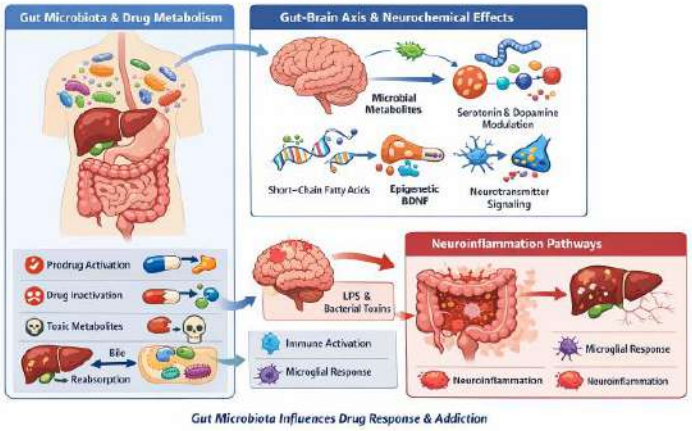

Figure 8. Mechanistic Pathways involved in gut microbiota and brain health

8. MICROBIOTA GUT BRAIN AXIS IN PSYCHOSTIMULANT DEPENDENCE

The recognition that gut microbiota modulates behavioral and neurochemical responses to psychostimulants has emerged from a growing body of preclinical evidence spanning the past decade. Early investigations demonstrated that germ-free animals, completely lacking microbial colonization, exhibit exaggerated locomotor responses to amphetamine and cocaine compared to conventionally colonized controls, establishing that the presence of gut microbes fundamentally alters psychostimulant sensitivity. Subsequent studies employing antibiotic-induced microbiota depletion confirmed these findings, revealing that reduced microbial diversity attenuates cocaine-induced conditioned place preference and amphetamine-induced behavioral sensitization, effects that are reversed following microbiota reconstitution. The specificity of these effects has been demonstrated through fecal microbiota transplantation experiments, wherein transfer of microbiota from cocaine-treated donors to antibiotic-treated recipients recapitulated aspects of cocaine-induced behavioral and neurochemical alterations (Diotaiuti et al., 2025).

These preclinical observations have been extended across multiple psychostimulant classes, including methamphetamine, methylphenidate, and MDMA, with consistent evidence that microbial status influences drug responses through convergent mechanisms involving dopamine signaling and neuroinflammation. The translational relevance of these findings is supported by emerging clinical evidence documenting altered gut microbial composition in individuals with stimulant use disorders compared to healthy controls. Collectively, this body of work establishes the microbiota-gut-brain axis as a critical determinant of psychostimulant responses with implications for understanding addiction vulnerability and developing novel interventions.

Mechanistic investigations have identified multiple pathways through which gut microbiota modulates psychostimulant actions at the molecular and neurochemical level. Microbial metabolism of dietary components generates short-chain fatty acids that function as histone deacetylase inhibitors, promoting epigenetic modifications that influence expression of dopamine receptors and transporters within reward circuitry. Germ-free and antibiotic-treated animals exhibit altered dopamine turnover in the nucleus accumbens and striatum, along with changes in D1 and D2 receptor density that correlate with modified behavioral responses to amphetamine and cocaine. The microbiota influences neuroinflammatory pathways activated by psychostimulants, with evidence that microbial depletion attenuates drug-induced microglial activation and pro-inflammatory cytokine expression in brain regions mediating reward and motivation (Cheng et al., 2024). Gut microbes contribute to tryptophan metabolism along the kynurenine pathway, thereby influencing the balance between neuroprotective and neurotoxic metabolites that modulate psychostimulant neurotoxicity and cognitive sequelae. The hypothalamic-pituitary-adrenal axis represents an additional mechanistic node, as microbiota status influences stress hormone responses that interact synergistically with psychostimulant effects on dopamine signaling. These convergent mechanisms position the gut microbiota as an integrative hub through which environmental, dietary, and pharmacological factors shape individual responses to psychostimulant drugs.

The bidirectional nature of psychostimulant-microbiota interactions has important implications for understanding addiction pathophysiology and treatment. Chronic psychostimulant administration consistently alters gut microbial composition, reducing beneficial taxa including Lactobacillus and Bifidobacterium while promoting expansion of potentially pathogenic organisms, effects that persist beyond drug cessation and may contribute to relapse vulnerability. These drug-induced microbial alterations correlate with behavioral measures of addiction severity, including the magnitude of conditioned place preference, the rate of extinction, and the propensity for drug-seeking reinstatement. The functional significance of psychostimulant-induced dysbiosis is supported by studies demonstrating that probiotic administration during drug exposure or withdrawal attenuates behavioral sensitization, normalizes dopamine signaling, and reduces relapse-like behavior in animal models. Dietary factors that shape microbial composition, including fiber content and polyphenol availability, modulate psychostimulant responses, suggesting nutritional interventions as potential adjunctive therapies (Rudrapal et al., 2026). The emerging understanding of microbiota contributions to psychostimulant dependence has prompted investigation of novel therapeutic strategies, including targeted probiotic formulations, prebiotic supplementation, and fecal microbiota transplantation, with preliminary evidence supporting their efficacy in preclinical models. Future research directions include identifying specific microbial strains and metabolites responsible for psychostimulant modulation, characterizing the developmental windows during which microbiota influences addiction vulnerability, and translating these findings into clinical interventions for stimulant use disorders.

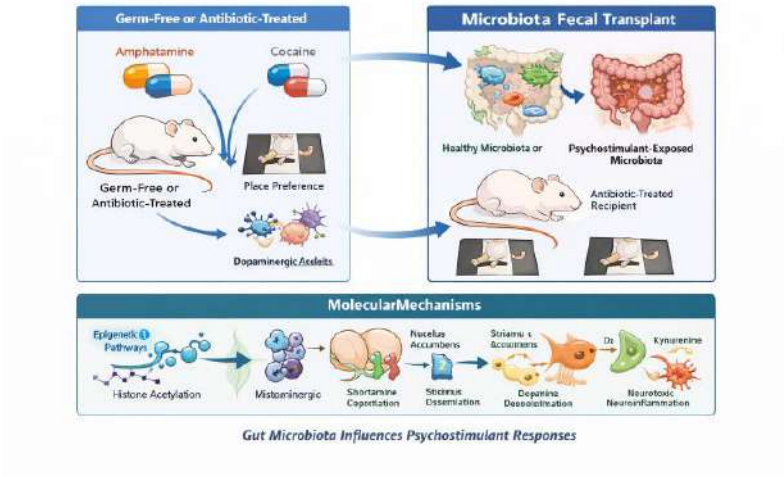

Figure 9. Gut microbiota and psychostimulant responses

9. GUT MICROBIOME IN BENZODIAZEPINE DEPENDENCE

The relationship between benzodiazepines and the gut microbiome has received comparatively less attention than psychostimulants or opioids, yet emerging evidence suggests clinically significant bidirectional interactions. Benzodiazepines, including midazolam, lorazepam, and diazepam, are widely prescribed for anxiety, insomnia, and seizure disorders, but their long-term use is limited by tolerance, dependence, and withdrawal syndromes that complicate clinical management. Preclinical investigations have begun to characterize the effects of benzodiazepine administration on gut microbial composition, revealing that repeated treatment with midazolam and lorazepam alters microbial diversity and reduces abundance of short-chain fatty acid-producing taxa including Lachnospiraceae and Ruminococcaceae. These microbial alterations correlate with behavioral measures of benzodiazepine dependence, including the magnitude of conditioned place preference, the severity of withdrawal symptoms, and the propensity for drug-seeking behavior following abstinence. The functional significance of benzodiazepine-induced dysbiosis is supported by antibiotic depletion studies demonstrating that microbiota disruption attenuates the reinforcing effects of midazolam and modifies the expression of benzodiazepine withdrawal (Rathore et al., 2025).

Sex differences in benzodiazepine responses may involve the gut microbiome, as male and female animals exhibit distinct microbial compositions and corresponding differences in benzodiazepine sensitivity and dependence liability. The recognition that benzodiazepines influence gut microbial ecology opens new avenues for understanding individual differences in treatment responses and for developing interventions that mitigate dependence risk while preserving therapeutic efficacy.

Mechanistic studies have identified multiple pathways through which the gut microbiome may influence benzodiazepine dependence and withdrawal. Benzodiazepines exert their pharmacological effects through positive allosteric modulation of GABA-A receptors, enhancing inhibitory neurotransmission throughout the central nervous system, and emerging evidence suggests gut microbes can influence GABAergic signaling through production of GABA itself and through modulation of the blood-brain barrier permeability to GABA precursors. The hypothalamic-pituitary-adrenal axis represents a critical interface, as benzodiazepines suppress stress hormone responses while the gut microbiome modulates basal and stress-induced cortisol release, creating potential interactions that influence dependence liability and withdrawal severity. Neuroinflammatory pathways contribute to benzodiazepine dependence, with evidence that repeated benzodiazepine administration activates microglia and promotes pro-inflammatory cytokine expression in brain regions mediating anxiety and reward, effects that are modified by microbiota status (Navarrete et al., 2026). The tryptophan-kynurenine pathway, regulated by gut microbes, generates metabolites that influence GABAergic and glutamatergic neurotransmission, potentially modulating the neurochemical adaptations underlying benzodiazepine tolerance and withdrawal. Short-chain fatty acids produced by gut bacteria influence blood-brain barrier integrity and neurotransmitter synthesis, with butyrate in particular demonstrating anxiolytic properties that may interact with benzodiazepine effects. These mechanistic insights suggest that the gut microbiome represents both a modulator of benzodiazepine pharmacodynamics and a potential therapeutic target for reducing dependence liability. Clinical studies examining the gut microbiome in benzodiazepine-dependent populations remain limited but suggest translational relevance of preclinical findings.

Cross-sectional investigations have documented altered microbial composition in individuals chronically using benzodiazepines compared to medication-free controls, with reduced diversity and depletion of butyrate-producing bacteria including Faecalibacterium and Roseburi. These microbial alterations correlate with clinical parameters including duration of benzodiazepine use, daily dose equivalents, and severity of anxiety symptoms, suggesting dose-dependent effects of benzodiazepines on gut microbial ecology. Withdrawal studies reveal that supervised benzodiazepine tapering is associated with partial restoration of microbial diversity, although recovery is often incomplete and highly variable between individuals, with the extent of microbial normalization predicting withdrawal symptom severity and successful discontinuation. The high prevalence of benzodiazepine use in elderly populations, who already exhibit age-related declines in microbial diversity, raises particular concerns about compounded dysbiosis and its contribution to cognitive impairment and fall risk (Ferretti, 2025). Emerging evidence suggests that probiotic supplementation during benzodiazepine withdrawal may attenuate anxiety symptoms and improve sleep quality, although controlled trials are needed to establish efficacy. The convergence of preclinical and clinical evidence supports the conceptualization of the gut microbiome as a previously unrecognized factor in benzodiazepine dependence, with implications for personalized prescribing, withdrawal management, and the development of adjunctive therapies that target the microbiota to improve outcomes for individuals requiring long-term benzodiazepine treatment.

10. THERAPEUTIC INTERVENTIONS

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have emerged as promising adjunctive interventions for substance use disorders based on their ability to restore healthy gut microbial composition and function. Preclinical studies demonstrate that oral administration of specific Lactobacillus and Bifidobacterium strains attenuates behavioral responses to psychostimulants, reduces alcohol preference, and ameliorates opioid-induced intestinal dysfunction and withdrawal severity.

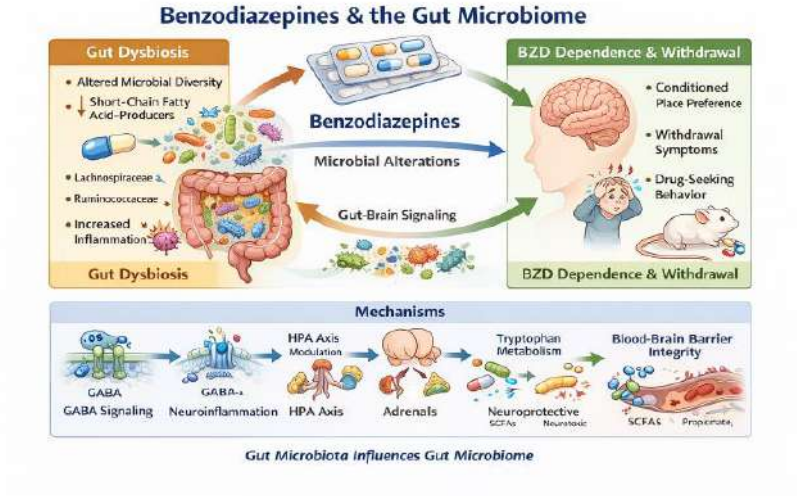

Figure 10. Benzodiazepines and gut microbiome interactions

The mechanisms underlying these effects involve probiotic restoration of intestinal barrier integrity, reduction of systemic inflammation, and modulation of neuroactive metabolite production including short-chain fatty acids and neurotransmitters that influence brain function. Clinical trials in alcohol-dependent populations have shown that probiotic supplementation reduces liver enzyme elevations, decreases circulating endotoxin levels, and may attenuate craving and consumption, although effects on abstinence rates remain mixed. Prebiotics, non-digestible fibers that selectively stimulate beneficial gut bacteria, offer an alternative approach that avoids concerns about live microorganism administration while promoting endogenous production of short-chain fatty acids and other beneficial metabolites (Wang et al., 2026). Synbiotic formulations combining probiotics with prebiotics may produce synergistic effects, with emerging evidence supporting their superiority over either intervention alone in restoring microbial diversity and reducing inflammation in substance use disorder populations. The growing recognition that individual probiotic strains exert distinct effects has prompted investigation of targeted formulations designed to address specific aspects of addiction pathophysiology, including craving, withdrawal, and cognitive impairment.

Fecal microbiota transplantation represents the most direct and comprehensive approach to microbiome restoration, involving transfer of entire microbial communities from healthy donors to recipients with dysbiosis-associated conditions. Originally developed for treatment of recurrent Clostridioides difficile infection, FMT is now being investigated across a range of neuropsychiatric disorders including substance use disorders based on compelling preclinical evidence that addiction-related behavioral phenotypes can be transferred through microbial transplantation. Animal studies demonstrate that transplantation of microbiota from alcohol-preferring strains confers increased ethanol consumption to recipient animals, while transfer from cocaine-treated donors recapitulates aspects of psychostimulant sensitization, establishing that microbial communities alone can transmit addiction-related behavioral traits. Early-phase clinical trials are exploring FMT in alcohol-associated liver disease, with preliminary evidence suggesting improvements in liver function, reduced inflammation, and possible benefits for alcohol craving and consumption (Uppala et al., 2026). The application of FMT to opioid and psychostimulant use disorders remains in earlier stages of investigation, with proof-of-concept studies needed to establish safety and efficacy before larger trials can be justified. Significant challenges confront the widespread implementation of FMT for addiction treatment, including donor screening standardization, optimal route of administration, dosing frequency determination, and long-term safety monitoring, particularly given the vulnerability of substance use disorder populations to infectious complications. Despite these challenges, FMT represents a powerful tool for establishing causal relationships between microbiota and addiction phenotypes while offering therapeutic potential for individuals with severe, treatment-refractory substance use disorders. Beyond probiotics, prebiotics, and FMT, emerging therapeutic strategies targeting the gut-brain axis in addiction treatment include precision microbiome modulation, postbiotic administration, and dietary interventions. Postbiotics, defined as preparations of inanimate microorganisms and/or their components that confer health benefits, offer advantages including standardized composition, reduced safety concerns, and the ability to deliver defined mixtures of microbial metabolites including short-chain fatty acids, neurotransmitters, and immunomodulatory compounds.

Phage therapy targeting specific pathogenic bacteria represents a highly selective approach to microbiome modulation, with potential applications in eliminating organisms that contribute to drug-induced dysbiosis or that metabolize drugs in ways that enhance their abuse liability. Dietary interventions, particularly adoption of Mediterranean-style or high-fiber diets, produce reproducible effects on microbial composition and metabolite production that may support addiction recovery through multiple mechanisms including reduced inflammation, improved cognitive function, and enhanced stress resilience (Chalotra et al., 2026). The convergence of microbiome science with precision medicine approaches promises to enable personalized interventions wherein an individual's baseline microbial composition guides selection of specific probiotic strains, prebiotic fibers, or dietary recommendations optimized for their unique microbial profile and addiction phenotype. Machine learning algorithms applied to metagenomic sequencing data are being developed to predict treatment responses and identify patients most likely to benefit from microbiome-directed interventions. The integration of microbiome-targeted therapies with established addiction treatments, including pharmacotherapy and behavioral interventions, offers the potential for synergistic effects that address the multiple biological and psychosocial dimensions of substance use disorders, moving beyond symptomatic management toward restoration of healthy gut-brain axis function.

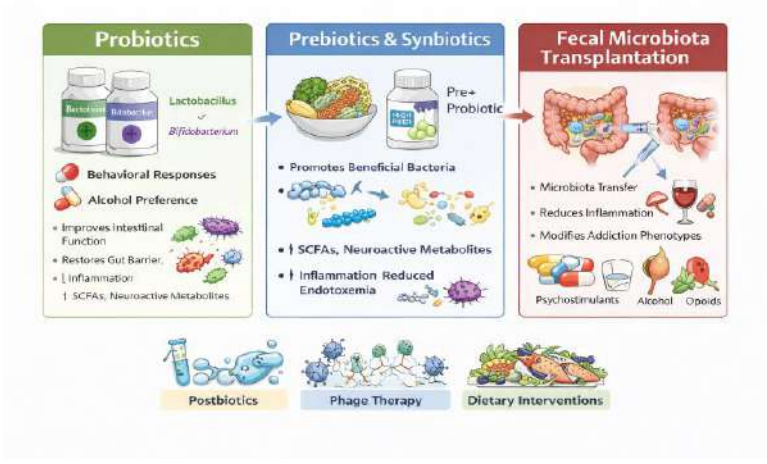

Figure 11. Microbiome therapies for substance use disorders

11. THE ROLE OF DIET AND NUTRITION IN ADDICTION RECOVERY

Dietary patterns represent one of the most powerful and rapidly acting determinants of gut microbial composition, with profound implications for addiction recovery through microbiome-mediated effects on brain function and behavior. The typical Western diet, characterized by high saturated fat, refined sugar, and low fiber content, promotes microbial dysbiosis marked by reduced diversity, depletion of short-chain fatty acid producers, and expansion of pro-inflammatory taxa that compromise intestinal barrier integrity and promote systemic inflammation. In contrast, plant-based diets rich in diverse fibers, polyphenols, and fermentable substrates support microbial ecosystems dominated by saccharolytic bacteria that generate beneficial metabolites with neuroactive properties. The transition from active substance use to recovery represents an opportune window for dietary intervention, as drug-induced dysbiosis creates a state of heightened microbial plasticity wherein dietary modifications may exert particularly pronounced effects. Clinical studies in alcohol-dependent populations demonstrate that adoption of Mediterranean-style diets during early abstinence accelerates restoration of microbial diversity, reduces inflammatory markers, and is associated with improved cognitive function and reduced craving compared to standard dietary advice (Zhang et al., 2026). The gut-brain axis mediates these effects through multiple mechanisms, including enhanced production of neuroprotective short-chain fatty acids, modulation of tryptophan metabolism along the kynurenine pathway, and reduced translocation of pro-inflammatory bacterial products that trigger neuroinflammation within reward circuitry. Recognition that dietary choices influence addiction recovery outcomes through microbiome-dependent pathways has prompted integration of nutritional counseling into comprehensive treatment programs and investigation of targeted dietary interventions as adjunctive therapies for substance use disorders. Specific dietary components with demonstrated effects on gut microbiota and brain function have attracted particular attention for their potential to support addiction recovery.

Dietary fiber, particularly from fruits, vegetables, and whole grains, serves as the primary substrate for microbial fermentation, with high-fiber intake promoting production of acetate, propionate, and butyrate that strengthen intestinal barrier function, reduce inflammation, and influence brain-derived neurotrophic factor expression and synaptic plasticity. Polyphenols abundant in berries, green tea, and dark chocolate exert prebiotic-like effects, selectively stimulating growth of beneficial bacteria while their metabolites cross the blood-brain barrier to exert direct neuroprotective and anti-inflammatory effects relevant to drug-induced neurotoxicity. Omega-3 fatty acids, found in fatty fish and certain plant sources, modulate microbial composition while simultaneously serving as precursors for specialized pro-resolving mediators that dampen neuroinflammation and promote synaptic health (Shah et al., 2025). Tryptophan-rich foods including dairy, eggs, and legumes influence the gut-brain axis through multiple mechanisms, providing substrate for both microbial metabolism and host serotonin synthesis while modulating the balance between neuroprotective and neurotoxic kynurenine pathway metabolites. Fermented foods containing live microorganisms, including yogurt, kefir, kimchi, and sauerkraut, may directly introduce beneficial bacterial strains while their bioactive metabolites exert immunomodulatory and neuroactive effects. The convergence of evidence supporting specific dietary components has informed development of "psychobiotic" diets designed to optimize microbial composition for mental health, with preliminary studies suggesting benefits for mood, anxiety, and cognitive function that may extend to addiction recovery populations.

Clinical implementation of dietary interventions for addiction recovery faces significant challenges but offers substantial promise when integrated into comprehensive treatment approaches. Substance use disorders are frequently accompanied by poor nutritional status, food insecurity, and disordered eating patterns that complicate dietary intervention and require multidisciplinary approaches addressing social determinants of health alongside nutritional counseling. The high prevalence of co-occurring medical conditions including liver disease, metabolic syndrome, and gastrointestinal disorders in substance use disorder populations necessitates individualized dietary recommendations that account for comorbidities and potential drug-nutrient interactions.

Figure 12. Western vs Mediterranean diet comparison

Behavioral interventions incorporating motivational interviewing and cognitive-behavioral techniques have been adapted to address dietary change, recognizing that the skills required for modifying eating behaviors overlap substantially with those needed for maintaining abstinence. Preliminary evidence from pilot studies suggests that structured dietary interventions during early recovery from alcohol, opioid, and stimulant use disorders are feasible, acceptable to patients, and associated with improved outcomes including reduced craving, lower relapse rates, and enhanced quality of life (García-Estrada et al., 2025). The integration of microbiome assessment into clinical practice may eventually enable personalized dietary recommendations based on individual microbial profiles, optimizing the selection of specific fibers, polyphenols, and fermented foods to address each patient's unique dysbiosis pattern and addiction phenotype. Future research priorities include large-scale randomized controlled trials evaluating the efficacy of specific dietary interventions, identification of microbial and metabolic mediators of dietary effects on addiction outcomes, and development of implementation strategies supporting sustained dietary change in diverse substance use disorder treatment settings.

12. FUTURE DIRECTIONS

The transition from association to causation in microbiome-addiction research represents a critical frontier that will determine the translational potential of this field. While cross-sectional studies have established reproducible associations between substance use disorders and altered microbial composition, establishing causal relationships requires integration of multi-omics approaches, mechanistic animal studies, and carefully designed human interventions. Advanced sequencing technologies combined with metabolomics and proteomics enable characterization not only of microbial taxonomy but also of functional capacity and metabolic output, revealing which microbial genes and metabolites actually drive effects on brain function and behavior. Machine learning algorithms applied to these multi-dimensional datasets are being developed to identify microbial signatures that predict addiction vulnerability, treatment response, and relapse risk with sufficient accuracy to inform clinical decision-making. The identification of specific microbial strains and their neuroactive metabolites responsible for modulating drug responses will enable development of targeted interventions, moving beyond broad-spectrum probiotics toward precisely engineered consortia designed to restore specific functions deficient in addiction-associated dysbiosis (Mylavarapu et al., 2026). Causal inference frameworks combining Mendelian randomization with microbiome genome-wide association studies may help disentangle the bidirectional relationships between host genetics, microbial composition, and addiction phenotypes. The ultimate goal of this research trajectory is to establish microbiome-based biomarkers that guide personalized treatment selection and to identify microbial targets amenable to therapeutic manipulation.

Personalized medicine approaches leveraging individual microbiome profiles promise to transform addiction treatment by enabling selection of interventions optimized for each patient's unique microbial configuration. Baseline microbial composition may predict responses to existing pharmacotherapies for addiction, with emerging evidence suggesting that the efficacy of medications including naltrexone, buprenorphine, and acamprosate varies as a function of gut microbial status.

Microbiome profiling could guide selection among probiotic strains, prebiotic fibers, and dietary recommendations, matching interventions to each patient's specific microbial deficits and metabolic requirements. The development of living biotherapeutic products containing defined microbial consortia designed to perform specific functions—such as restoring butyrate production, enhancing intestinal barrier integrity, or modulating dopamine signaling—represents a next-generation approach to microbiome-directed therapy. Integration of real-time microbiome monitoring using point-of-care devices could enable dynamic treatment adjustment, with probiotic or dietary interventions modified based on changes in microbial composition during different phases of recovery. The identification of microbial metabolites that serve as biomarkers of treatment response could streamline this process, providing readily measurable indicators of target engagement and therapeutic efficacy (Yaqub et al., 2025). Ethical considerations surrounding microbiome-based personalization, including data privacy, equitable access, and the potential for discrimination based on microbial profiles, must be addressed proactively as these technologies approach clinical implementation.

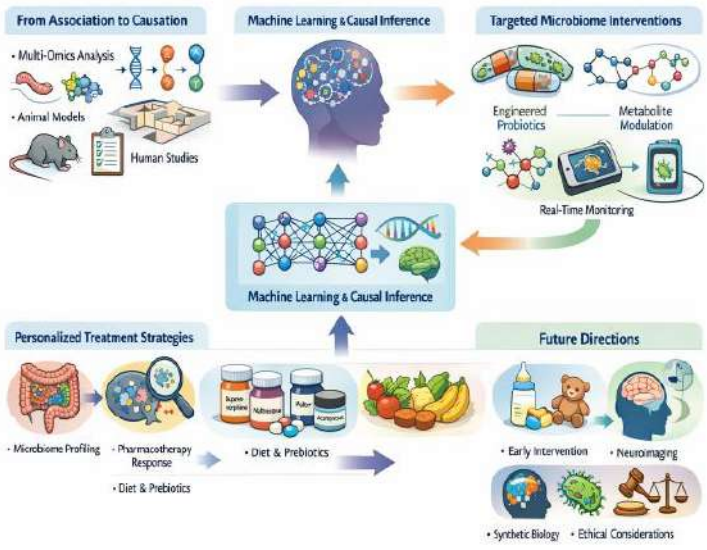

Figure 13. Microbiome in addiction future research

Beyond treatment personalization, the future of microbiome research in addiction medicine encompasses prevention strategies, early intervention, and integration with other emerging technologies. Early-life microbial colonization represents a critical window during which environmental factors shape both microbiota composition and subsequent addiction vulnerability, suggesting that probiotic or dietary interventions during infancy and childhood could reduce population-level risk for substance use disorders. The convergence of microbiome science with digital health technologies, including smartphone-based dietary tracking and personalized feedback, offers scalable platforms for delivering and monitoring microbiome-targeted interventions in real-world settings. Integration of microbiome assessment with neuroimaging, genetics, and behavioral phenotyping promises to reveal novel endophenotypes that transcend diagnostic boundaries and may better capture the biological heterogeneity underlying substance use disorders. The application of synthetic biology to engineer microorganisms with specific therapeutic functions—such as drug-metabolizing enzymes that reduce the addictive potential of abused substances or receptors that sequester drugs in the gut—represents a futuristic but increasingly plausible approach (Robinson & Breed, 2025). Overcoming barriers to clinical translation will require standardized protocols for microbiome sample collection, processing, and analysis, establishment of reference ranges for healthy microbial composition across diverse populations, and rigorous randomized controlled trials demonstrating that microbiome-directed interventions improve clinically meaningful outcomes. The successful integration of microbiome science into addiction medicine will require sustained interdisciplinary collaboration among microbiologists, neuroscientists, clinicians, and bioethicists, working together to translate fundamental discoveries into interventions that reduce the enormous individual and societal burden of substance use disorders.

CONCLUSION

The gut-brain axis has emerged as a critical mediator of substance use disorder pathophysiology, fundamentally expanding our understanding of addiction beyond traditional neurocentric models.

Preclinical evidence across multiple drug classes, including psychostimulants, opioids, alcohol, and benzodiazepines, demonstrates that gut microbiota composition actively shapes behavioral and neurochemical responses to drugs of abuse through mechanisms involving pharmacokinetic modulation, neurochemical signaling, and neuroinflammatory pathways. Clinical investigations confirm that substance use disorders are associated with reproducible alterations in gut microbial composition that correlate with craving severity, treatment outcomes, and relapse vulnerability, supporting the translational relevance of preclinical findings. The bidirectional nature of drug-microbiota interactions, wherein substances of abuse induce dysbiosis that in turn perpetuates drug-seeking behavior, creates a vicious cycle that represents an attractive target for therapeutic intervention. Probiotic, prebiotic, and dietary interventions have demonstrated preliminary efficacy in preclinical models and early-phase clinical trials, offering safe, well-tolerated adjunctive approaches to conventional addiction treatments. Fecal microbiota transplantation represents a more comprehensive strategy for microbiome restoration with potential application in treatment-refractory populations, although significant challenges remain before widespread implementation. Personalized medicine approaches leveraging individual microbiome profiles to guide selection of targeted interventions promise to optimize treatment outcomes and move beyond one-size-fits-all strategies. The integration of microbiome science with emerging technologies, including multi-omics platforms, machine learning, and synthetic biology, will accelerate the identification of microbial biomarkers and the development of next-generation therapeutics. Ultimately, the recognition that the gut microbiome represents both a modifiable risk factor and a therapeutic target in substance use disorders opens unprecedented opportunities for reducing the enormous individual and societal burden of addiction through restoration of healthy gut-brain axis function.

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CHAPTER 2
THE GUT-BRAIN AXIS IN 2026: HOW THE MICROBIOME SHAPES OUR PSYCHOLOGICAL STATE

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INTRODUCTION

In 2026, the frontier between psychiatry and metabolic medicine has definitively blurred. We no longer view anxiety disorders, depression, or brain fog as exclusively psychogenic or neural entities, but as expressions of a profound physiological imbalance, whose roots often lie in the small intestine and colon. This conceptual revolution is fueled by two decades of cutting-edge research on the gut microbiome – the ecosystem of trillions of bacteria, viruses, and fungi that inhabit the gastrointestinal tract – and its systemic impact, collectively termed the "psychobiota" (Cryan & Dinan, 2023).

This manuscript, based on a synthesis of scientific data from 2024-2026 and specialized clinical practice, aims to map the precise mechanisms through which this "second brain" shapes our psychological state. We start from the premise that hidden metabolic disorders – subclinical insulin resistance, low-grade inflammation caused by endotoxemia, mitochondrial dysfunction – are essential mediators in the relationship between dysbiosis and psychopathology (Grimm, 2026). They function as a constant "background noise" of the nervous system, transforming metabolic signals into psychological reality.

The purpose of this paper is to provide clinicians and researchers with a comprehensive and updated framework, structured on:

- Fundamental molecular mechanisms of microbiome-brain communication.
- Clinical forms of psychological disorders with metabolic-microbial substrate.
- Next-generation diagnostic tools available in 2026.
- Integrated therapeutic strategies, from precision nutrition to psychobiotics.

We will demonstrate that addressing depression or anxiety without investigating and correcting potential imbalances at the level of this axis represents incomplete therapy, partially explaining the significant rates of non-response to conventional psychotropic treatments. Conceptual Map of the Gut-Brain-Metabolism Axis: From Triggering Factors to Symptom and Intervention

To facilitate an integrative understanding of the complex mechanisms detailed in the following chapters, we present a synoptic conceptual diagram (Figure 1).

This illustrates the main flow through which lifestyle and nutritional factors influence the gut microbiome, triggering three central pathological pathways (inflammatory, metabolic, and neurochemical) that converge towards specific psychological manifestations. The diagram also highlights the critical points of diagnostic and therapeutic intervention available in 2026, supporting the integrative approach promoted in this article.

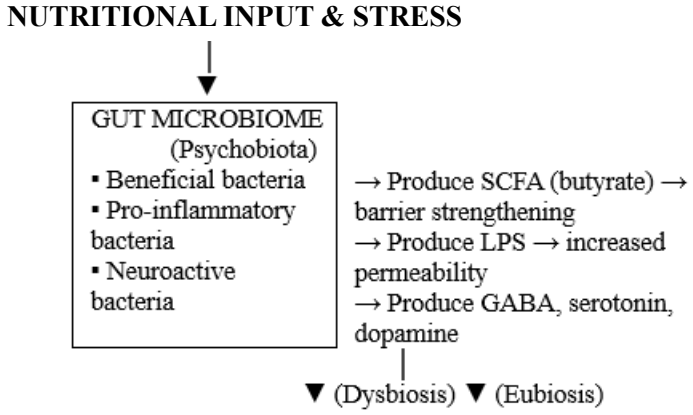


Figure 1. Conceptual map of the Gut-Brain-Metabolism Axis (2026).

Red arrows indicate pathological pathways from trigger to symptom. Green boxes indicate domains of therapeutic and diagnostic intervention. Blue dashed arrows illustrate feedback and rebalancing mechanisms. Abbreviations: SCFA - Short-Chain Fatty Acids; LPS - Lipopolysaccharides; BBB - Blood-Brain Barrier; HPA - Hypothalamic-Pituitary-Adrenal axis; NGS - Next-Generation Sequencing; CGM - Continuous Glucose Monitoring; OAT - Organic Acids Test.

1. FUNDAMENTAL MECHANISMS OF THE GUT-BRAIN-METABOLISM AXIS

The gut-brain axis is not a one-way street, but a bidirectional and multimodal highway. In 2026, we understand that communication occurs through at least four main, interdependent pathways: neural (vagal), endocrine, metabolic, and immune. The microbiome is the conductor of this symphonic complex, influencing each pathway.

1.1 The Microbiome as a Neuroactive "Chemical Factory": Direct Synthesis of Neurotransmitters

One of the most profound discoveries of the last decade is the ability of gut bacteria to directly produce neuroactive molecules or decisively modulate their synthesis by the host (Yano et al., 2025). This process transforms the gut into a primary neuroendocrine organ.

- GABA (Gamma-Aminobutyric Acid): The main inhibitory neurotransmitter of the central nervous system, with a strong anxiolytic effect, is produced in significant amounts in the intestinal lumen. Species ubiquitous in probiotics, such as *Lactobacillus* spp. and *Bifidobacterium* spp., possess the enzyme glutamate decarboxylase (GAD), which converts glutamate (an amino acid abundant in food) into GABA (Strandwitz et al., 2024). The GABA produced in the gut does not easily cross the blood-brain barrier (BBB), but acts locally on enteric and vagal nerve endings, transmitting calming signals to the brain within milliseconds. A deficit in these GABA-producing species is directly correlated with neuronal hyperactivity and symptoms of generalized anxiety.
- Serotonin (5-HT): Approximately 95% of the body's serotonin is synthesized and stored in the gut, mainly in enterochromaffin cells (EC). This process is strongly influenced by the microbiome. Commensal bacteria such as *Streptococcus, Enterococcus*, and some strains of *Escherichia* produce enzymes that catalyze the conversion of tryptophan into 5-hydroxytryptophan (5-HTP), the direct precursor of serotonin (Chen et al., 2025). Low levels of peripheral serotonin, influenced by dysbiosis, not only affect intestinal motility but also the general affective tone, as precursors and metabolites can influence brain state.
- Dopamine and Norepinephrine: Bacterial species from the genera *Bacillus* and *Serratia* have complete metabolic pathways for the synthesis of catecholamines. Dopamine produced in the gut acts locally on the enteric nervous system but also on reward circuits via vagal signals.

A healthy microbiota supports a balanced dopaminergic tone, essential for motivation and the ability to experience pleasure (anhedonia being a key marker of imbalance).

- Acetylcholine: Certain bacteria, such as *Lactobacillus plantarum*, stimulate the production of acetylcholine in the gut, influencing memory, learning, and intestinal muscle tone.

Recent meta-analysis (Liu et al., 2025): A systematic review of 45 animal studies and 18 human studies confirmed a significant positive correlation between the abundance of *Lactobacillus* and *Bifidobacterium* and tissue levels of GABA and serotonin in murine models, as well as an amelioration of anxiety and depression symptoms in human subjects after supplementation with these strains.

1.2 Precursor Control: The Tryptophan Pathway and Neurotoxic Diversion

Bacteria not only control final synthesis but also the flow of raw materials. Tryptophan, an essential amino acid, is the most critical bifurcation point. It can be metabolized via three competing pathways:

- The Serotonin/Melatonin Pathway (in gut and brain).
- The Direct Microbial Pathway (towards indole and derivatives, which regulate inflammation).
- The Kynurenine Pathway (in immune cells and hepatocytes).

Under conditions of microbiome equilibrium and absence of inflammation, a healthy proportion of tryptophan is directed towards serotonin production. Conversely, in a state of dysbiosis and low-grade systemic inflammation (caused by a pro-inflammatory diet, chronic stress, or infections), pro-inflammatory cytokines (IL-6, TNF-α) activate the enzymes IDO-1 and TDO, which massively divert tryptophan towards the kynurenine pathway.

The psychological consequence is devastating: The kynurenine pathway produces neuroactive metabolites. On one hand, kynurenic acid, which has neuroprotective effects, can be produced. However, under conditions of oxidative stress and prolonged inflammation, the balance tilts towards the production of quinolinic acid, a strong NMDA receptor agonist with direct excitotoxic and neurotoxic effects (Erhardt et al., 2024).

Elevated levels of quinolinic acid in the cerebrospinal fluid are consistently associated with severe depression, suicidal tendencies, and neurodegeneration in post-mortem and brain imaging studies. Thus, an unbalanced microbiome "steals" the raw material for happiness (tryptophan) and transforms it into a neurotoxin, explaining the biological substrate of depression that does not respond to SSRIs.

1.3 Short-Chain Fatty Acids (SCFAs): Metabolic Mediators of Calm

The production of short-chain fatty acids (SCFAs) – butyrate, propionate, acetate through bacterial fermentation of dietary fiber is one of the most beneficial services the microbiome offers us. In 2026, their role has expanded beyond colonocyte nutrition.

Butyrate: Epigenetic Regulator and Guardian of Barriers

- *Epigenetic action:* Butyrate is a strong natural inhibitor of histone deacetylases (HDACs). By maintaining an optimal degree of histone acetylation, butyrate promotes the expression of genes involved in neuroplasticity, neurogenesis, and stress resilience in the hippocampus. Animal studies show that butyrate supplementation has antidepressant and anxiolytic effects similar to those of some medications (Sun et al., 2025).
- *Strengthening barriers:* Butyrate is the main energy source for colonocytes, promoting the formation of strong tight junctions. This maintains the intestinal barrier intact, preventing "leaky gut." An intact barrier is essential to prevent the entry into the bloodstream of lipopolysaccharides (LPS) – endotoxins from the walls of gram-negative bacteria. Circulating LPS is a strong trigger of systemic inflammation.

Propionate and Acetate: Dual Metabolic Role

- *Propionate* is a precursor for gluconeogenesis in the liver and can modulate energy metabolism. In excess and produced by certain pathogenic strains (e.g., *Clostridium*), it can have disruptive effects on neuronal mitochondria, contributing to brain fog.

- *Acetate* reaches the brain and can influence the satiety centers in the hypothalamus, as well as neurotransmitter synthesis.

Recent meta-analysis (Vincenzi et al., 2025): An aggregated analysis of 30 clinical studies highlighted that individuals with major depressive disorders have significantly lower total SCFA and butyrate levels in stool compared to healthy controls. Interventions with fermentable fibers (especially resistant starch) increased SCFA levels and led to moderate clinical improvements in depressive symptoms in over 60% of participants.

1.4 The Vagus Nerve: The Real-Time Neural Highway

The vagus nerve is the longest cranial nerve and the main conduit for rapid transmission of information from the gut to the brainstem and back. The signals are not only mechanical (feeling of fullness) but also chemical.

Enterochromaffin cells (EC) in the intestinal epithelium are specialized in detecting microbial metabolites, nutrients, and hormones. When bacteria produce serotonin or other compounds, they stimulate ECs, which in turn emit rapid electrical signals to the brain via afferent vagal fibers. This circuit explains why a change in gut flora (e.g., after an infection or administration of a probiotic) can induce rapid changes in mood or acute anxiety, without the molecules having physically reached the brain. It is the body's real-time alarm and feedback system.

1.5 The Immune System and Neuroinflammation: The Endotoxemic Link

This is probably the most important pathogenic pathway in chronic mental disorders. Dysbiosis, characterized by reduced diversity and increased pro-inflammatory bacteria, weakens the intestinal barrier (leaky gut). This allows the passage of bacterial endotoxins, especially Lipopolysaccharide (LPS), into the portal and systemic circulation.

Circulating LPS creates a state of metabolic endotoxemia or silent inflammation. LPS activates immune cells (macrophages), which release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). These cytokines can:

- Cross the BBB via active transport.
- Activate microglia – the resident immune cells of the brain.

Activated microglia enter a "pro-inflammatory" (M1) state, releasing even more cytokines and reactive oxygen species, creating chronic neuroinflammation. This neuroinflammation is toxic to neurons: it inhibits neurogenesis, disrupts synaptogenesis, induces oxidative stress, and alters energy metabolism. It is the biological foundation of "inflammatory depression" and background anxiety, where the patient feels constantly under a cloud of threat without a clear external stressor.

The described interactions – neurochemical, metabolic, immune, and neural do not act in isolation. They converge into three main pathogenic pathways, synthetically illustrated in Figure 2, explaining the transition from dysbiosis to specific psychological manifestations.

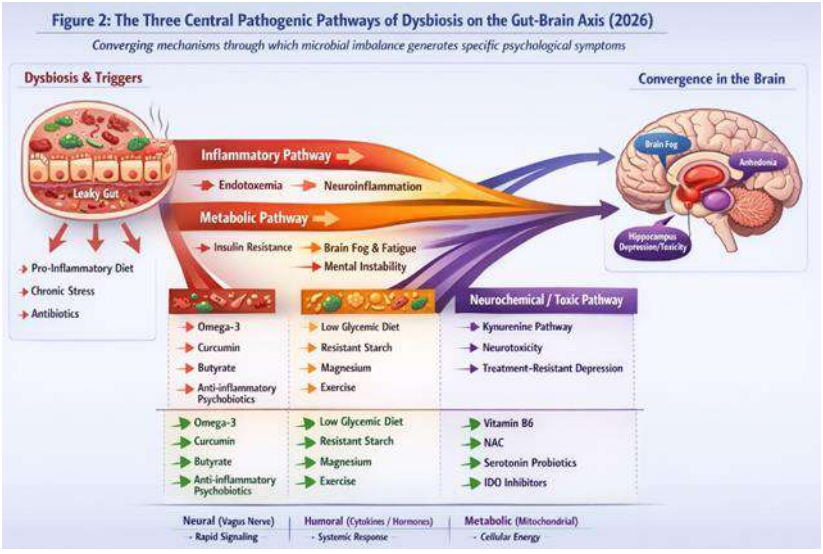


Figure 2. The three central pathogenic pathways through which intestinal dysbiosis (left) contributes to mental disorders (right).

- Inflammatory Pathway (red): intestinal permeability allows the passage of endotoxins (LPS) which trigger a systemic and brain inflammatory cascade, leading to anhedonia.
- Metabolic Pathway (blue): dysbiosis induces peripheral and cerebral insulin resistance, depriving neurons of energy and leading to brain fog.

- Neurochemical/Toxic Pathway (purple): inflammation diverts tryptophan metabolism from serotonin production towards the synthesis of neurotoxins (quinolinic acid), contributing to treatment-resistant depression and neuronal toxicity.

Resulting symptoms are localized in distinct brain circuits. Therapeutic interventions (green) specifically target each pathogenic pathway.

Abbreviations: LPS - lipopolysaccharides; BBB - blood-brain barrier; IDO - indoleamine 2,3-dioxygenase.

2. HIDDEN METABOLIC DISORDERS AS A SUBSTRATE OF PSYCHOPATHOLOGY

In 2026, the differential diagnosis of a mental disorder must include an extensive metabolic evaluation. Many "psychological" disorders are actually epiphenomena of physiological imbalances invisible to standard tests.

2.1 "Cerebral" Insulin Resistance and Brain Fog

Definition: A state in which brain cells (neurons, astrocytes) become less sensitive to insulin, a hormone essential not only for glucose metabolism but also for neuronal survival, synaptogenesis, and plasticity. This can exist even when blood glucose is normal (normoglycemic hyperinsulinemia).

Microbial Link: A low-diversity microbiome, especially deficient in *Akkermansia muciniphila* (a bacterium that feeds on intestinal mucus), leads to thinning of the protective mucus layer. This promotes local inflammation and permeability, increasing metabolic burden and inducing peripheral and central insulin resistance. Pro-inflammatory bacteria (e.g., excess *Bacteroides*) grown in a high refined sugar environment also release metabolites that interfere with insulin signaling.

Psychological Manifestation – "Brain Fog":

- Difficulty concentrating and labile attention.
- Short-term memory problems ("why did I enter this room?").
- Slow information processing and the feeling of thinking "through cotton wool" or "fog."
- Rapid mental fatigue after minor cognitive effort.

- Mild emotional instability, because the prefrontal cortex (the center of executive and emotional control) is energy-dependent.

Mechanism: Insulin-resistant neurons cannot efficiently take up glucose, their primary energy source. As a result, they enter a state of "energy hunger," even if blood glucose levels are normal. This leads to suboptimal synaptic function and a decrease in ATP production at the mitochondrial level. Brain fog is, in fact, a localized neuronal energy crisis.

2.2. Metabolic Endotoxemia (ME): The Silent Inflammation that "Steals" Pleasure

Definition: The presence of elevated, chronic, subclinical levels of bacterial LPS in the systemic circulation, caused by increased intestinal permeability (leaky gut) and dysbiosis.

Psychopathological Cascade:

- LPS entry into blood: LPS from the intestinal lumen passes through the damaged epithelium.
- Systemic Immune Activation: LPS binds to TLR-4 receptors on macrophages, triggering a storm of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β).
- Penetration into the CNS: Cytokines and LPS (in small amounts) cross the BBB.
- Microglial Activation: Microglia recognizes LPS and enters a pro-inflammatory M1 state.
- Attack on Reward Circuits: Neuroinflammation concentrated in the nucleus accumbens, prefrontal cortex, and mesolimbic tissues interferes with dopamine release and reuptake.
- Clinical result – Metabolic Anhedonia: The patient loses the ability to feel pleasure (anhedonia). Activities that used to provide satisfaction (socializing, hobbies, food) become bland. This is a cardinal sign of inflammatory depression. The patient reports a feeling of "emptiness," "numbness," or emotional "darkness," rather than deep sadness. This type of depression responds poorly to standard serotonergic antidepressants, requiring anti-inflammatory approaches.

Recent meta-analysis (Huang et al., 2025): Serum levels of LPS (endotoxemia) and cytokines (e.g., IL-6) were evaluated in 28 studies comparing patients with major depression (n=2,450) with healthy controls (n=2,800). The average LPS levels were 35% higher in depressed patients ($p<0.001$). Subgroups with "inflammatory" depression (defined by CRP>3 mg/L) had the highest LPS levels and the poorest remission with SSRI treatment.

2.3 Microbiome-Induced Mitochondrial Dysfunction

Mitochondria are the powerhouses of cells. Their health is essential for neuronal function.

Microbial mechanism: Gut bacteria produce metabolites that can have diametrically opposite effects on mitochondria.

- Protection: Butyrate and urolithin A (derived from polyphenols) stimulate mitochondrial biogenesis (formation of new mitochondria) and autophagy (removal of old cells).
- Attack: In dysbiosis, some pathogenic strains (e.g., *Desulfovibrio*, certain Clostridia) produce excess propionic acid and other short organic acids that can disrupt the mitochondrial respiratory chain. This leads to decreased ATP production and an increase in reactive oxygen species (ROS), causing oxidative stress.

Psychological manifestation – "Lead-like" Fatigue and Decreased Resilience:

- Chronic, profound fatigue that does not improve with sleep.
- Feeling of heaviness in limbs and general inertia.
- Low resilience to stress: A minor challenge completely depletes mental and physical resources.
- Cognitive delays and slowness of movement.

It is a state of "power outage" at the level of the entire organism, and the brain, as the most energy-consuming organ, suffers first.

Specific Clinical Manifestations – The Signal Dictionary (2026)

Based on the described mechanisms, we can classify a set of distinct clinical forms. This "dictionary" serves the clinician for screening and diagnostic orientation.

Table 1. Gut–Brain Axis-Associated Psychological Symptoms in Substance Use Disorders: Potential Microbial and Metabolic Drivers, Mechanisms, and Biomarkers

Psychological Symptom (How the Patient Feels)	Probable "Hidden" Metabolic/ Microbial Cause	Main Mechanism	Potential Biomarkers to Investigate (2026)
1. Metabolic Anhedonia ("Feeling empty, not sad")	Metabolic Endo-toxemia (Elevated LPS)	Neuroinflamm ation in mesolimbic circuits; Diversion of tryptophan to quinolinic acid.	Serum LPS, IL-6, hs-CRP, Quinolinic acid/Kynurenic acid ratio in serum.
2. "Background" Anxiety (Permanent unease, "knot in the stomach")	Deficit of GABA-producing bacteria (Lacto., Bifido.); Vagal hypertonus due to inflammatio	Decrease in GABAergic inhibitory tone; Constant vagal alarm signals.	Low abundance of *Lactobacillus* and *Bifidobacterium* in NGS; Low heart rate variability (HRV).
3."BrainFog" (Mental fog, poor concentration)	Cerebral Insulin Resistance; Excess proteolytic bacteria	Neuronal energy deficit; Production of ammonia and biogenic amines.	HOMA-IR index >2.5; 120-min insulin (OGTT) >60 µU/mL; Serum ammonia.

Psychological Symptom (How the Patient Feels)	Probable "Hidden" Metabolic/ Microbial Cause	Main Mechanism	Potential Biomarkers to Investigate (2026)
4. "Hangry" Irritability (Anger/irritability when hungry)	Acute Glycemic Instability; Dysbiosis disrupting the HPA axis.	Sudden drops in glucose activating survival and stress centers (cortisol).	Continuous Glucose Monitoring (CGM) showing "peaks and valleys"; Diurnal salivary cortisol.
5.3AMInsomnia (Nighttime awakenings with anxiety)	Disruption of the Microbiome's Circadian Rhythm.	Intestinal serotonin/melatonin production is compromised; Aberrant nighttime cortisol peaks.	Salivary melatonin test; NGS sequencing showing disruptions in circadian-rhythm bacteria.
6. Food Cravings (Uncontrollable sugar cravings)	Overdominance of sugar-dependent bacteria (e.g., *Candida, Prevotella*).	Bacteria release peptides that mimic Ghrelin (the hunger hormone), hacking reward circuits.	OAT test showing *Candida* metabolites; Presence of certain strains in NGS.
7. "Lead-like" Fatigue (Exhaustion unrelieved by sleep)	Microbiome-Induced Mitochondrial Dysfunction.	Insufficient neuronal ATP production; Poisoning with excess propionic acid.	OAT test for organic acids (lactic acid, citric acid); Oxidative stress markers (8-OHdG).

Partial conclusion of the Chapter: These forms are not exclusive and often overlap. A patient with inflammatory depression will also have brain fog and fatigue. However, identifying the dominant symptom can guide the initial metabolic investigation.

For a quick synthesis and an overview of these key correlations, which can serve as a mental screening tool in clinical practice, we present:

Figure 3: Visual Signal Dictionary: Decoding Psychological Symptoms (2026)

Visual guide for quickly correlating psychological symptoms with the metabolic-microbial mechanism and indicated investigations.

Figure 3. Visual Signal Dictionary – a clinical navigation map (2026).

This rosette synthesizes the 7 key psychological manifestations suggesting a metabolic-microbial substrate. For each symptom (colored slice), the probable pathogenic mechanism and priority biomarkers to investigate are indicated. The purpose of this visual guide is to facilitate clinical screening and guide the initial metabolic investigation without losing sight of the individual's complexity.

HRV – Heart Rate Variability; CGM – Continuous Glucose Monitoring; NGS – Metagenomic Sequencing; OAT – Organic Acids Test. (Cojocaru M, Giurgiu Ghe, Tihan E, 2026)

This graphical representation does not replace the nuance and details offered by specific investigations, but complements the previous table by providing an accessible visual map of the connections between the psychological, metabolic, and microbial.

3. PRECISION DIAGNOSIS IN 2026 – FROM STANDARD TESTS TO METAGENOMICS

The year 2026 has democratized access to technologies that make hidden metabolic disorders visible.

3.1. Standard (But Essential) Biochemical and Metabolic Investigations

- HOMA-IR Index: Calculated from fasting glucose and insulin. Values >2.5 indicate insulin resistance even with normal glucose. A mandatory analysis in any evaluation of chronic anxiety or depression.
- High-Sensitivity C-Reactive Protein (hs-CRP): General marker of systemic inflammation. Values between 1-3 mg/L suggest low-grade inflammation, most likely metabolic/microbial.
- OGTT with Insulin (2 hours): Detects postprandial hyperinsulinemia, a common disturbance in irritable bowel syndrome with anxiety.
- Serum Zonulin or Lactulose/Mannitol: Direct marker for intestinal permeability (leaky gut).
- Organic Acids Test (OAT): Analyzes over 70 metabolites in urine reflecting: imbalances in bacterial flora (overgrowth of *Candida* or *Clostridium*), vitamin deficiencies (B6, B12), oxidative stress, and mitochondrial dysfunction. It is a "master key" to microbial metabolism.

3.2. The Metagenomic Sequencing Revolution (Shotgun NGS)

Next-Generation Sequencing (NGS) technology ended the era of bacterial cultures. By sequencing all DNA fragments from a stool sample, it provides:

- Complete inventory: Identifies not only bacteria but also archaea, fungi, viruses, and their functions (functional metagenomics).

- Precise abundances: Not just "presence/absence," but the proportion of each species.
- Psychobiotic biomarkers: Can directly measure the abundance of genes encoding enzymes like GAD (for GABA) or TPH (for serotonin), providing a score of the patient's microbiome's potential for neurotransmitter production.
- Detection of Metabolic Risk: Some microbial profiles are predictive for insulin resistance or inflammatory tendency years before clinical onset.

Example of NGS Report (2026):

"The patient presents with moderate-low microbial diversity (Shannon index 2.1). A significant deficit of butyrate-producing species (*Faecalibacterium prausnitzii* - 0.5% vs. normal >5%) and GABA producers (*Lactobacillus* spp. - below detection threshold) is observed. There is an overdominance of the *Bacteroides* genus (45%), associated with insulin resistance. The serotonin production score is reduced. Recommendation: Intervention with resistant fibers and probiotic *Lactobacillus helveticus* R0052 + *Bifidobacterium longum* R0175."

3.3. Continuous Glucose Monitoring (CGM) for Psychiatry

Dexcom G7 or FreeStyle Libre 4 sensors are used not only by diabetics but also to correlate glycemic variations with mood, energy, and anxiety. A "rollercoaster" model (peaks and valleys) of blood glucose is a strong indicator of metabolic instability and dysbiosis disrupting blood sugar regulation.

3.4. Artificial Intelligence (AI) in Interpretation

AI platforms like Palantir integrate data from NGS, CGM, OAT, and blood tests, generating "personalized metabolic maps" and prioritized intervention protocols. Algorithms can predict response to certain psychobiotics or diets based on each individual's unique microbial profile.

Integrating these advanced diagnostic tools (NGS, OAT, CGM) and interpreting them through artificial intelligence enables the transition from reactive to predictive and personalized medicine.

To synthesize this approach, we present in Figure 2 the clinical precision algorithm for the evaluation and management of mental disorders through the lens of the gut-brain-metabolism axis, as applied in 2026. Figure 4. Precision Clinical Algorithm for the Gut-Brain Axis (2026). *Subtitle:From clinical presentation to personalized integrative intervention*

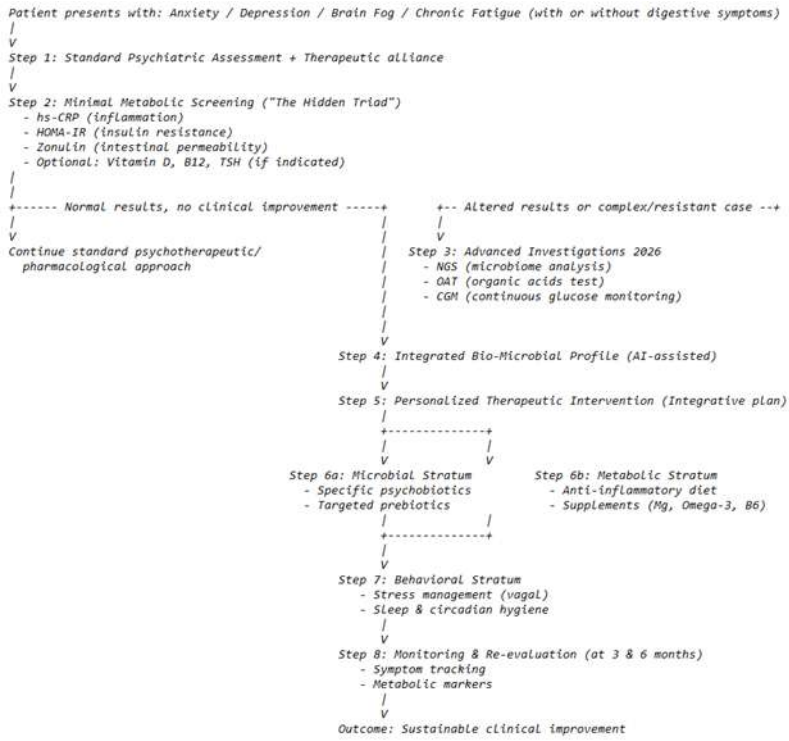


Figure 4. Precision clinical algorithm for the evaluation and management of mental disorders with metabolic-microbial substrate (2026).

The algorithm emphasizes the need for a minimal metabolic screening (the "hidden triad": inflammation, insulin resistance, intestinal permeability) in routine evaluation. For complex or resistant cases, advanced technologies (metagenomic sequencing - NGS, organic acid testing - OAT, continuous glucose monitoring - CGM) allow the development of an integrated bio-microbial profile.

This forms the basis of a personalized therapeutic plan, with interventions stratified across microbial, metabolic, and behavioral domains, periodically monitored. Abbreviation: AI - Artificial Intelligence.

Side Legends:

1. Decision Logic:

- Minimal screening is mandatory for any chronic mental disorder.
- Advanced investigation is triggered by: (a) screening abnormalities, (b) resistance to standard treatment, (c) complex clinical presentation.

2. Key Technologies 2026:

- NGS (Metagenomics): Identifies microbial imbalances, neurotransmitter synthesis potential, metabolic risk.
- OAT (Metabolomics): Detects intoxication with microbial metabolites, mitochondrial dysfunction, enzymatic deficiencies.
- CGM (Biomonitoring): Correlates glycemic variations with psychological state in real time.

3. Personalization of Intervention:

- Intervention is modulated based on the bio-microbial profile:
- *GABAergic deficit (NGS)* → Psychobiotics with *Lactobacillus/Bifidobacterium* + Mg.
- *Endotoxemia (hs-CRP↑, Zonulin↑)* → Anti-inflammatory diet, butyrate, Ω-3.
- *Glycemic instability (CGM)* → Stabilizing dietary regimen, chrono-nutrition.

4. Integrative Approach:

Treatment is a stratified and synergistic protocol:

- *Foundation:* Psychotherapy +/- psychiatric pharmacology (if necessary).
- *Microbial & Metabolic Layer:* Correcting the physiological substrate.
- *Behavioral Layer:* Supporting autonomic and circadian regulation.

This algorithm emphasizes the need for minimal metabolic screening and defines the criteria for advanced investigation, leading to an integrative and stratified therapeutic plan. In the following chapters, we will detail the key components of this plan.

4. INTEGRATED THERAPEUTIC STRATEGIES – REPROGRAMMING THE AXIS

Treatment in 2026 is synonymous with "reprogramming" the microbiome-metabolism-brain balance. It is a staged approach, synergistic with existing psychotropic treatments, not a replacement for them.

4.1. Psychobiotics: Third-Generation Probiotics

Definition: "Live organisms that, when administered in adequate amounts, confer a psychological health benefit on the host" (Dinan et al., 2023). Not every probiotic is a psychobiotic.

Strains with robust evidence (2026):

- *Lactobacillus helveticus* R0052 & *Bifidobacterium longum* R0175: The most studied combo for reducing anxiety and depressive symptoms, by increasing BDNF levels and reducing cortisol.
- *Bifidobacterium infantis* 35624: Effective in irritable bowel syndrome with anxiety comorbidity, by modulating the immune response.
- *Lactobacillus rhamnosus* JB-1: Demonstrates strong anxiolytic effects in animal studies, mediated by the vagus nerve and GABA receptors.
- Dose and Duration: Minimum 10^9 CFU/day, for a period of at least 8-12 weeks for observable psychological effects.

5.2. Precision Nutrition and the 2026 Psychobiotic Protocol

Diet is no longer "one size fits all." The goal is to provide substrate for beneficial bacteria and starve pathogenic ones.

Basic Principles:

1. Feeding Butyrate Producers:

- *Resistant Starch (RS):* Cooked and cooled potatoes, green bananas, cooked and cooled rice, legumes. Feeds *Faecalibacterium prausnitzii*.
- *Diverse fibers:* Flax, chicory, chia, asparagus, garlic, onion (sources of inulin and FODMAPs beneficial for some).

2. Optimizing Neurotransmitter Precursors:

- *For Serotonin:* Quality proteins (especially containing tryptophan) at lunch, associated with complex carbs (oats, quinoa) at dinner. Carbs facilitate tryptophan's passage through the BBB.

- *For Dopamine:* Foods rich in tyrosine (almonds, pumpkin seeds, eggs, avocado).

3. Controlling the Kynurenine Pathway and Reducing Inflammation:

- *Eliminating Refined Sugar:* Sugar is the number one disruptor, feeding pro-inflammatory bacteria and fungi.
- *Magnesium and Vitamin B6:* Essential cofactors for GABA synthesis and many other enzymatic processes. Source: leafy greens, nuts, seeds.
- *Polyphenols as Selective Fertilizers:* Berries, dark cocoa (>85%), green tea, spices (clove, turmeric). "Fertilize" beneficial bacteria.

4. Anti-inflammatory Fats: Omega-3 (EPA/DHA) from wild salmon, sardines, quality fish oil supplements. Directly reduces neuroinflammation.

Example of Daily "Functional" Menu (Psychobiotic Protocol 2026):

- Breakfast: Full-fat Greek yogurt (with live cultures) + frozen blueberries (polyphenols) + 1 tbsp ground flax seeds (prebiotic fiber) + a few nuts.
- Lunch: Grilled salmon + steamed asparagus + quinoa + green salad with olive oil.
- Snack: 2 squares of 90% dark chocolate + a handful of almonds.
- Dinner: Lentil salad (resistant starch when cooled) + fermented vegetables (raw sauerkraut) + chicken breast.
- Hydration: Green/rooibos tea, 2L water.

4.2 Stress Management and Circadian Rhythm

Chronic stress is a destroyer of the microbiome. It increases cortisol, which changes intestinal pH and reduces *Lactobacillus*. It is vital to reintroduce:

- Vagal Co-regulation Practices: Diaphragmatic breathing (4-7-8), meditation, cold exposure (cold showers).
- Sleep and Meal Hygiene: Eating within a restricted window (e.g., 10-12 hours), morning exposure to natural light, avoiding blue light in the evening. The microbiome has its own circadian rhythm and synchronizes with that of the host.

4.3 Concurrent and Advanced Pharmacotherapy

- Anti-inflammatories: In depression with elevated inflammatory markers, agents with anti-inflammatory effects can be considered (e.g., Lithium, Agomelatine, or even curcumin/omega-3 in therapeutic doses).
- Adjacent Supplements: NAC (N-acetylcysteine) for glycemic stability and detoxification; Magnesium L-threonate for cerebral permeability; peppermint oil for IBS.

4.4 Phytotherapy and Phytocompounds with Psychobiotic and Neuro-Metabolic Action

In addition to nutritional supplements and bacterial psychobiotics, a valuable therapeutic area consists of medicinal plants and isolated phytocompounds, which act simultaneously on the microbiome and directly on neurochemistry or inflammation. Unlike many supplements, some of these plants have a long history of use and a well-documented safety profile, now supported by elucidated mechanisms of action.

- *Hypericum perforatum* (St. John's Wort): Remains the most studied phytotherapy for mild to moderate forms of depression. In 2026, its action is seen as synergistic: in addition to inhibiting serotonin reuptake (similar to SSRIs), standardized extracts have a modulating effect on the microbiome, reducing the abundance of some pro-inflammatory species and stimulating the growth of some *Lactobacillus* spp. This offers an explanation for the 2-4 week delay in effect and the different side effect profiles compared to synthetic SSRIs. (Bengoa et al 2023)
- *Crocus sativus* (Saffron): Clinical studies in recent years have consolidated it as an effective adjuvant in depression and anxiety. Its active principles, crocin and safranal, have direct serotonergic and anti-inflammatory effects. More recently, it has been observed that they also promote an increase in butyrate producers in the intestine, such as *Faecalibacterium*, offering a dual action on the axis. (Poursina, D., Vahidi, O., Mousavi, S. E., & Rahimlou, M., 2024)
- *Withania somnifera* (Ashwagandha): The classic adaptogen, used for stress and anxiety management. It lowers cortisol levels by modulating the HPA axis.

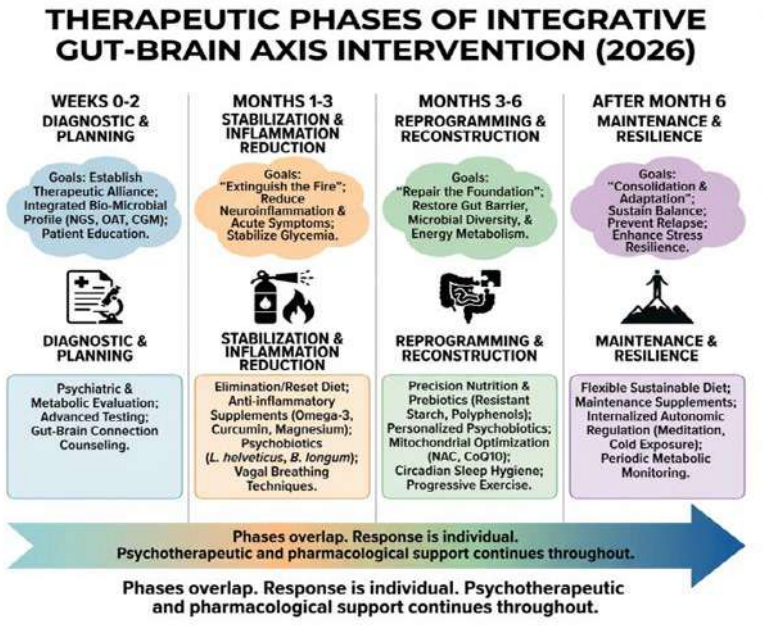
This effect reduces stress on the microbiome, preventing the reduction in bacterial diversity induced by chronic cortisol. Additionally, it has direct neuroprotective effects and can ameliorate mitochondrial dysfunction. (Salve, J.et al, 2024)

- *Curcuma longa* (Turmeric) – Curcumin: Already mentioned as an anti-inflammatory, curcumin deserves a separate place for its prebiotic and selective antimicrobial action. It stimulates the growth of *Lactobacillus* and *Bifidobacterium* while inhibiting pathogenic strains. Formulations with increased bioavailability (combined with piperine or in nanoparticles) are considered first-line interventions in depressive syndromes with high inflammatory markers. (Di Meo, F. et al., 2023)
- *Ginkgo biloba:* Used for improving cognition and "brain fog," it acts by improving cerebral blood flow and reducing oxidative stress. New data shows that its metabolites can help restore the blood-brain barrier and modulate the microbiome composition towards a more anti-inflammatory profile and help restore the blood-brain barrier. *Ginkgo biloba* (Yang, X. et al., 2023):
- Modulates the Microbiome: Reverses the composition of the gut microbiota disturbed by diet, increasing the abundance of some beneficial bacteria associated with short-chain fatty acid (SCFA) production.
- Reduces Permeability and Inflammation: Strengthens the intestinal barrier (reduces "leaky gut") and lowers levels of systemic inflammatory markers (LPS, TNF-α, IL-6).
- Protects the Blood-Brain Barrier (BBB): Prevents deterioration of the BBB structure and reduction of tight junction protein levels (claudin-5, occludin), essential for its integrity.
- Improves Cognitive Function: All these peripheral effects correlate with reduced microglial activation (neuroinflammation) in the brain and recovery of performance in memory and learning tests.
- Concentrated Polyphenols (e.g., Resveratrol, Quercetin, EGCG from green tea):

These are not just antioxidants. They act as "selective fertilizers" for the intestinal microbiota. Bacteria metabolize polyphenols into bioactive metabolites (e.g., urolithin from ellagitannins) which then, absorbed, have strong anti-neuroinflammatory and pro-neurogenic effects in the brain. Their administration is, essentially, an indirect therapy via the microbiome. (Duda-Chodak et al., 2023)

Attention and Precautions: Phytotherapy is not without risks. Drug interactions are critical (*Hypericum* is a strong CYP450 inducer). Extract quality (standardization of active principles), dosage, and purity are essential. Counseling by a knowledgeable clinician is imperative to safely and effectively integrate these options into the therapeutic plan.

The therapeutic components presented – psychobiotics, precision nutrition, phytotherapy, and lifestyle management – are not applied simultaneously or at random. Maximum efficacy is achieved by integrating them into a phasic protocol, adapted to severity and individual profile. Figure 6 presents this phasic framework, from urgent stabilization to sustainable maintenance.



Phases overlap. Response is individual. Psychotherapeutic and pharmacological support continues throughout.

Figure 5. Therapeutic phases of integrative intervention on the gut-brain axis (2026)

From urgent stabilization of symptoms to sustainable reprogramming of the psychosomatic ecosystem.

Figure 5. Therapeutic phases of integrative intervention on the Gut-Brain Axis (2026). This temporal model illustrates a stratified and realistic treatment approach.

Phase 0 (Diagnostic) establishes the scientific foundation and the alliance.

Phase 1 (Stabilization) aims at rapid reduction of inflammation and acute suffering.

Phase 2 (Reprogramming) focuses on the structural restoration of barriers and microbial diversity.

Phase 3 (Maintenance) transitions from treatment to a sustainable lifestyle that supports resilience.

The phases are not rigid and overlap significantly; the plan is personalized based on the bio-microbial profile and clinical response. The model emphasizes that healing is a process, not an event.

This temporal approach highlights that reprogramming the axis is a process requiring patience and adjustment, with different objectives over 6-12 months.

5. PERSPECTIVES AND ETHICS IN METABOLIC PSYCHOPATHOLOGY 2026

The field is evolving rapidly. The future brings:

- Fourth-Generation Psychobiotics: Genetically modified bacteria to produce certain neurotransmitters or degrade specific toxins.
- Targeted Fecal Microbiota Transplant (FMT): Not only for *C. difficile*, but also for certain treatment-resistant psychiatric disorders, with donors selected for their psychobiotic profile.
- Continuous Microbial Monitoring: Digestive sensors that monitor compounds produced by the microbiome in real time.
- Ethics and Access: Democratizing expensive technologies (NGS, CGM) remains a challenge.

It is crucial to prevent excessive biological determinism ("I'm depressed just because of my bacteria") and to maintain an integrative biopsychosocial perspective.

The gut-brain axis in 2026 has ceased to be a scientific curiosity to become a central pillar of practical medicine. Our microbiome is an active metabolic organ, a predictive biomarker, and a therapeutic target of remarkable flexibility. Understanding that our psychological state is partly sculpted by the chemical conversations between bacteria and our gut and brain cells pushes us towards an era of personalized, predictive medicine.

5.1. Advanced Research Directions and Future Applications

In 2026, the research frontier in the gut-brain axis field is moving towards four major directions, all with the potential to redefine the treatment of mental disorders in the next decade:

- Personalized Microbiome as a Pharmaceutical Target: The development of "microbial pharmaceuticals" represents a qualitative leap from current psychobiotics. These involve synthetically modified bacterial strains (through synthetic biology) to express or suppress certain genes in a controlled manner. For example, work is being done on a modified strain of *E. coli Nissle 1917* to express high levels of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, or a strain of *Bacteroides thetaiotaomicron* capable of selectively degrading quinolinic acid in the intestinal lumen, blocking its neurotoxic flow to the brain. This would allow for precision pharmacological intervention, with localized effect and minimal risk of adverse systemic effects.
- Therapy through Modulation of Bile Acid Receptors (Bile Acid Signaling): Bile acids, especially secondary ones formed by bacterial action on primary bile acids (e.g., ursodeoxycholic acid), are recognized in 2026 as important metabolic messengers between microbiome, liver, and brain. They activate receptors such as FXR (Farnesoid X Receptor) and TGR5, which regulate glucose metabolism, inflammation, and even neurogenesis. Current research explores synthetic modulators of these receptors, as well as the administration of specific secondary bile acids,

as potential therapies for both metabolic disorders and associated brain fog and cognitive deficit.

- Integration of Multi-Omics Data and Advanced Bioinformatics: The future of diagnosis lies in integrating data from:
- Metagenomics (what bacteria and genes are present)
- Metatranscriptomics (what genes are active)
- Metabolomics (what compounds are produced)
- Host Proteomics and Epigenomics

This "pan-omic" approach allows the construction of predictive causal models, not just correlational ones. Through machine learning, specific interaction networks leading from a microbial profile to a particular psychopathological manifestation can be identified. Dedicated cloud platforms now allow clinicians to upload a patient's data and receive a simulation of the potential impact of different interventions (diet X, probiotic Y) on their personal metabolic network.

- Neurostimulation of the Axis through Non-Invasive Interventions: If the vagus nerve is the highway, then influencing it non-invasively can change the traffic. Transcranial Magnetic Stimulation (TMS) applied to the insular cortex (which processes visceral signals) and transcutaneous vagus nerve stimulation (tVNS) at the ear level are studied not only for their direct neuromodulatory effects but also for their ability to "recalibrate" gut-brain signaling. Preliminary data from 2025 suggests that tVNS can increase vagal tone and, indirectly, promote a less inflammatory and more commensal bacteria-friendly intestinal environment.

5.2. Ethico-Social Challenges and Current Limitations

Despite the enthusiasm, numerous challenges must be addressed with pragmatism and ethical responsibility:

- Causality vs. Correlation: Although mechanisms are becoming clearer, for many associations it remains difficult to establish whether dysbiosis is the cause, consequence, or just a contributing factor of the mental disorder. Chronic anxiety and depression themselves change eating behavior and cortisol levels, disrupting the microbiome.

It is a bidirectional vicious cycle. Interventions must be holistic, attacking both ends of the axis.

- Biological Hyper-Reductionism: There is a real danger of reducing the complex human experience (existential anxiety, psychological pain) to a simple bacterial imbalance. This could lead to excessive medicalization of normal suffering and neglect of essential psychological, social, and existential factors in therapy. Metabolic psychiatry must be a complement, not a replacement, for psychotherapy and humanistic approaches.
- Unequal Access and Costs: Cutting-edge technologies (shotgun NGS, continuous CGM monitoring, comprehensive OAT tests) remain expensive and are not covered by insurance in many countries. This risks creating a two-tier mental health system: those with resources benefit from precision medicine, while the majority still rely on standard approaches. Democratizing these tools is a health equity priority.
- Regulation and Quality of Supplements: The probiotic and psychobiotic market is a "Wild West." Many commercial products do not contain the strains or doses specified on the label and lack solid human clinical studies. Stricter regulations and patient education are needed to choose products with scientific evidence (e.g., strains with codes like R0052 or R0175 denoting specific research).
- Confidentiality of Microbial Data: The microbiome profile is as unique and identifying as a genetic fingerprint. Metagenomic data could theoretically reveal predispositions to certain metabolic or psychiatric diseases. The storage, sharing, and use of this data require rigorous ethical and cybersecurity frameworks.

6. IMPLICATIONS FOR CLINICAL PRACTICE AND FINAL RECOMMENDATIONS

Implementing knowledge about the gut-brain axis in the clinical office requires a practical algorithm and a change in "mindset" (vision).

6.1. Clinical Algorithm for the Practicing Physician (2026)

- Standard psychiatric evaluation: Always start with rigorous psychiatric diagnosis and establishment of a therapeutic alliance.
- Minimal metabolic screening (the "HIDDEN TRIAD"):
- Inflammation: hs-CRP.
- Insulin Resistance: HOMA-IR index (fasting glucose + insulin).
- Intestinal permeability: Serum zonulin or alternative marker.
- (If symptomatology is predominantly Brain Fog/Fatigue, add Vitamin D, B12, Ferritin, and TSH).
- Advanced evaluation (For resistant or complex cases):
- Metagenomic Test (NGS) of the fecal microbiome.
- Organic Acids Test (OAT) in urine.
- Continuous Glucose Monitoring (CGM) for 10-14 days.
- Integrative Therapeutic Intervention:
- *Foundation:* Psychotherapy +/- standard psychopharmacology (if indicated).
- *Metabolic layer:* Personalized nutritional interventions based on test results (e.g., anti-inflammatory diet, Mg, Omega-3 supplementation).
- *Microbial layer:* Administration of proven psychobiotics for 3-6 months. Possible supplementation with specific prebiotic fibers (e.g., inulin, resistant starch) if tolerated.
- Monitoring and Reevaluation: Reevaluation of psychiatric symptomatology and metabolic markers (HOMA-IR, hs-CRP) at 3 and 6 months.

6.2. Recommendations for the Patient and Health Education

It is crucial for the patient to become an active partner in their own care. The key message is: "Your brain is fed from your gut."

Start simple: Before spending money on advanced tests, implement high-impact basic changes:

- Eliminate or drastically reduce added sugar and refined grains.
- Gradually introduce fermented foods (kefir, sauerkraut, kimchi) and diversified fiber (colorful vegetables, nuts, seeds).
- Manage stress through movement (walks in nature) and breathing.

- Respect a stable circadian rhythm for meals and sleep.
- Be an informed consumer: When choosing a probiotic, look on the box for the exact strain code (e.g., *Lactobacillus helveticus* R0052) and a guaranteed number of CFUs (≥10 billion). If digestive symptoms are severe (bloating, diarrhea), consult a gastroenterologist before trying strong prebiotics.
- Realistic expectations: Reprogramming the microbiome is a process of months, not days. Improvements may be subtle at first (more energy, better sleep) and sometimes precede significant improvement in mood.

6.3. Final Conclusion: A New Ontology of Mental Health

In 2026, the gut-brain axis is not just another discovered physiological mechanism. It represents an ontological shift in how we conceptualize mental health. We are no longer just a brain enclosed in a skull and a body serving it. We are a holobiont – a symbiotic superorganism, whose cognitive and emotional center is constantly influenced by the millions of microorganisms we host.

This manuscript has highlighted how:

- Bacteria are internal pharmacists, and their imbalance leads to neurotransmitter deficits, neuro-metabolic intoxication, and brain inflammation.
- "Hidden" metabolic disorders (insulin resistance, endotoxemia) are mandatory translators between dysbiosis and psychopathology.
- Technology (NGS, AI) now allows us to map this invisible territory and act with unprecedented precision.
- Treatment becomes ecological: healing no longer means just adjusting a brain chemical imbalance, but reconstituting a healthy intestinal ecosystem that naturally supports neuronal function.

The future is of an ecological and metabolic psychiatry, where the psychotherapist, psychiatrist, nutritionist, and gastroenterologist collaborate to treat the whole organism. Next time a patient presents with anxiety, depression, or brain fog, the fundamental question will no longer be only "What is happening in your mind?" but also "What is happening in your gut?"

The answer, as we have seen, profoundly shapes the former.

Essentially, managing mental health through the lens of this axis represents the transition from a vicious cycle of self-perpetuating dysfunction to a virtuous circle of rebalancing and resilience. This dynamic model is synthesized in Figure 6: The Vicious Cycle and Virtuous Circle of the Gut-Brain Axis (2026).

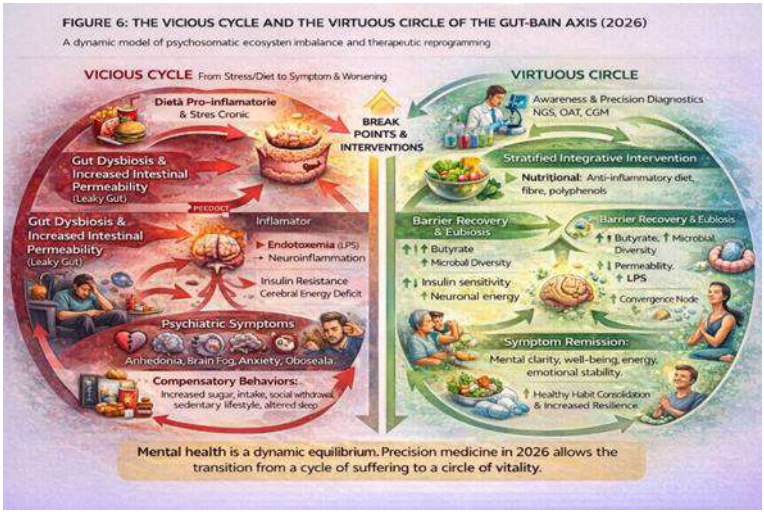


Figure 6. Dynamic model of the Vicious Cycle and Virtuous Circle in the functioning of the Gut-Brain-Metabolism Axis. (Cojocaru M, Giurgiu Ghe., Tihan E, 2026)

Dynamic model of imbalance and therapeutic reprogramming of the psychosomatic ecosystem

The left part illustrates how pro-inflammatory lifestyle factors trigger a physiological cascade (dysbiosis → pathogenic pathways → symptoms) which, through the negative behaviors they generate, perpetuates and aggravates the initial cause.

The right part demonstrates how precise diagnosis and an integrative intervention, targeted at all layers (microbial, metabolic, behavioral), can initiate a virtuous circle of repair, rebalancing, and consolidation of resilience. The yellow arrows on the central line indicate the critical points where clinical intervention can "break" the vicious cycle and "fuel" the virtuous circle.

Therefore, the perspective offered by metabolic psychiatry in 2026 is not deterministic, but one of possibility – the possibility to reprogram, with precision and empathy, the fundamental conversation between gut and brain.

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CHAPTER 3
BIOLOGICAL EFFECTS OF MODERN DIETARY MODELS: THE ROLE OF THE MEDITERRANEAN DIET IN HEALTH PROMOTION AND THE PREVENTION OF CHRONIC DISEASES

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INTRODUCTION

In recent decades, chronic non-communicable diseases—such as cardiovascular diseases, type 2 diabetes mellitus, cancer, and neurodegenerative disorders have become the leading causes of morbidity and mortality worldwide (Upadhyay, 2022). These conditions arise from complex etiological backgrounds involving genetic, environmental, and lifestyle-related factors. Among lifestyle determinants, nutrition plays a particularly critical role, as it directly influences metabolic processes, inflammatory pathways, oxidative stress, and the composition of the gut microbiome (Ma et al., 2025). Consequently, modern nutritional science increasingly focuses on the investigation of overall dietary patterns rather than isolated nutrients, recognizing that dietary models exert complex and synergistic effects on human biological systems (Lehoczki, et al., 2025).

Among the various dietary models, the Mediterranean diet represents one of the most extensively studied and scientifically supported dietary patterns (Varga, et al., 2025; Ungvari et al., 2025). This dietary model is based on the traditional eating habits of populations living in the Mediterranean region and is characterized primarily by a high intake of plant-based foods, including vegetables, fruits, legumes, whole grains, and nuts, as well as the use of extra virgin olive oil as the principal source of dietary fat (Fekete et al., 2025). In addition, the diet includes moderate consumption of fish, seafood, and dairy products, while the intake of red meat and ultra-processed foods is generally low (Csípő, et al., 2023; Fekete et al., 2022).

The health-promoting effects of the Mediterranean diet have been supported by numerous epidemiological studies, randomized clinical trials, and meta-analyses (Guasch-Ferré & Willett, 2021). Evidence suggests that adherence to this dietary pattern is associated with a reduced risk of cardiovascular diseases, metabolic syndrome, obesity, as well as certain types of cancer and neurodegenerative disorders (Cianciabella et al., 2025). These beneficial health outcomes are largely attributed to the high content of antioxidants, dietary fiber, polyphenols, and unsaturated fatty acids present in the diet (Madarász et al., 2023). These bioactive compounds contribute to the reduction of oxidative stress, the modulation of inflammatory pathways, and the maintenance of metabolic homeostasis (Lehoczki, et al., 2023).

Furthermore, growing evidence indicates that the Mediterranean diet exerts favorable effects on the composition and functional activity of the gut microbiota, which plays a fundamental role in immune regulation and metabolic balance (García-Montero et al., 2021).

Importantly, the Mediterranean diet represents not only a dietary pattern but also a broader lifestyle model that includes regular physical activity, the cultural tradition of shared meals, and the use of fresh, minimally processed ingredients (Diolintzi et al., 2019). Together, these factors contribute to the recognition of the Mediterranean dietary pattern as one of the most promising preventive strategies for reducing the burden of chronic diseases and promoting healthy aging (Dobroslavska et al., 2024). The aim of this book chapter is to provide a comprehensive overview of the key nutritional characteristics of the Mediterranean diet and to discuss the molecular and physiological mechanisms through which this dietary model may contribute to health maintenance and the prevention of chronic diseases.

1. HISTORICAL BACKGROUND OF THE MEDITERRANEAN DIET

The scientific concept of the Mediterranean diet gained widespread recognition in the mid-twentieth century, when epidemiological studies first highlighted the association between dietary habits and the incidence of chronic diseases (Medina, 2021). Although the dietary patterns of Mediterranean populations originate from thousands of years of agricultural traditions and cultural practices, scientific interest in this dietary model began to intensify primarily in the 1950s (Nestle, 1995). During this period, researchers observed that populations living in the Mediterranean region particularly on the Greek island of Crete and in Southern Italy exhibited lower rates of cardiovascular mortality and longer life expectancy despite comparatively modest socioeconomic conditions when compared with several Western European and North American populations (Stivachtis, 2002).

One of the most influential figures in the scientific investigation of the Mediterranean diet was the American epidemiologist Ancel Keys, who began studying dietary patterns and their health consequences across different populations following the Second World War (Menotti & Puddu, 2025).

Keys and his colleagues observed that the dietary habits of people living in Mediterranean countries differed markedly from those prevalent in industrialized nations (Major et al., 2026). While diets in the United States and Northern Europe were characterized by higher consumption of animal-derived foods rich in saturated fatty acids, the dietary patterns in Mediterranean regions were dominated by plant-based foods, fish, and olive oil (Quarta et al., 2021). These observations ultimately led to the initiation of one of the most influential epidemiological studies in nutritional science, the Seven Countries Study, which began in the late 1950s (Willett, 2013). This large-scale prospective investigation examined dietary habits, lifestyle factors, and cardiovascular risk profiles among middle-aged men in seven countries: the United States, Finland, the Netherlands, Italy, Yugoslavia, Greece, and Japan (Danesh et al., 2007). One of the most significant findings of the study was the strong association between dietary fatty acid composition, serum cholesterol levels, and the incidence of coronary heart disease (Kromhout et al., 2012).

The study demonstrated that populations living in Mediterranean regions particularly in Crete and Southern Italy experienced significantly lower rates of coronary heart disease and cardiovascular mortality compared with populations in Northern European countries (Timmis et al., 2023). These differences were largely attributed to variations in dietary patterns. The diets of Mediterranean populations were characterized by a high intake of plant-derived foods, complex carbohydrates, dietary fiber, and unsaturated fatty acids, while the consumption of saturated fats remained relatively low. In its traditional form, the Mediterranean diet reflects the dietary habits of predominantly agrarian societies. The central components of this dietary pattern include locally produced, seasonal foods that undergo minimal processing (Fatima et al., 2025). The Mediterranean dietary pattern is primarily based on the following food groups:

- vegetables and fruits
- whole grains
- legumes
- nuts and seeds
- extra virgin olive oil as the primary source of dietary fat
- fish and other seafood

These foods are rich in bioactive compounds, including antioxidants, polyphenols, dietary fiber, and unsaturated fatty acids. Such nutrients play an important role in reducing oxidative stress, modulating inflammatory processes, and regulating metabolic pathways, all of which are key factors in the prevention of chronic diseases (Real et al., 2020).

It is important to emphasize that the Mediterranean diet represents not merely a specific list of foods but rather a broader cultural and lifestyle framework (Donini et al., 2015). Traditional Mediterranean lifestyles incorporate regular physical activity, the social tradition of communal meals, and the slow and mindful consumption of food (Kushkestani et al., 2024). Dairy products primarily yogurt and cheese are consumed in moderate amounts, whereas the intake of red meat and highly processed foods is generally low.

Over recent decades, the importance of the Mediterranean diet has continued to grow, supported by a substantial body of epidemiological and clinical evidence demonstrating its health-promoting effects (Guasch-Ferré & Willett, 2021). Numerous studies have shown that adherence to the Mediterranean dietary pattern is associated with a reduced risk of cardiovascular diseases, metabolic syndrome, obesity, type 2 diabetes mellitus, as well as certain cancers and neurodegenerative disorders (Medina-Remón et al., 2018). These beneficial effects are thought to result from the complex nutrient composition of the diet and the synergistic actions of its bioactive components. Consequently, modern nutritional science increasingly regards the Mediterranean diet not merely as a regional dietary tradition but as a scientifically grounded dietary model with substantial potential for the prevention of chronic diseases and the promotion of healthy aging.

2. NUTRITIONAL COMPOSITION OF THE MEDITERRANEAN DIET

One of the most distinctive characteristics of the Mediterranean diet is its high nutrient density, meaning that it provides substantial amounts of essential nutrients and bioactive compounds while maintaining relatively moderate energy content (Castro-Barquero et al., 2023; Fekete et al., 2019).

The predominance of plant-based foods, the use of fat sources rich in unsaturated fatty acids, and the emphasis on minimally processed ingredients collectively contribute to the favorable metabolic and anti-inflammatory properties of this dietary pattern. The complex interactions between macro- and micronutrients present in the Mediterranean diet play a key role in regulating cellular processes, reducing oxidative stress, and maintaining metabolic homeostasis (Lehoczki, et al., 2025; Ungvari et al., 2025). The nutritional profile of the Mediterranean diet includes several key groups of nutrients that have been consistently associated with a reduced risk of chronic diseases. Among these, healthy fats, dietary fiber, and a wide range of antioxidant and polyphenolic compounds are of particular importance (Fekete et al., 2024; Pandics et al., 2023; Tosti et al., 2018).

2.1 Healthy Fats

One of the defining features of the Mediterranean diet is the qualitative composition of dietary fat intake (Davis et al., 2015). The primary source of fat in this dietary pattern is extra virgin olive oil, which contains high concentrations of monounsaturated fatty acids, particularly oleic acid. Oleic acid is one of the most abundant monounsaturated fatty acids and has been shown to exert beneficial effects on lipid metabolism (Yubero-Serrano et al., 2019). Specifically, it contributes to the reduction of low-density lipoprotein (LDL) cholesterol levels while maintaining or increasing concentrations of high-density lipoprotein (HDL) cholesterol. In addition to its favorable fatty acid composition, extra virgin olive oil contains numerous bioactive compounds, including polyphenols, tocopherols, and other antioxidant molecules. These compounds play an important role in protecting against oxidative stress and modulating inflammatory pathways. Polyphenols present in olive oil—such as oleuropein and hydroxytyrosol—have been shown to reduce the oxidation of LDL cholesterol, which represents a key step in the development of atherosclerosis. Furthermore, these bioactive molecules may positively influence endothelial function, improve vascular elasticity, and enhance the production of nitric oxide, which plays a central role in maintaining vascular homeostasis (Crespo et al., 2018; Ungvari et al., 2025).

In the Mediterranean diet, the intake of saturated fatty acids is generally lower than that observed in Western dietary patterns (Fekete et al., 2024; Lehoczki et al., 2025). A substantial proportion of fat consumption originates from plant-based sources such as olive oil, nuts, and seeds. In addition, regular consumption of marine fish contributes to the intake of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which possess well-documented anti-inflammatory and cardioprotective properties (Ungvari et al., 2025).

2.2 Dietary Fiber

Another fundamental component of the Mediterranean diet is its high dietary fiber content. Fiber in this dietary pattern is primarily derived from whole grains, legumes, vegetables, and fruits. Dietary fibers are complex carbohydrates that largely resist digestion in the human gastrointestinal tract but exert several important physiological effects (Kiani et al., 2022). One of the most significant roles of dietary fiber is the regulation of gut microbiota composition and activity. Fermentable fibers serve as substrates for microorganisms residing in the colon, which metabolize these compounds into short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate (Ye et al., 2022). These metabolites play a crucial role in maintaining intestinal epithelial integrity, regulating inflammatory processes, and modulating immune system function.

Dietary fiber also contributes to the maintenance of glucose homeostasis. By slowing carbohydrate digestion and absorption in the small intestine, fiber attenuates postprandial glycemic responses and improves insulin sensitivity (Giuntini et al., 2022). In addition, dietary fiber can bind bile acids and cholesterol in the gastrointestinal tract, promoting their excretion and thereby contributing to the reduction of serum cholesterol levels (Singh et al., 2019). Another important effect of fiber-rich diets is their ability to enhance satiety, which may lead to reduced energy intake and improved body weight regulation. Consequently, adherence to a Mediterranean-style dietary pattern may contribute to the prevention of obesity and metabolic syndrome.

2.3 Polyphenols and Antioxidants

A further key biological feature of the Mediterranean diet is the high intake of foods rich in polyphenols and antioxidant compounds. Polyphenols are secondary plant metabolites that exert a wide range of physiological effects. Within the Mediterranean dietary pattern, these compounds are present in substantial quantities in foods such as olive oil, red wine, berries, leafy green vegetables, legumes, and various culinary herbs (Varga et al., 2025) .

One of the most important properties of polyphenols is their antioxidant activity. These molecules can neutralize reactive oxygen species (ROS), which are generated during oxidative processes within cells (Varga, et al., 2025). Excessive oxidative stress may contribute to cellular damage, DNA mutations, and the pathogenesis of numerous chronic diseases, including cardiovascular diseases, cancer, and neurodegenerative disorders (Fekete et al., 2024; Ungvari, Bartha, et al., 2025).

Beyond their antioxidant effects, polyphenols can also influence several cellular signaling pathways. Numerous studies have demonstrated that these compounds can regulate the production of inflammatory mediators, inhibit the activation of nuclear factor kappa-B (NF-κB), and promote the expression of endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase (Nani et al., 2021). Importantly, the antioxidant compounds present in the Mediterranean diet often act synergistically, meaning that their combined biological effects may exceed the effects of individual components alone (Gantenbein & Kanaka-Gantenbein, 2021). This complex interaction between nutrients and bioactive compounds contributes to the protective properties of the Mediterranean dietary pattern against diseases associated with oxidative stress and chronic inflammation. Overall, the nutritional composition of the Mediterranean diet—particularly its high content of healthy fats, dietary fiber, polyphenols, and antioxidant compounds—plays a fundamental role in mediating its health-promoting effects (Gantenbein & Kanaka-Gantenbein, 2021). These components influence metabolic regulation, inflammatory responses, and oxidative balance through interconnected biological pathways, thereby contributing to the reduction of chronic disease risk and supporting healthy aging (Major et al., 2026; Zábó et al., 2025; Fekete, et al., 2025).

3. MOLECULAR MECHANISMS UNDERLYING THE HEALTH BENEFITS OF THE MEDITERRANEAN DIET

The beneficial physiological effects of the Mediterranean diet are supported not only by epidemiological observations but also by a wide range of molecular and cellular mechanisms. Bioactive compounds present in this dietary pattern—including polyphenols, unsaturated fatty acids, dietary fiber, vitamins, and various antioxidant molecules—are capable of influencing cellular signaling pathways, inflammatory responses, oxidative stress regulation, and microbial metabolism (Tosti et al., 2018). Together, these mechanisms contribute to a reduced risk of chronic non-communicable diseases, particularly cardiovascular, metabolic, and neurodegenerative disorders. The health-promoting effects of the Mediterranean diet are primarily mediated through three major biological processes: modulation of inflammatory pathways, regulation of oxidative stress, and the influence on the composition and metabolic activity of the gut microbiome (Mikó et al., 2024).

3.1 Anti-Inflammatory Effects

Chronic low-grade inflammation plays a central role in the pathogenesis of numerous chronic diseases. Conditions such as obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases are characterized by persistently elevated levels of inflammatory mediators. One of the most important health-promoting effects of the Mediterranean diet is its ability to reduce the concentration of inflammatory biomarkers in the body (Minihane et al., 2015). Several clinical and epidemiological studies have demonstrated that populations adhering to the Mediterranean diet exhibit lower levels of inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Tehrani et al., 2025). These molecules are key mediators of inflammatory responses and contribute to endothelial dysfunction, the development of insulin resistance, and the progression of atherosclerotic vascular changes (Cao et al., 2025; Fekete et al., 2025). Bioactive compounds present in the Mediterranean diet influence inflammatory signaling pathways through multiple mechanisms.

Polyphenols, omega-3 fatty acids, and antioxidant vitamins have been shown to inhibit the activation of nuclear factor kappa B (NF-κB), one of the most important transcription factors regulating inflammatory gene expression. Inhibition of NF-κB activation reduces the production of pro-inflammatory cytokines and adhesion molecules, thereby attenuating endothelial inflammation and slowing the progression of atherosclerotic processes (Nani et al., 2021). Phenolic compounds found in extra virgin olive oil—such as oleocanthal and oleuropein—also contribute to the reduction of inflammatory responses. These molecules have been shown to inhibit the activity of certain inflammatory enzymes, including cyclooxygenase (COX), demonstrating mechanisms of action similar to those observed with some anti-inflammatory pharmacological agents. The attenuation of inflammatory processes is particularly important for the prevention of chronic diseases, as persistent inflammation contributes to endothelial damage, insulin resistance, and cellular metabolic dysfunction (Romani et al., 2019).

3.2 Regulation of Oxidative Stress

Oxidative stress occurs when the production of reactive oxygen species exceeds the capacity of the body's antioxidant defense systems. ROS molecules can damage various cellular structures, including lipids, proteins, and nucleic acids. Oxidative stress is recognized as a key contributor to the pathogenesis of numerous chronic diseases, including atherosclerosis, cancer, and neurodegenerative disorders (Qin et al., 2026).

The Mediterranean diet is rich in foods containing antioxidant compounds that contribute to the neutralization of reactive oxygen species. Vegetables, fruits, olive oil, nuts, and moderate consumption of red wine provide a wide range of antioxidant molecules, including vitamins C and E, carotenoids, flavonoids, and other phenolic compounds (Gonçalves et al., 2024; Rodríguez-Morató et al., 2015; Valls-Pedret et al., 2012; Visioli & Galli, 2001). These antioxidants exert their effects through several mechanisms. First, they can directly neutralize ROS molecules, thereby reducing oxidative damage at the cellular level. Second, they may enhance endogenous antioxidant defense systems, including enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Qin et al., 2026).

Reducing oxidative stress is particularly important for preventing the oxidation of low-density lipoprotein cholesterol. Oxidized LDL particles play a critical role in the formation of atherosclerotic plaques, as they promote lipid uptake by macrophages and the formation of foam cells. Antioxidant compounds present in the Mediterranean diet can inhibit this process, thereby contributing to a lower risk of cardiovascular disease. Furthermore, antioxidants provide protection against oxidative DNA damage, which is an important factor in cellular aging and carcinogenesis (Pozo Giráldez et al., 2026; Toth et al., 2017). Consequently, the reduction of oxidative stress is essential not only for cardiovascular health but also for maintaining cellular integrity and overall physiological function.

3.3 Modulation of the Gut Microbiome

In recent decades, increasing scientific evidence has demonstrated that the composition and metabolic activity of the gut microbiome play a significant role in human health. The complex microbial community residing in the gastrointestinal tract participates in digestive processes, nutrient metabolism, and the regulation of immune responses (Ma & Lee, 2025).

The Mediterranean diet has been shown to positively influence the diversity and functional activity of the gut microbiota. Plant-based foods rich in dietary fiber including whole grains, legumes, fruits, and vegetables create a favorable environment for the proliferation of beneficial microbial taxa. Such dietary patterns promote the growth of bacterial genera such as Bifidobacterium and Lactobacillus, which are important for maintaining intestinal health (Shen et al., 2023).

During the fermentation of dietary fibers, gut bacteria produce short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. These metabolites exert multiple physiological effects. Butyrate, for example, serves as a primary energy source for colonocytes and possesses anti-inflammatory properties. Short-chain fatty acids also contribute to maintaining intestinal barrier integrity and play a regulatory role in immune responses and metabolic processes.

In addition, the Mediterranean diet may reduce the formation of certain harmful microbial metabolites, such as trimethylamine N-oxide (TMAO), which has been associated with an increased risk of cardiovascular diseases. Plant-derived nutrients and polyphenols present in this dietary pattern can beneficially modulate microbial metabolic activity, thereby contributing to the maintenance of metabolic and immunological balance (Ali et al., 2022; Koh et al., 2016).

4. THE MEDITERRANEAN DIET AND CARDIOVASCULAR HEALTH

Cardiovascular diseases (CVDs) represent one of the leading causes of mortality worldwide and pose a significant global public health burden (Mensah et al., 2019). The development of cardiovascular diseases results from complex pathophysiological processes involving disturbances in lipid metabolism, endothelial dysfunction, chronic inflammation, oxidative stress, and structural as well as functional alterations of the vascular wall. In recent decades, a growing body of scientific evidence has demonstrated that dietary patterns play a substantial role in influencing these processes (Man et al., 2020).

The Mediterranean diet is one of the most extensively studied dietary models in the field of cardiovascular prevention (Martínez-González et al., 2019). Numerous epidemiological studies, prospective cohort investigations, and randomized controlled clinical trials have demonstrated that adherence to the Mediterranean dietary pattern is associated with a lower incidence of cardiovascular diseases and reduced cardiovascular mortality (Becerra-Tomás et al., 2020).

One of the most well-known clinical trials examining the cardiovascular benefits of the Mediterranean diet is the PREDIMED (Prevención con Dieta Mediterránea) study, which investigated the role of this dietary pattern in primary prevention among individuals at high cardiovascular risk (Wang et al., 2017).

The results of this randomized controlled trial demonstrated that participants following a Mediterranean diet experienced a significant reduction in major cardiovascular events such as myocardial infarction, stroke, and cardiovascular mortality compared with individuals in the control group. Importantly, the study highlighted that supplementation of the Mediterranean diet with extra virgin olive oil or nuts provided substantial cardioprotective effects (Estruch et al., 2018; Martínez-Lapiscina et al., 2013). The cardiovascular benefits of the Mediterranean diet are mediated through several interconnected biological mechanisms (Martínez-González et al., 2019).

4.1 Improvement of Lipid Profile and Reduction of LDL Cholesterol

One of the most important effects of the Mediterranean diet is its favorable influence on lipid metabolism. The monounsaturated fatty acids present in this dietary pattern—particularly oleic acid found in olive oil—contribute to reductions in low-density lipoprotein cholesterol levels while maintaining or increasing concentrations of high-density lipoprotein cholesterol. Polyunsaturated fatty acids found in nuts and marine fish, especially omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), also exert beneficial effects on lipid metabolism. These fatty acids reduce triglyceride levels, attenuate inflammatory processes, and inhibit platelet aggregation, thereby contributing to a lower risk of thrombotic events (Scaglione et al., 2025). In addition, antioxidant compounds present in the Mediterranean diet can reduce the oxidation of LDL particles. Oxidized LDL plays a critical role in the pathogenesis of atherosclerosis, as it promotes lipid uptake by macrophages and contributes to the formation of foam cells within the vascular wall.

4.2 Improvement of Endothelial Function

Endothelial cells line the inner surface of blood vessels and play a crucial role in maintaining vascular homeostasis. Endothelial dysfunction represents an early and critical step in the development of atherosclerosis and is characterized by impaired vasodilatory capacity and increased inflammatory activity within the vascular wall (Młynarska et al., 2025).

Bioactive components of the Mediterranean diet—particularly polyphenols and unsaturated fatty acids—have been shown to improve endothelial function. Phenolic compounds present in olive oil can enhance the production of nitric oxide in endothelial cells. Nitric oxide is a key vasodilatory molecule that promotes vascular relaxation and improves blood flow. Increased nitric oxide production also reduces platelet aggregation and inhibits leukocyte adhesion to the vascular wall, thereby attenuating the progression of atherosclerotic processes (Salvo & Tuttolomondo, 2025).

4.3 Regulation of Blood Pressure

The Mediterranean diet may also play a significant role in reducing blood pressure and preventing the development of hypertension. Vegetables, fruits, and legumes—key components of this dietary pattern—are rich sources of potassium, magnesium, and antioxidant compounds, which contribute to maintaining vascular elasticity and regulating blood pressure. Consumption of fiber-rich foods further supports metabolic regulation and improves insulin sensitivity, which is also involved in blood pressure control. Several studies have also suggested that regular consumption of extra virgin olive oil may reduce both systolic and diastolic blood pressure, partly due to its antioxidant and anti-inflammatory properties (Kokkinos et al., 2005).

4.4 Attenuation of Inflammatory Processes

Chronic inflammation plays a central role in the development and progression of cardiovascular diseases. The Mediterranean diet contains numerous components with anti-inflammatory properties, including polyphenols, omega-3 fatty acids, and antioxidant vitamins. These bioactive molecules reduce the concentrations of inflammatory cytokines such as CRP, IL-6, and TNF-α and inhibit inflammatory signaling pathways. The attenuation of inflammatory processes contributes to the protection of endothelial cells, stabilization of atherosclerotic plaques, and reduction of thrombotic risk (Calcaterra et al., 2024).

The combined effects of improved lipid profiles, enhanced endothelial function, blood pressure reduction, and decreased inflammation contribute to the overall cardioprotective properties of the Mediterranean diet.

Based on decades of epidemiological and clinical research, the Mediterranean diet is now widely regarded as one of the most scientifically supported dietary models for the prevention of cardiovascular diseases (Martínez-González et al., 2019).

5. THE MEDITERRANEAN DIET AND METABOLIC DISEASES

Metabolic diseases particularly obesity, metabolic syndrome, and type 2 diabetes mellitus represent a growing global public health challenge (Dayi & Ozgoren, 2022; Scaglione et al., 2025). These conditions arise from complex metabolic disturbances involving insulin resistance, chronic low-grade inflammation, adipose tissue dysfunction, and alterations in lipid metabolism. Dietary habits play a critical role in modulating these processes; therefore, nutritional interventions are increasingly recognized as key strategies in both the prevention and management of metabolic disorders. A substantial body of epidemiological and clinical evidence indicates that adherence to the Mediterranean dietary pattern is associated with a lower risk of obesity, metabolic syndrome, and type 2 diabetes (Salas-Salvadó et al., 2015). The high nutrient density of the Mediterranean diet, together with its elevated content of dietary fiber, unsaturated fatty acids, and bioactive compounds, contributes to the maintenance of metabolic homeostasis.

5.1 Body Weight Regulation and Prevention of Obesity

Obesity represents one of the most important risk factors for metabolic diseases (Cao et al., 2025; Varga, et al., 2025). The Mediterranean diet incorporates several nutritional characteristics that may facilitate body weight regulation. High-fiber foods such as whole grains, vegetables, fruits, and legumes promote satiety, which may lead to reduced energy intake. In addition, the Mediterranean diet is rich in foods with a relatively low glycemic index, resulting in slower glucose absorption and reduced postprandial glycemic fluctuations (Tosti et al., 2018). This effect may contribute to improved appetite regulation and the maintenance of energy balance. Another important factor is the quality of dietary fat sources.

The monounsaturated fatty acids that predominate in the Mediterranean diet particularly oleic acid found in olive oil have been shown to favorably influence adipocyte metabolism and may contribute to reduced accumulation of visceral adipose tissue (Capurso, 2021).

5.2 Reduction of the Risk of Metabolic Syndrome

Metabolic syndrome is characterized by the coexistence of several metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension (Dayi & Ozgoren, 2022; Scaglione et al., 2025). The Mediterranean diet can influence these risk factors through multiple interconnected mechanisms. Unsaturated fatty acids present in this dietary pattern improve lipid profiles by reducing triglyceride concentrations and potentially increasing high-density lipoprotein cholesterol levels. Furthermore, polyphenols and antioxidant compounds found in plant-based foods can attenuate inflammatory processes, which are key contributors to the pathogenesis of metabolic syndrome. The high dietary fiber content of the Mediterranean diet may also promote favorable alterations in the gut microbiome, which in turn can influence energy metabolism and metabolic regulation (Abrignani et al., 2024).

5.3 Prevention of Type 2 Diabetes and Metabolic Effects

Insulin resistance and disturbances in glucose metabolism play central roles in the development of type 2 diabetes mellitus (Scaglione et al., 2025). Numerous studies have demonstrated that adherence to the Mediterranean diet may improve insulin sensitivity and contribute to the stabilization of blood glucose levels. Whole grains and legumes provide carbohydrates with a relatively low glycemic index, resulting in slower glucose absorption and reduced glycemic variability. In addition, dietary fiber and polyphenols have been shown to influence insulin signaling pathways and reduce chronic inflammation, which represents an important contributor to insulin resistance. Healthy fats present in the Mediterranean diet also play a significant role in glucose metabolism (Scaglione et al., 2025). Monounsaturated fatty acids may enhance insulin receptor function and reduce metabolic damage associated with lipotoxicity.

Overall, the complex metabolic effects of the Mediterranean dietincluding improved insulin sensitivity, reduced inflammation, and favorable modulation of lipid metabolism may play a significant role in the prevention and management of metabolic diseases.

6. NEUROPROTECTIVE EFFECTS

Research over recent decades has increasingly demonstrated that nutrition plays a significant role in maintaining nervous system health and influencing the risk of neurodegenerative diseases. Disorders such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions are associated with multiple pathological processes, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and metabolic disturbances (Jurcau, 2021). The Mediterranean diet may contribute to neuroprotection through several biological mechanisms that favorably influence brain metabolism and neuronal function (Lahoda Brodska et al., 2023).

6.1 Reduction of Oxidative Stress in the Nervous System

Brain tissue is particularly vulnerable to oxidative stress due to its high oxygen consumption and elevated lipid content. Antioxidant compounds present in the Mediterranean diet—including flavonoids, carotenoids, polyphenols, and various vitamins—can reduce the accumulation of reactive oxygen species within neuronal cells (Franco et al., 2023). These antioxidants provide protection against lipid peroxidation of neuronal membranes and reduce oxidative damage to DNA and proteins. Such effects may contribute to the long-term preservation of neuronal structure and function (Franco et al., 2023).

6.2 Attenuation of Neuroinflammation

Chronic neuroinflammation represents an important pathogenic mechanism in many neurodegenerative diseases. Activated microglia and astrocytes produce inflammatory mediators that contribute to neuronal damage and disease progression. Bioactive compounds present in the Mediterranean diet can modulate these inflammatory processes.

Omega-3 fatty acids, for example, can inhibit the production of pro-inflammatory cytokines and promote the synthesis of specialized pro-resolving mediators, which facilitate the resolution of inflammatory responses (Adamu et al., 2024).

6.3 Support of Mitochondrial Function

Mitochondria play a critical role in supplying energy to neurons. Mitochondrial dysfunction has been identified as an important factor in the pathogenesis of several neurodegenerative disorders. Antioxidants and polyphenolic compounds present in the Mediterranean diet may improve mitochondrial function and reduce oxidative damage. These bioactive compounds may also promote mitochondrial biogenesis and enhance the efficiency of ATP production, thereby supporting the metabolic stability and survival of neuronal cells (Franco et al., 2023).

6.4 Modulation of the Gut–Brain Axis

The interaction between the gut microbiome and the central nervous system—commonly referred to as the gut–brain axis—plays an important role in regulating neural function. The Mediterranean diet, which is rich in dietary fiber and polyphenols, positively influences the composition and functional activity of the gut microbiota. During microbial fermentation of dietary fibers, short-chain fatty acids are produced. These metabolites can influence neural signaling pathways and modulate immune responses (Barrea et al., 2021). Furthermore, SCFAs may contribute to the reduction of neuroinflammation and help maintain neurological homeostasis. Consequently, the Mediterranean diet may represent a promising preventive strategy for reducing the risk of neurodegenerative diseases and supporting healthy cognitive function (Franco et al., 2023).

7. FUTURE RESEARCH DIRECTIONS

The beneficial health effects of the Mediterranean diet have been demonstrated in numerous epidemiological, clinical, and mechanistic studies over recent decades.

Nevertheless, a comprehensive understanding of the complex interactions between nutrition and human health requires further investigation. Future research should particularly focus on the molecular and systems-level mechanisms that determine how the Mediterranean diet influences metabolic, immunological, and neurological functions in different individuals (Lehoczki, et al., 2023).

One of the most promising areas of research is nutrigenomics, which investigates the interactions between nutrients and the human genome. Nutrigenomic research aims to elucidate how dietary components influence gene expression and how individual genetic variability modifies the response to dietary interventions. Bioactive compounds present in the Mediterranean diet—such as polyphenols and unsaturated fatty acids—have been shown to regulate various gene networks involved in inflammatory processes, oxidative stress regulation, and energy metabolism.

Metabolomics also plays an important role in advancing our understanding of the mechanisms underlying the effects of the Mediterranean diet. Metabolomic approaches involve the comprehensive analysis of small-molecule metabolites present in biological systems, reflecting the current metabolic state of cells and tissues. Through such analyses, it may be possible to identify metabolic biomarkers associated with long-term adherence to the Mediterranean diet and to clarify metabolic pathways that contribute to the prevention of chronic diseases.

In recent years, microbiome research has gained increasing attention in nutritional science (Hadrich, 2018). The composition and metabolic activity of the gut microbiome exert profound effects on immune regulation, inflammatory processes, and energy metabolism. Foods rich in dietary fiber and polyphenols—characteristic components of the Mediterranean diet—can positively influence microbial diversity and functional microbial profiles. Future studies should aim to clarify how diet-induced alterations in the gut microbiome mediate health benefits and how microbial metabolites contribute to the prevention of metabolic and neurodegenerative diseases. These research directions are closely related to the concept of personalized nutrition.

Precision nutrition aims to optimize dietary recommendations by considering individual genetic background, metabolic profiles, microbiome composition, and lifestyle factors. In the future, multidisciplinary approaches integrating genomic, metabolomic, and microbiome data are expected to play an increasingly important role in improving the effectiveness of dietary interventions. Overall, future research on the Mediterranean diet is increasingly moving toward systems-level and multi-omics approaches. These methodologies allow a deeper understanding of the complex interactions between nutrition and health and may contribute to the development of more effective preventive and therapeutic nutritional strategies (Mansour et al., 2024).

CONCLUSION

The Mediterranean diet represents a complex and scientifically well-established dietary model that exerts its health-promoting effects through multiple biological mechanisms. The plant-based foods, unsaturated fatty acids, dietary fiber, antioxidants, and polyphenolic compounds that characterize this dietary pattern collectively contribute to the favorable regulation of metabolic and cellular processes. Based on the current body of scientific evidence, adherence to the Mediterranean diet represents an effective strategy for the prevention of chronic diseases, particularly cardiovascular diseases, metabolic disorders, and neurodegenerative conditions. This dietary pattern has been shown to improve lipid metabolism, reduce chronic inflammation, attenuate oxidative stress, and exert beneficial effects on the composition and functional activity of the gut microbiome.

These biological effects contribute to cardiovascular protection, improved insulin sensitivity, and the maintenance of neurological health. Importantly, the Mediterranean diet should not be viewed solely as a dietary pattern but rather as a broader lifestyle model that incorporates regular physical activity, the cultural tradition of communal meals, and the consumption of fresh, minimally processed foods. Future research is expected to further clarify the molecular and metabolic mechanisms through which the Mediterranean diet contributes to healthy aging and disease prevention.

Advances in nutrigenomics, metabolomics, and microbiome-based research may open new perspectives for the development of personalized nutritional recommendations. Overall, the Mediterranean diet is widely regarded as one of the most scientifically supported dietary models of our time. Its implementation may play a significant role in addressing major global public health challenges, particularly the growing burden of chronic diseases, while promoting improved quality of life and increased longevity.

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