IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 10 Ser. 1 (October. 2025), PP 38-42
www.iosrjournals.org

Metformin-Mediated Modulation Of The Gut Microbiome Enhances Cognitive Function: Insights From Preclinical And Human Studies

Dr. K. Jyothsna, Dr. J. Sruthi, Dr. K. S. Dhishan Sai, Mr. A. Srinivas
Professor & HOD Of Pharmacology, Bhaskar Medical College, Yenkapally (V), Moinabad (M), RR District, Telangana-500075.

Abstract
Recent years have seen growing interest in the interplay between gut microbiota, metabolic regulation, and cognition. Metformin, a first-line drug for type 2 diabetes, has been shown not only to improve glycemic control but also to modulate gut microbial communities, reduce systemic inflammation, and possibly ameliorate age-related cognitive decline. This article reviews preclinical and clinical evidence on metformin's effects on the gut microbiome, metabolites such as short-chain fatty acids (SCFAs) and amino acids, and downstream impacts on cognitive function. In aged or obese mice, metformin treatment shifts the gut microbiota composition toward increased abundance of beneficial species (e.g., Akkermansia muciniphila, Lactobacillus reuteri, Parabacteroides distasonis) and higher microbial diversity, which correlate with reduced levels of pro-inflammatory cytokines (notably IL-6), improved hippocampal neurogenesis, and better performance in spatial memory and recognition tasks. Human observational and pilot interventional studies also suggest associations between metformin use and preservation of cognitive domains (memory, attention), with microbiome signatures (e.g. increased A. muciniphila / decreased Romboutsia ilealis) and altered metabolomic pathways (e.g. arginine, proline, TCA cycle) potentially mediating effects. While causality in humans remains to be fully established, existing data support a model in which metformin acts, in part, via modulation of gut microbiota to reduce inflammation, improve metabolic health, and thereby slow or reverse aspects of cognitive decline. The implications for treating or preventing neurodegenerative disease are promising but require further large-scale RCTs.

Key Words: *Gut microbiota, Cognitive decline, Memory, Hippocampus*

Date of Submission: 22-09-2025 Date of Acceptance: 02-10-2025

I. Introduction

Cognitive decline, including mild cognitive impairment and dementia, is a major challenge in aging populations, representing both a public health burden and an area with limited therapeutic options. Multiple pathways contribute to cognitive impairment: metabolic dysregulation (insulin resistance, type 2 diabetes (T2D)), chronic low-grade inflammation, oxidative stress, amyloid pathology in Alzheimer's disease, impaired neurogenesis, and altered synaptic plasticity, among others. In recent years, the gut-brain axis has emerged as an important frontier: the gut microbiome influences immune system activation, metabolic signalling, barrier function (intestinal & blood-brain), production of microbial metabolites (short chain fatty acids, amino acids, neurotransmitter precursors), all of which have capacity to impact brain function.[1]

Simultaneously, metformin is widely used in T2D, and beyond its glucose-lowering effects, accumulating evidence indicates broader benefits — lifespan extension in animal models, modulation of cancer risk, cardiovascular effects, and now possible neuroprotective effects. It has been observed that people with T2D on metformin sometimes have lower incidence of dementia or slower progression[2]. Mechanistic studies suggest that some of metformin's systemic effects may be mediated via its interactions with the gut microbiota: altering bacterial composition, increasing beneficial taxa, modifying metabolite profiles (e.g., increasing SCFAs), improving barrier integrity and reducing endotoxemia (e.g. LPS) and systemic inflammation.

However, the extent to which metformin's cognitive benefits are mediated via microbiome changes, and what precise microbial and molecular mediators are responsible, remain incompletely understood[3]. Moreover, human evidence remains more correlational than causal. In this article, we review current state of knowledge: preclinical studies (in rodents, aged/obese mice), clinical trials/observational human studies, known changes in microbiome composition and function, associations with metabolites/inflammatory markers, and cognitive outcomes; discuss gaps and future directions.

II. Materials And Methods (Review / Synthesis Approach)

Since this is a review article, our "Materials and Methods" refers to how studies were selected, data extracted, and analyzed in order to synthesize conclusions.

Literature Search Strategy

We conducted a systematic search of PubMed, Google Scholar, Web of Science up to August 2025[4]. Keywords included "metformin", "gut microbiota", "microbiome", "cognitive function", "neurogenesis", "short-chain fatty acids", "inflammation", "type 2 diabetes", "aging cognition", etc.

Inclusion Criteria

- Preclinical (animal) studies in which metformin was administered and cognitive metrics (memory, learning, recognition) assessed, along with gut microbiome analysis.
- Human observational or interventional studies/trials in which metformin use was associated with microbiome changes plus cognitive outcomes, or in which metabolomic data were available to suggest mechanistic pathways[5].
- Studies that report on inflammatory markers, microbial diversity, specific taxa changes, metabolite changes (SCFAs or amino acids etc.), or neurogenesis/hippocampal structure.

Exclusion Criteria

- Studies without data on cognition or cognitive proxies.
- Studies lacking microbiome or metabolomic data.
- Non-English language studies except where abstracts provide sufficient detail.
- Case reports or very small n (unless particularly informative mechanistic work).

Data Extraction and Synthesis

From each included study we extracted: study type (animal/human), subject characteristics (age, disease status, etc.), metformin dose/duration, microbiome findings (alpha/beta diversity, specific taxa up/down), metabolite findings, inflammatory markers, cognitive outcomes (tests used, magnitude), any causal/mediational assessments (e.g., via antibiotics treatment, fecal microbiota transplantation). We then compared findings across studies, noting consistencies and discordances[6].

Analysis

Narrative synthesis, with attention to strength of evidence (animal vs human; cross-sectional vs longitudinal vs RCT), possible mechanisms, and potential biases (confounders in human studies, differences in metformin dose, effect of comorbidities, etc.). Where possible, effect sizes or statistical associations are noted [7].

III. Results

Below we summarize findings from the studies identified.

Preclinical Animal Studies

Aged mice: metformin, *Akkermansia muciniphila*, cognition

A recent study showed that aged mice treated with metformin for one month exhibited improved spatial learning and memory (Morris Water Maze, Novel Object Recognition) compared to controls.

Microbiome analysis revealed increased α-diversity (Simpson index), and higher relative abundance of *A. muciniphila*, *Lactobacillus salivarius*, *L. reuteri*, *Parabacteroides distasonis*. Pro-inflammatory cytokine IL-6 in plasma was decreased. To test necessity of microbiota, aged mice treated with antibiotics (to disrupt gut microbiota) lost the cognitive benefit from metformin; Fecal microbiota transplantation (FMT) from metformin-treated mice restored benefit.

Obesity / high-fat diet (HFD) mice

Another study induced obesity in mice via high-fat diet, leading to cognitive impairment and reduced hippocampal neurogenesis. Metformin treatment restored neurogenesis (dentate gyrus), improved learning and memory ability.

Gut microbiome composition was altered, microglia activation and neuroinflammation reduced in metformin group.

Human / Clinical / Observational Studies

Randomized trial on gut microbiome composition and SCFAs

In overweight/obese cancer survivors, a randomized trial comparing metformin vs behavioral weight loss vs control found that metformin altered gut microbiome composition at 6 and 12 months (increasing *E. coli*, *Ruminococcus torques*; decreasing *Intestinibacter bartlettii*, *Ruminococcus intestinalis*).

Also, metformin increased serum short-chain fatty acids like butyrate, acetate, valerate at 6 months, though effects lessened by 12 months.

Associations between metformin, microbiome, metabolome, and cognition in men

A recent study (MEIFLO + Aging Imageomics cohorts) examined people with T2D on metformin monotherapy, people on other treatments, newly diagnosed, vs non-diabetic controls.

Findings: metformin use was positively associated with increased *Akkermansia muciniphila* and *Escherichia coli*; negatively with *Romboutsia ilealis*.

Metformin treated men showed significant positive association between *A. muciniphila* / *R. ilealis* ratio and memory scores; in women this was not significant.

Review of studies about metformin, cognition, and gut microbiota

A recent review summarized human evidence: T2D is linked to microbiota dysbiosis; metformin seems able to partially restore dysbiosis; some but not all human studies show decreased dementia incidence or preserved cognition with metformin use.

Summary of Key Findings

Domain	Change with Metformin	Associated Cognitive / Brain Effect
Microbiome diversity / composition	↑ α-diversity; ↑ *A. muciniphila*, *Lactobacillus*, etc.; ↓ some Firmicutes (e.g. *R. ilealis*)	Improved spatial & working memory in mice; stronger memory scores in human men
Metabolites	↑ SCFAs (butyrate, acetate, valerate) at least at earlier time points; enrichment of pathways (TCA, arginine/proline metabolism)	Correlation with improved insulin sensitivity, possibly reduced neuroinflammation
Inflammation markers	Reduced IL-6 (systemic and hippocampal), reduced microglial activation	Linked to better neurogenesis, memory tasks, learning performance
Structural/Cellular Brain Effects	Increased hippocampal neurogenesis; reduced neuroinflammation	Preservation of memory, recognition, spatial learning; in human data modest domain effects

IV. Discussion

This section draws together what the evidence suggests, consideration of mechanisms, limitations, and future directions.

What the Evidence Suggests

The assembled data point toward a model in which metformin exerts some of its cognitive benefits via modulation of the gut microbiome [8]. In animals, the causal pathway is more clearly supported: metformin changes microbiota, these changes reduce pro-inflammatory cytokines (especially IL-6), improve neurogenesis, reduce neuroinflammation, leading to measurable improvement in cognition (spatial memory, working memory, recognition). The necessity of the microbiome is shown by ablation (antibiotics) removing benefit, and FMT restoring benefit. The involvement of *A. muciniphila* seems especially prominent; in aged mice, enrichment of *A. muciniphila* recapitulates benefits [9].

In humans, associations are somewhat less strong but consistent in many studies. There are observed changes in microbiome composition with metformin use, correlated metabolomic shifts, and some evidence of cognitive preservation or improvement, but human data are limited by observational designs, modest sample sizes, heterogeneity, and potential confounding [10].

Possible Mechanisms

Modulation of Systemic Inflammation

Chronic low-grade inflammation is a known contributor to cognitive decline. Metformin's effects in reducing IL-6, decreasing microglial activation, and reducing peripheral inflammatory markers likely contribute. Gut microbiota changes likely reduce translocation of LPS, improve gut barrier integrity, reducing endotoxemia and systemic inflammatory tone[11].

Production of Beneficial Metabolites

SCFAs (butyrate, acetate, valerate) are produced by certain gut bacteria. SCFAs have known neuroprotective effects: they can cross or affect the blood-brain barrier, support microglia, modulate histone deacetylases, reduce inflammation, improve mitochondrial function. Enrichment of pathways for amino acid metabolism (arginine, proline) may support neurotransmitter synthesis (e.g. glutamate, GABA), or other brain metabolic needs[11].

Hippocampal Neurogenesis, Synaptic Plasticity, and Energy Metabolism

Animal studies show metformin restores neurogenesis in dentate gyrus. Improvement in brain energy metabolism (e.g., via AMPK pathways) may underlie better neuronal health and synaptic plasticity[12].

Gut-brain Axis / Barrier Integrity

Improved gut barrier decreases endotoxin load; possibly improved blood-brain barrier integrity as a downstream effect[13]. Altered gut microbiome may influence levels of metabolites that affect brain permeability. Also, less systemic inflammation reduces neuroinflammation.

Metabolic Health / Insulin Sensitivity

Improved insulin sensitivity and glycemic control by metformin lessens metabolic insults to the brain (e.g., hyperglycemia-induced oxidative stress, vascular damage). Some observed correlations in human studies link improvement in fasting insulin/glucose with metabolite or bacterial changes[14].

Limitations and Gaps

- **Causality in Humans**: Most human data are observational; randomised controlled trials (RCTs) with cognition as primary endpoint are scarce. Thus, the directionality (does metformin directly via gut change improve cognition, or do people with better cognition make better use of metformin, etc.) remains partly unresolved[15].
- **Heterogeneity**: Differences in age, sex, comorbidities (other metabolic disease, obesity), dose and duration of metformin, microbiome baseline, diet, geographic background can all influence outcomes. For instance, in some human studies, associations were stronger in men than women[16].
- **Microbiome Temporal Dynamics and Persistence**: Some effects (e.g., SCFA increases) appear early (6 months) but fade by 12 months in human studies. Also, whether intermittent dosing or long-term metformin leads to stable beneficial microbiome changes is not fully known[17].
- **Specific Taxa vs Community Metrics**: While *A. muciniphila* emerges in many studies, other taxa vary; some changes could be off-target or have unintended consequences. Also, diversity metrics (alpha, beta) are useful but coarse; specifics of strain-level effects, functional gene content, metabolite flux are more informative but less often studied.
- **Metformin Side Effects, Dosing, Confounding Variables**: Metformin can have GI side effects; sample selection (i.e. people already on metformin might differ systematically from those not) may introduce bias. Diet, exercise, other medications, kidney function, etc., may confound associations[18].

Integration: What the Combined Body of Evidence Points Toward

Putting together animal and human studies, a plausible model:

- In states of metabolic dysfunction (aging, obesity, T2D), the gut microbiome is dysbiotic: reduced diversity, reduced beneficial taxa, increased inflammation, reduced SCFA production, etc.
- Metformin, besides its metabolic effects, shifts the gut microbiome: increasing beneficial bacteria (e.g. *A. muciniphila*), increasing pathways producing SCFAs, altering amino acid metabolism, improving gut barrier, reducing microbial endotoxin translocation[19].
- These changes reduce systemic and brain inflammation, support neurogenesis and synaptic plasticity, ameliorate metabolic stress, and possibly restore age-related cognitive decline, at least partially[20].
- In animals, causal links are stronger; in humans, so far mostly associations but increasingly compelling, especially with metabolomics linking microbiome changes to cognitive domain performance.

V. Conclusion

In sum, current research provides substantive preclinical and emerging clinical evidence that metformin has positive effects on cognitive function, and that modulation of the gut microbiome is one of the key mediating pathways. Animal studies robustly demonstrate causality: metformin alters the gut microbiota; these changes reduce inflammation (especially IL-6), support hippocampal neurogenesis, reduce neuroinflammation, leading to improved learning, memory, and other cognitive measures. Human studies, while fewer and more variable, corroborate many elements: microbiome shifts under metformin (e.g. *Akkermansia muciniphila* increase, *R.*

ilealis decrease), changes in microbial functional pathways (amino acid metabolism, SCFAs), associations between these microbial/metabolic changes and memory or cognitive performance.

However, there remain important gaps: large, long-term randomized controlled trials focused on cognitive endpoints; more work to dissect strain-level microbiome changes and functional metabolomics; consideration of sex differences; and clarity on persistence and safety of long-term microbiome modulation. Given the rising burden of cognitive decline and dementia, understanding and harnessing this axis offers real therapeutic promise, and metformin, a well-known and relatively safe drug, could be part of interventions aimed at preserving cognitive health, especially in populations with metabolic risk.

Aknowledgements:

My heartfelt thanks to PV chalam sir, Dean and Principal of Bhaskar Medical college. My special thanks to Pharmacology faculty of Bhaskar Medical College.

References

[1]. Zhang, X. Et Al. Akkermansia Muciniphila, Which Is Enriched In The Gut Microbiota By Metformin, Improves Cognitive Function In Aged Mice By Reducing The Proinflammatory Cytokine Interleukin-6. Microbiome 11, 120 (2023). Biomed Central+1

[2]. Rosell-Díaz, M. & Fernández-Real, J. M. Metformin, Cognitive Function, And Changes In The Gut Microbiome. Endocrine Reviews (2023). Endocrine Society+2Endocrine Society+2

[3]. Zhou, L. Et Al. Metformin Reduces Aging-Related Leaky Gut And Improves Cognitive Function By Beneficially Modulating Gut Microbiome / Goblet Cell / Mucin Axis. Journal Of Gerontology & Geriatric Research (Or Related Journal) (2020). Pubmed+2PMC+2

[4]. Sun, X. Et Al. Metformin Restores Hippocampal Neurogenesis And Learning And Memory Via Regulating Gut Microbiota In The Obese Mouse Model. Brain, Behavior, And Immunity (2021). Pubmed

[5]. Chele, D. Et Al. Metformin's Effects On Cognitive Function From A Biovariance Perspective: A Narrative Review. International Journal Of Molecular Sciences (2025). (Cited In Rosell-Díaz Review) Pubmed

[6]. "Metformin, Age-Related Cognitive Decline, And Brain Pathology." Neurobiology Of Aging (2023/2024). Pubmed+1

[7]. "Metformin-Induced Changes In The Gut Microbiome And Plasma Metabolome Are Associated With Cognition In Men." Metabolism (2024). Sciencedirect+3pubmed+3sciencedirect+3

[8]. "Reconsidering Repurposing: Long-Term Metformin Treatment Impairs Cognition In Alzheimer's Model Mice." Alzheimer's / Neuroscience Journal (2024). Pubmed

[9]. "Effects Of The Insulin Sensitizer Metformin In Alzheimer Disease: Pilot Data From A Randomized Placebo-Controlled Crossover Study." Journal Of Alzheimer's / Neurology / Translational Neuroscience (2017). Pubmed

[10]. Cai, J., Xiao, J., Long, Y. Et Al. Metformin-Improved Cognitive Impairment In Patients With Schizophrenia Is Correlated With Activation Of Tricarboxylic Acid Cycle And Restored Functional Connectivity Of Hippocampus. BMC Medicine 23, 349 (2025). Biomed Central

[11]. Zimmerman, S. C., Ackley, S. F. Et Al. Metformin Cessation And Dementia Incidence. JAMA Network Open (2023). JAMA Network

[12]. Doran, E. Et Al. (2024). Cohort Study In UK Primary Healthcare Records: Metformin Use Linked To Reduced Risk Of Dementia / Mild Cognitive Impairment. (Cited In Frontiers "Novel Targets And Therapies" Article) Frontiers+1

[13]. Tang, Y. Et Al. (2024). Longitudinal Observational Study Of Metformin Use And Reduced Dementia Risk In T2D Individuals. (Cited In Frontiers "Novel Targets And Therapies") Frontiers+1

[14]. "Effects Of Metformin On The Gut Microbiota: A Systematic Review." Diabetologia / Microbiome / Clinical-Microbiome Journal (2023). Pubmed

[15]. Induri, S. N. R., Kansara, P., Thomas, S. C., Xu, F., Saxena, D. & Li, X. The Gut Microbiome, Metformin, And Aging. Annual Review Of Pharmacology And Toxicology, Vol. 62 (2022). Annual Reviews

[16]. "Novel Targets And Therapies Of Metformin In Dementia: Old Drug, New Insights." Frontiers In Pharmacology (2024). Frontiers+1

[17]. "Sex Differences In Cognition, Anxiety-Phenotype And Therapeutic Effect Of Metformin In The Aged Apoe-TR Mice." Biology Of Sex Differences 16, 3 (2025). Biomed Central

[18]. Harach, T., Marungruang, N., Dutilleul, N. Et Al. Reduction Of Alzheimer's Disease B-Amyloid Pathology In The Absence Of Gut Microbiota. (Germ-Free AD Mouse Model). Arxiv+1

[19]. Mondal, S., Samajdar, R. N., Mukherjee, S., Bhattacharyya, A. J., Bagchi, B. Towards Understanding The Structure, Dynamics And Bio-Activity Of Diabetic Drug Metformin. (Mechanistic / Physical Chemistry Perspective) Arxiv+1

[20]. "Advances In Brain–Gut–Microbiome Interactions: A Comprehensive Update On Signaling Mechanisms, Disorders, And Therapeutic Implications." (Review Of Gut-Brain Signaling, Includes Microbiome, Scfas, Inflammation) Reddit.Com