

A micro review on the role of recently emerged Artificial Intelligence (AI) tools and algorithms in microbiome-gut-brain-axis associated disease therapy via psychobiotics

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ABSTRACT

The microbiome-gut-brain axis involves the bidirectional connection between the gastrointestinal tract, gut microbiome, and central nervous system, and it is pivotal for mental well-being. Imbalances in the gut microbiome (dysbiosis) can disrupt neurotransmitter synthesis, leading to neurodegenerative diseases. Recent researches highlight psychobiotics as effective treatments for mental health conditions like depression. With advancements in artificial intelligence (AI) and large datasets, psychobiotic research has accelerated. AI tools are increasingly used for the prediction, identification, and diagnosis of gut microbiome compositions, enabling faster and more accurate discovery of therapeutic candidates. This review explores the role of AI in enhancing microbiome-gut-brain-axis-related disease therapies through psychobiotics and discusses future directions for this rapidly evolving research field.

Introduction

The microbiome-gut-brain axis is a dynamic and two-way interconnections between the gastrointestinal tract, gut microbiome and the central nervous system. The homeostasis across this axis is pivotal in the orchestration of mental well-being and health of an individual¹. The gut microbiome is vastly deemed as “super organ” and it is greatly associated with various health conditions of human, including cancer and tumour progression². The microbiome-gut-brain axis involves various pathways, namely the neural, endocrine, immune and metabolic pathways¹. Dysbiosis (gut microbiome imbalance) can cause detrimental effects on the biosynthesis of neurotransmitters, and subsequently leading to mood and behaviour alterations, Alzheimer’s disease, neurodegenerative disease, depression, anxiety, depressive hypertension, autism spectrum disorder as well as multiple sclerosis¹. In the recent years, psychobiotics, which are probiotic and prebiotic microbiota used in treating mental disorders, have been put into the limelight of research as it can effectively aid in managing depression and other mental health disorders^{3,4}. With the emerging artificial intelligence (AI) technologies and huge datasets^{5–7} in this era, the rate of psychobiotic development has reached an unprecedented pace. AI algorithms are now widely utilized in the prediction, identification and diagnosis of the gut microbiome landscape in a short amount of time

and high accuracy, this has significantly accelerate the discovery of novel therapeutic candidates and bioindicators in the form of psychobiotics in ameliorating the detrimental conditions of microbial-gut-brain axis associated disease^{1,8}. In this review, the potential of AI tools and algorithms in microbiome-gut-brain-axis associated disease therapy via psychobiotics will be discussed before diving deep into future outlooks and directions for this indispensable field of research to soar to greater heights in the future.

Methodology

For this narrative review, the selection of literature focused on recently emerged Artificial Intelligence (AI) tools and algorithms applied in the study of microbiome-gut-brain axis (MGBA) associated disease therapies via psychobiotics. Articles were selected from peer-reviewed journals published between 2020 and 2025, sourced primarily from databases such as PubMed, Scopus, and Web of Science. Preference was given to studies written in English that explored the integration of AI in predicting MGBA interactions, disease progression, and therapeutic outcomes involving psychobiotics. Key inclusion criteria involved relevance to AI-driven diagnostics, machine learning applications, or computational modeling in MGBA-related neurological and psychiatric conditions. Review articles, original research, and recent systematic

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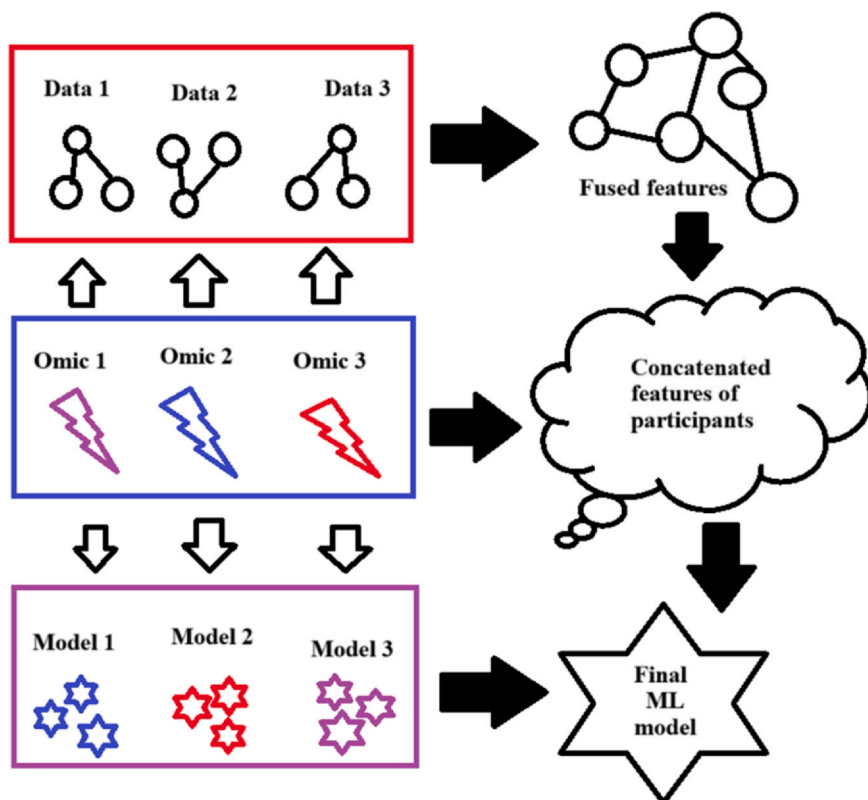


Fig. 1. The graphical workflow of how machine learning model is designed based on omic data.

reviews were all considered to provide a comprehensive overview. Studies focusing solely on traditional microbiome or brain-gut research without AI application were excluded.

Significance of AI in elucidating the microbiome-gut-brain axis

The AI tools and algorithms can greatly facilitate the elucidation of the complex and multifaceted microbiome-gut-brain axis heterogeneous high-dimensional data both rapidly and accurately. It can conduct data integration and analysis to discover novel interconnections and patterns beyond the cognitive and analytical potentiality of human beings (Fig. 1). It can comprehend and process huge datasets and produce high throughput outcomes in a reliable manner. Besides, AI tools and algorithms are also used widely in predictive modeling, feature selection and pattern identification. Machine learning AI algorithm can accurately predict the probability of an individual in developing mental disorders by scanning and interpreting the gut microbiome landscape of the particular individual and further develop constructive downstream personalized treatment strategies that are customized to the particular patient.

Furthermore, the deep learning AI algorithm assists researchers and medical practitioners in the identification of crucial and vital features (genes, metabolites, species and more) to investigate in order to combat the targeted culprit in causing mental disorders and depressions. The complexity of the gut microbiome landscape which involves multi-omics (genomics, transcriptomics, proteomics, metagenomics and metabolomics) pathways and molecules can be used to train AI models effortlessly. The trained machine learning and deep learning AI algorithms can then be utilized to generate insights and hypotheses on ways to combat mental disorders and depression in the most non-invasive and less harmful manner (Fig. 2). Some of the AI algorithms that have been employed in the past for microbiome research are Random Forest, Support Vector Machine, Convolutional Neural Networks, Recurrent Neural Networks, Gradient Boosting Machines and Autoencoders¹.

Recently emerged AI tools and algorithms in microbiome-gut-brain-axis associated disease therapy via psychobiotics

The microbiome-gut-brain-axis associated illnesses identified to date are depression, anxiety, depressive hypertension, Alzheimer's disease, neurodegenerative disease, autism spectrum disorder as well as multiple sclerosis (Table 1). In 2021, Stevens et al.⁹ performed machine-learning multivariate analyses to uncover the novel microbiome associated with depressive hypertension, namely the co-occurrence of *Streptococcus salivarius*, *Alistiped obesi*, *Lachnospiraceae bacterium 1.1.57FAA*, *Eubacterium siraeum* and *Holdemania filiformis*. The artificial model of the human gastrointestinal tract named ABIOME designed by Westfall et al.¹⁰ allows real-time monitoring of gastrointestinal conditions, optimizes psychobiotic therapies and identifies combinations that leads to the biosynthesis of bioactive metabolites with strong therapeutic potential. The automated active machine learning approach by McCoubrey et al.¹¹ successfully predicted the effects of 111 untested excipients on the proliferation of psychobiotics. Laterza et al.¹² utilized advanced AI algorithms to discover microbial bioindicators that contribute to optimal gastrointestinal health in patients recently recovered from COVID-19.

Climent-Pérez et al.¹³ conducted a systematic review on the use of AI tools in the analysis of autism spectrum disorder and they deduced that the *Bifidobacterium* is the best biomarker and psychobiotic for the disease with the greatest potential. Qiu et al.¹⁴ performed a systematic profiling of multi-omics landscape between gut microbial metabolites and non-olfactory G-protein-coupled receptors omics (GPCRome) in Alzheimer's disease using machine learning AI algorithm. They have examined a sum of 1.09 million metabolite-protein pairs that interlinks 335 gut microbial metabolites and 408 human GPCRs. As a result, they have identified orphan GPCRs (the GPCR84) as the most promising therapeutic target in Alzheimer's disease based on the integrative analyses of human brain transcriptomic and proteomic profiles and genetics-derived Mendelian randomization.

In the search of microbiome signature for autism spectrum disorder across different studies, Peralta-Marzal et al.¹⁵ employed recursive

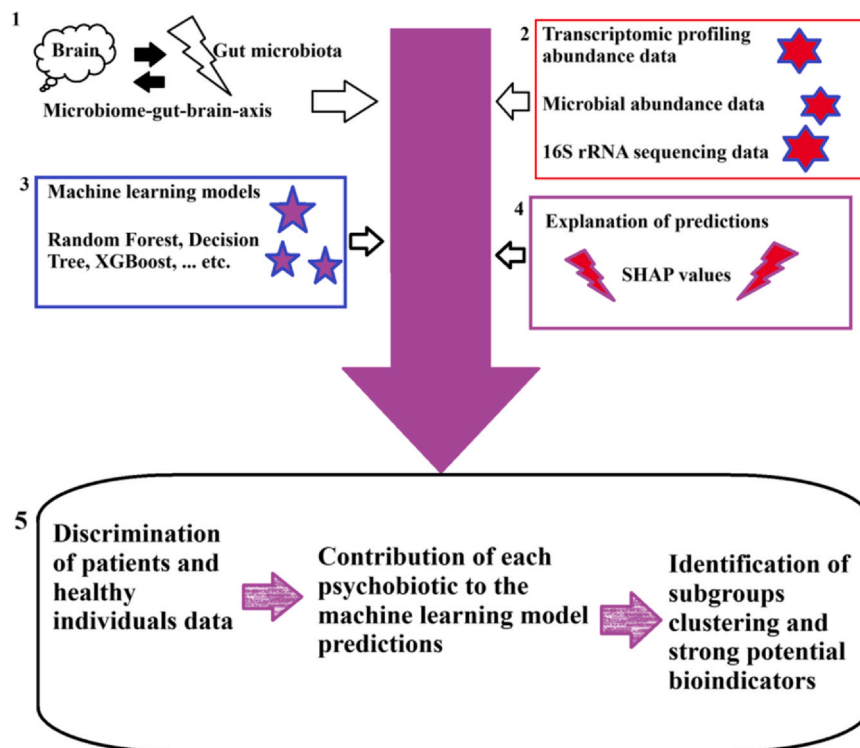


Fig. 2. Graphical summary of how AI machine learning models can be used to predict strong potential psychobiotic biomarkers via SHAPley Additive exPlanations (SHAP) values generated based on transcriptomic profiling and microbial abundance data.

ensemble feature selection machine learning AI approach to successfully identified the bacterial taxa that can be used as biomarkers for autism spectrum disorder prediction among children, with average area under curve (AUC) of over 80 % achieved for the classifier based in 16S rRNA sequencing datasets. The *Clostridia*, *Parabacteroides* and *Sarcina* are found to be enriched in children with autism spectrum disorders whereas the *Eubacterium eligens* and *Butyrivicoccus* were found to have diminished in children with autism spectrum disorders¹⁵. Both *Eubacterium* and *Butyrivicoccus* identified as potential psychobiotics as they are capable of biosynthesising health-promoting short-chain fatty acids, regulating immune response as well as reversing gut dysbiosis¹⁵.

Another group of researchers utilized explainable artificial intelligence (unsupervised clustering and local explanation embeddings) in deciphering the associations of individual microbial species to autism spectrum disorder¹⁶. Their classifier achieved high AU-PRC of 0.967 and AU-ROC of 0.965. Interestingly, a plethora of bacterial species have been identified as potential autism spectrum disorder bioindicators, namely

Barnesiella, *Sutterella*, *Prevotella*, *Holdemanella* and *Christensenellaceae*¹⁶. Moreover, a myriad of *Lachnospiraceae* and *Ruminococcaceae* bacterial species and strains have been unearthed as promising psychobiotics as they actively orchestrate the metabolism of short-chain fatty acids¹⁶. Most recently, Khan & Gajbhiye¹⁷ utilized AI-driven framework integrating multi-omics and deep reinforcement learning to successfully model the microbial interactions and enhance strain selection by focusing on neurotransmitter production, minimizing reliance on trial-and-error in psychobiotic research. Early findings demonstrate increased accuracy in identifying beneficial strains, indicating a promising and efficient approach for microbiome-driven mental health treatments¹⁷. The graph neural networks (GNNs) and recurrent neural networks (RNNs) used by Khan & Gajbhiye¹⁷ in their AI model have successfully deduced that *Lactobacillus rhamnosus* can increase gamma-aminobutyric acid production that is beneficial for mood regulation and stress management, *Bifidobacterium longum* is capable of reducing cortisol levels and anxiety whereas *Bacteroides fragilis* can elevate serotonin bioproduction and improve behavioral symptoms.

Table 1

Comparison of performances of different AI tools and algorithms.

Approach/Author	Performances
Machine-learning multivariate analyses ⁹ AI systematic review ¹³ AI systematic profiling of multi-omics landscape ¹⁴ Feature selection machine learning AI ¹⁵	Discover novel microbiome associated with depressive hypertension Revealed that <i>Bifidobacterium</i> is the best biomarker and psychobiotic for autism spectrum disorder Identified orphan GPCRs (the GPCR84) as the most promising therapeutic target in Alzheimer's disease Identified the bacterial taxa that can be used as biomarkers for autism spectrum disorder prediction among children
Unsupervised clustering and local explanation embeddings ¹⁶ AI-driven framework integrating multi-omics and deep reinforcement learning ¹⁷	Identified potential autism spectrum disorder bioindicators Models microbial interactions and enhances strain selection by focusing on neurotransmitter production, minimizing reliance on trial-and-error in psychobiotic research. Early findings demonstrate increased accuracy in identifying beneficial strains, indicating a promising and efficient approach for microbiome-driven mental health treatments.
Artificial model of the human gastrointestinal tract named ABIOME ¹⁰ Automated active machine learning ¹¹ Advanced AI algorithms ¹²	Allows real-time monitoring of gastrointestinal conditions, optimizes psychobiotic therapies and identifies combinations that leads to the biosynthesis of bioactive metabolites with strong therapeutic potential Predicted the effects of 111 untested excipients on the proliferation of psychobiotics Discover microbial bioindicators that contribute to optimal gastrointestinal health in patients recently recovered from COVID-19

Case studies, research gaps, controversies and critical evaluation

One of the most interesting case studies that can be emulated in the field of psychobiotic treatment of the microbiome-gut-brain axis is the strain design optimization approach described by Sabzevari et al.¹⁸ using multi-agent reinforcement learning. The pivotal highlight of their AI-based approach is that their method is completely model-free and does not necessitate previous knowledge on the psychobiotic's regulation and metabolic network. Their AI tool can predict the optimal dosage of psychobiotics to achieve the desired maximal effects. This tool will not only save time, reduce labour, but also minimize errors due to small sampling size during the wet lab optimization process¹⁸. This aspect is often not being put into the limelight of research when designing AI models listed in the previous section. The current research gap in this field is the determination of the optimal dosage to be addressed to patients after the accurate prediction of the required psychobiotic combinations to be delivered to patients. The optimal dosage enumeration also needs performed based on the individual patient's genetic makeup to achieve the maximal therapeutic effects. The precision and personalized psychobiotic medication will not only cure the patient in the shortest amount of time, but also reduce the side effects post medications in patients.

The controversies that arise from this field of research include the overfitting, reproducibility, interpretability as well as ethical concerns. Some complex AI models may impose the risk of overfitting small datasets and this greatly impedes the reproducibility of the research. Besides, many deep learning models lack transparency and thus reducing clinical trust. Furthermore, AI-driven decision making in mental healthcare, must be ethically managed by government and private entities with high integrity, especially with vulnerable populations. The selection of AI tools in psychobiotic microbiome-gut-brain axis treatment requires critical evaluation on whether the data suits the particular AI algorithm and also whether the required outcomes can be generated and utilized to produce meaningful datasets to aid decision making processes of medical practitioners and researchers. The various AI machine learning tools are selected and utilized based on their differing prediction uses, data requirements and versatility. For instance, deep learning models like convolutional neural networks (CNNs) have shown superior performance in classifying microbiome profiles linked to mental health conditions. Random Forests and XGBoost are preferred for feature selection and interpretation due to their robustness and ability to handle complex, high-dimensional microbiome data. Meanwhile, deep reinforcement learning (DRL) is particularly useful for simulating microbial ecosystems and optimizing strain combinations based on neurotransmitter production. Each algorithm is selected based on its strengths: prediction accuracy, interpretability, or adaptability in dynamic, multi-variable environments like the gut-brain axis.

Limitations of AI in microbiome-gut-brain axis psychobiotic treatment

Despite its promising applications, Artificial Intelligence (AI) in microbiome-gut-brain axis (MGBA) psychobiotic therapy still faces several limitations. One major challenge is the lack of standardized and high-quality datasets. Microbiome data is highly complex and influenced by numerous variables such as diet, geography, genetics, and environment, making it difficult for AI models to generalize findings across populations. Additionally, the current AI models often function as "black boxes," providing little insight into how decisions are made, which is problematic in clinical settings where transparency and explainability are critical. The integration of multi-omics data (genomics, transcriptomics, proteomics, metagenomics and metabolomics) further adds to the computational burden, requiring robust infrastructure and expertise not always readily available. Moreover, AI models trained on limited or biased datasets may produce misleading conclusions, especially when applied to diverse patient populations. Finally, translating AI-generated insights into real-world psychobiotic therapies remains a

hurdle due to regulatory, ethical, and clinical trial constraints. These limitations must be addressed to fully realize AI's potential in MGBA-targeted treatments.

Future outlooks and conclusion

This micro review has gathered all the recently emerged AI approaches used in the psychobiotic treatment of microbiome-gut-brain-axis associated diseases. The future development of these tools and algorithms will be skewed towards the predictive monitoring and tracking of psychobiotic-derived neuroactive compounds circulation¹⁹ from the gut to the brain in terms of concentration and the resulting cascade effects. Besides, it is also imperative to investigate whether a psychobacterial consortium works better than an individual psychobiotic in mental illness therapies both *in silico* and *in vivo*²⁰. The future of this field of research is both exciting and highly anticipated as we decipher the ultimate cure for the detrimental mental illnesses troubling mankind for centuries.

Declarations

Not applicable.

Authors' contributions

L.W.K. Lim: Conceptualization, Literature search and review, Writing—original draft, Writing—review & editing, Critical analysis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The author has read and approved the final manuscript, and consent to its publication.

Availability of data and materials

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Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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