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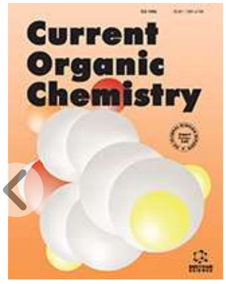

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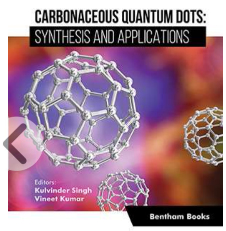

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Chemosphere
Volume 342, November 2023, 139950

Energy generation from bioelectrochemical techniques: Concepts, reactor configurations and modeling approaches

P. Mullai [a], S. Vishali [b], S.M. Sambavi [c], K. Dharmalingam [d], M.K. Yogeswari [a], V.C. Vadivel Raja [a], B. Bharathiraja [e], Büşra Bayar [f], Haris Nalakath Abubackar [f], Md Abdullah Al Noman [g], Eldon R. Rene [g]

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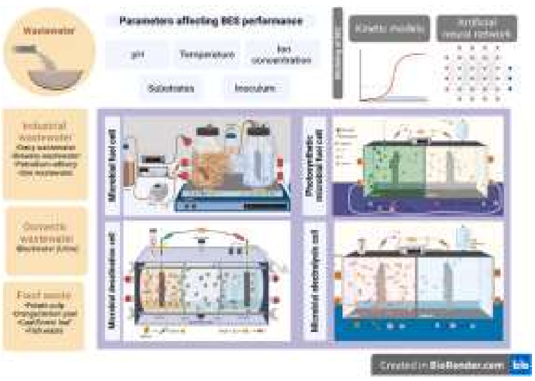
Highlights

- Different types of bioelectrochemical systems (BESs) used for waste treatment are discussed
- Parameters influencing the performance of BESs are listed and examined
- Artificial neural network models used to evaluate the performance of BESs are presented
- Microorganisms involved in waste degradation and future trends in BESs are highlighted

Abstract

The process industries play a significant role in boosting the economy of any nation. However, poor management in several industries has been posing worrisome threats to an environment that was previously immaculate. As a result, the untreated waste and wastewater discarded by many industries contain abundant organic matter and other toxic chemicals. It is more likely that they disrupt the proper functioning of the water bodies by perturbing the sustenance of many species of flora and fauna occupying the different trophic levels. The simultaneous threats to human health and the environment, as well as the global energy problem, have encouraged a number of nations to work on the development of renewable energy sources. Hence, bioelectrochemical systems (BESs) have attracted the attention of several stakeholders throughout the world on many counts. The bioelectricity generated from BESs has been recognized as a clean fuel. Besides, this technology has advantages such as the direct conversion of substrate to electricity, and efficient operation at ambient and even low temperatures. An overview of the BESs, its important operating parameters, bioremediation of industrial waste and wastewaters, biodegradation kinetics, and artificial neural network (ANN) modeling to describe substrate removal/elimination and energy production of the BESs are discussed. When considering the potential for use in the industrial sector, certain technical issues of BES design and the principal microorganisms/biocatalysts involved in the degradation of waste are also highlighted in this review.

Graphical abstract



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Introduction

The energy demand to meet industrialization and population growth is expanding day by day and is considered a primary global threat. The energy requirement is a major driving force of the global economy (Mullai et al., 2022; Jåstad and Bolkesjø, 2023). The economic activities are directly influenced by limiting energy use. The amount of energy needed to lift developing countries out of poverty is tremendous. The probabilities of elevating energy needs are mostly questionable (Srikanth et al., 2016a; Yogeswari et al., 2019; de Fouchécour et al., 2022). Simultaneously, with the global increase in energy demand, waste generation and pollution-related problems are also rising globally. For example, the excessive production of waste has created waste management issues, such as landfill space shortages, environmental contamination, and resource depletion. To address these issues, societies and governments are employing technologies for waste minimization, recycling, and waste-to-energy conversion (Akinyemi et al., 2019; Duarte et al., 2019; Gredilla et al., 2019; Oliveira et al., 2019a, 2019b, b; Dutta et al., 2020; Saikia et al., 2020; Silva et al., 2020a, 2020b). Therefore, sustainable waste management and energy practices are necessary to establish a society that is more environmentally conscious and resource-efficient. This includes reducing waste production, increasing recycling rates, shifting to renewable energy sources, and promoting energy-efficient technologies.

Environmental experts have tried in many ways to derive energy from the waste components, viz., biogas from anaerobic digestion, electricity generation along biosolids incineration, energy revival from biogas utilization, and energy recovery from biosolids incineration. The biogas that is obtained through the treatment of various wastes can bae an efficient source of fuel in a process industry as well as a sustainable way of effluent treatment (Mullai et al., 2018). In this aspect, different reactors have been tested at the lab-scale and pilot-scale (Rossi and Logan, 2022; Tsapekos et al., 2022). There are studies that show high rates of methane production (Mullai et al., 2020) and treatment of wastes with different reactor setups, such as as anaerobic sequential batch reactor (Arreola-Vargas et al., 2016) , anaerobic membrane bioreactor (Moideen et al., 2023), continuous stirred tank reactor (CSTR) (Wei et al., 2022), upflow anaerobic sludge blanket reactor (UASB) (Wu et al., 2020a), anaerobic fluidized bed reactor (de Souza Dornelles et al., 2020), anaerobic expanded granular sludge bed reactor (Granatto et al., 2021) and continuous hybrid fixed bed anaerobic filter reactor (Ahmed et al., 2021).

It has been a long decade before renewable energy production in the form of methane from the solid and liquid waste streams has been established via anaerobic digestion. Energy generation from the waste streams concurrently supports the power needs, inclusive of pollutant removal from the effluent. The hunt for a sustainable solution to overcome energy demand and waste remediation inspired the technological evolution of energy recovery from waste (Yang et al., 2022). Bioelectrochemical systems (BESs) are energetic entities and serve as an ideal platform for the generation of valuable energy sources from organic waste through chemical energy conversion, viz. electric power, hydrogen fuel cells, and value-added products. It utilizes microbes as a catalyst, and common microbial-electrochemical reactions are engaged in this system, which facilitates both the oxidation and reduction reactions. Electrically active bacteria can be assessed as catalysts (Bajracharya et al., 2016; Sambavi et al., 2020). The summary of the outcome of the BESs in terms of effluent treatment efficiency and electrochemical performance is listed in Table 1.

This review seeks to identify and discuss the various factors influencing the efficacy of BESs for waste and effluent treatment. Besides, the evaluation and prediction of the performance of BESs using artificial neural networks has been discussed because this topic has received a lot of interest from the research community. In addition, the treatment of a wide variety of wastes and wastewaters, as well as the function of microorganisms and biocatalysts in the process of waste degradation in BESs, are both covered in this review paper.

Section snippets

Configuration of bioelectrochemical systems

The configuration of BESs based on their application is majorly grouped into microbial fuel cell (MFC), microbial solar cell (MSC), microbial electrolysis cell (MEC), and microbial desalination cell (MDC) (Pant et al., 2012). The detailed methodological description and concepts of MFC, MSC, MEC, and MDC are discussed as follows (Fig. 1, Fig. 2, Fig. 3, Fig. 4).…

Parameters affecting the performance of BESs

The different physicochemical and biological characteristics of the environment in which the BESs are operated can have an effect on their performance.. The primary parameters are the source, initial pH, and initial concentration of the pollutants. Environmental properties such as the oxygen level, moisture content, and temperature are also influencing its performance. The combination of electrodes, types of anode, and cathode are the general parameters that always influence the efficiency of…

Treatment of various wastes and wastewaters

In the current scenario, with the growth in population and globalization, there is a dramatic increase in the amount of waste generated. This waste generally includes food waste, domestic waste, agro-waste, and water streams that contain various pollutants such as pharmaceutical pollutants, synthetic dyes, heavy metals, and many others.

Food waste is generated from a variety of sources, such as households, restaurants, and so on, and mostly consists of high molecular weight polymers like…

Predominant microbes/biocatalysts for waste degradation in BESs

In the process of waste degradation, with the help of microbes, the chemical structure of the contaminant breaks down into water, carbon dioxide, and biomass sludge. For their survival, microbes consume nutrients and chemical compounds in waste. Almost all the chemical compounds, including hydrocarbons, could be degraded using different kinds of bacteria (Table 5). In BESs, *Geobacter sulfurreducens*, which is an iron-reducing bacteria (exoelectrogen), produces electrical current and highpower…

Kinetic models

The BESs is a complicated biological system that is made up of a variety of different physical, electrochemical, and biological processes. These processes interact with one another to produce a non-linear pattern in the performance of the system. Hence, finding the best conditions for improving system performance via experimental work would not be a cost-effective or time-efficient strategy. In this regard, mathematical models that consider microbial population dynamics, mass transfer in bulk…

Artificial neural network (ANN) modeling

Artificial neural networks (ANNs) are regarded as a powerful modeling tool for complex non-linear systems, such as BESs, whose performance is highly sensitive to changes in the environment and whose parameters, such as biofilm thickness, electroactive microbes' activities, electron transfer mechanism, etc., are difficult to regulate or control. By training the neural network with relevant inputs that could impact the outputs, ANN could obviate the need for prior knowledge of the system's…

Opportunity and future perspectives

The microbial fuel cell is a technology that can produce energy from the action of microorganisms. BESs are very cheap, fast, simple, and also rectify the current electricity needs. This technology has been widely used in the past few years. However, it is very important to consider the production of low current density in microbial fuel cell operation. The existing design parameter for the optimization of the reduction of losses is affected by ohmic, activation, and concentration…

Conclusions

BESs are advanced treatment techniques that have been extensively studied in the lab and have demonstrated their reliability in producing energy using the inherent features of a biocatalyst. In this review, the performance of various biocatalysts utilized in BESs for electricity generation has been summarized, along with the process/environmental conditions used/tested by researchers who treated various types of wastewaters. In various systems, low current density/yields have been noticed;…

CRediT authorship contribution statement

P. Mullai: Conceptualization, Visualization, Writing – review & editing, Supervision. **S. Vishali:** Conceptualization, Visualization, Writing – review & editing, Supervision. **S.M. Sambavi:** Conceptualization, Writing – review & editing. **K. Dharmalingam:** Conceptualization, Visualization, Writing – review & editing, Supervision. **M.K. Yogeswari:** Conceptualization, Writing – review & editing. **V.C. Vadivel Raja:** Conceptualization, Writing – review & editing. **B. Bharathiraja:** Conceptualization, Writing…

Declaration of competing interest

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

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EDITORIAL article

Front. Pharmacol., 13 April 2023

Sec. Pharmacology of Anti-Cancer Drugs

Volume 14 - 2023 |
https://doi.org/10.3389/fphar.2023.1190354

This article is part of the Research Topic

Anti-Cancer Bioactive Molecules from Microbial Sources

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Editorial: Anti-cancer bioactive molecules from microbial sources

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Edited by

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Centre de Pharmacologie et de Thérapeutique, Institut de recherche expérimentale et clinique, Faculté de pharmacie et des sciences biomédicales, Université catholique de Louvain,

one of the world's leading causes of death, with a projected annual mortality rate of 16.4 million by 2040. In general, its mortality rate has decreased over the years; however, there is still an increased mortality rate in poorer countries where healthcare professionals pay special attention. About 200 types of cancer affect humans, and for the majority of these, just a handful of approved treatments exist (Law et al., 2020).

To prevent cancer-related mortality, it is essential to develop novel, strong anticancer drugs. The discovery of anti-cancer drugs has witnessed significant technological advancement in recent years. Traditional cell-based screening for antiproliferative effects has been replaced with a particular technique to scan for compounds that can target major cancer proteins or pathways (Izadi et al., 2020).

In recent decades, the hunt for bioactive compounds from microbes has garnered increasing interest. Numerous anticancer medicines generated from actinobacteria groups of microorganisms (e.g., *Streptomyces parvulus*, *Streptomyces antibioticus*, *Streptomyces cheonanensis*, *Streptomyces anandii*, etc.) have been studied in clinical trials. Notable examples of anti-cancer bioactive chemicals include actinomycin D, bleomycin, anthracyclines, epirubicin, and doxorubicin (Silva et al., 2020). One of the most exciting areas of study for treating the cancer cells is immunotherapy, which can involve the application of particular microbes (e.g., *Alistipes shaii*, *Bacteroides fragilis*, *Bifidobacterium*, *Faecalibacterium*, etc.). The immune system is stimulated through T cell

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References

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understanding of the development, characteristics, and mechanistic studies of microorganism-derived anti-cancer compounds. Under the subject theme, three experimental research publications and two review articles have been published.

Li et al. did an interesting study on how calf thymus polypeptide (CTP) stops colorectal cancer (CRC) in B6/JGpt-*Apc* $^{em1Cin\ (MinC)}$/Gpt mice by controlling their intestinal microbiota and immune response. The immune system is altered by CTP via the intestinal micro biota, which is linked to the drug's anti-CRC effect. This establishes a connection between CTP and the use of therapeutic drugs or drug combinations in a clinical setting for the management of CRC. CTP makes CRC less likely to happen because it helps the immune system work well through the Interleukin-2 (IL-2)-associated signaling pathway. Even though this current topic confirmed that CTP associated with T cells has an effect on CRC that slows it down, more research is needed to find out how it changes and be sure it works in the clinical trials.

Another noteworthy study in this Research Topic by Zhang et al. claims that synergistic effects of *Pseudomonas aeruginosa* and ambient particulate matter with a diameter of 2.5 m (PM 2.5) disrupt alveolar macrophage function and cause inflammation. Moreover, PM 2.5 and *P. aeruginosa* were used to excite alveolar macrophages in an enclosed broiler house, whereas PM 2.5 in combination with *P. aeruginosa* was found to reduce phagocytosis, block autophagy, promote apoptosis, and

Cytotoxic Compounds: A Review

Fazilath Uzma, Chakrabhavi D. Mohan, Abeer Hashem, Narasimha M. Konappa, Shobith Rangappa, Praveen V. Kamath, Bhim P. Singh, Venkataramana Mudili, Vijai K. Gupta, Chandra N. Siddaiah, Srinivas Chowdappa, Abdulaziz A. Alqarawi and Elsayed F. Abd_Allah

Chloroquine Inhibits Stemness of Esophageal Squamous Cell Carcinoma Cells Through Targeting CXCR4-STAT3 Pathway

Dongli Yue, Daiqun Zhang, Xiaojuan Shi, Shasha Liu, Anqi Li, invasion, metastasis, and proliferation in animal models at micro molar concentrations. Computational target prediction methods also uncovered cannabinoid G-protein coupled receptor type 1 (CB1) as a putative biological target mediating, at least in part, the anticancer actions of acetylaszonalenin.

Omole et al. investigate the field of oncolytic viruses, which have become a viable immunotherapeutic choice for the treatment of many tumors. In this review, they have looked at the primary traditional therapeutic methods for the treatment of cancer and each one's specific shortcomings, as well as how severe the burden of cancer is on a global scale, especially in sub-Saharan Africa. Several pre-clinical and clinical trials have used the alleged mechanisms of action of oncolytic viruses and other viruses that have found application in the fight against various types of oncolytic viruses to treat cancer. The use of oncolytic viro-immunotherapy for the treatment of malignancies has raised concerns about toxicity and safety. This study also looked at the anticipated future directions for researchers and the general public who desire updated information.

Li et al. look at the latest research on cell penetrating peptides (CPPs), peptide-based vaccinations, and anticancer peptides for treating and preventing breast cancer. Moreover, different types of peptides that work as targeted nanovectors, cancer vaccines, and anti-cancer drugs to treat breast cancer were looked at in detail. Anticancer treatment using microorganisms is usually ignored or marginalized. A very small group of scientists microorganism's attenuation and its capacity to excite the immune system.

The authors and reviewers of these manuscripts are to be commended for their hard work and dedication. Moreover, the reviewers are highly appreciated for their helpful remarks that enhanced the quality of the manuscripts.

Our objective is that this compilation of articles will serve as a resource for researchers from a wide range of disciplines who are interested in evaluating anti-cancer bioactive molecules from microbial sources in their quest to develop novel pharmacological approaches.

Author contributions

BM, SM, HB, KT, and YM have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Restricted access | Research article | First published online May 24, 2023

Fabrication and Characterization of Organo Modified Polysiloxane Softened Linen Fabrics by On-Loom Integrated Finishing

P Vasu, K Dharmalingam, [...], and C Prakash +1 View all authors and affiliations

Volume 10, Issue 6 | https://doi.org/10.1177/24723444231172225

Abstract

In this study, the fabrication – that is, weaving and softening of linen fabric – was accomplished by on-loom integrated finishing on a handloom using a special attachment. The optimization of the process parameters (finish liquor concentration, temperature and curing time) for these on-loom integrated softening finished fabrics were investigated. The softened linen fabric was studied for their physical properties like softness, drapeability, wickability, water vapour permeability, air permeability, total crease recovery angle, tensile

https://journals.sagepub.com/doi/10.1177/24723444231172225#core-collat... mpared with similar finished market sample.

Algal Research
Volume 71, April 2023, 103039

Review article

Biological detoxification of mycotoxins: Emphasizing the role of algae

Rajasri Yadavalli, Praharshita Valluru, Roshni Raj, C. Nagendranatha Reddy, Bishwambhar Mishra

https://doi.org/10.1016/j.algal.2023.103039

Highlights

- Wide applications and cost-effectiveness of algal detoxification of mycotoxins makes it a sustainable process
- Aflatoxin and Fusarium toxins are of special interest because of their prevalence across the globe
- Polysaccharides, particularly sulphated polysaccharides, and antioxidants are abundant in algae.
- Aflatoxin breakdown by laccase and algal chlorophyllin is accomplished by spirulina.

Abstract

Mycotoxins viz., aflatoxins, the secondary fungal metabolites, are hepatotoxic, genotoxic, carcinogenic, and teratogenic. According to several studies, mycotoxins have been linked to financial losses in all phases of food and feed production, including crop and animal production, processing, and distribution due to the reduction in crop yield and animal productivity. Due to their widespread existence, Aflatoxin and Fusarium toxins, such as deoxynivalenol and fumonisins, are of particular interest because they can seriously contaminate feed and food, adversely affect farm animals with acute or chronic mycotoxicosis, and affect humans with nausea, vomiting, abdominal pains, and other symptoms of acute liver injury. Consequently, there is an increased need for a revolutionary method for preventing mycotoxins in food and livestock and the effects of current contamination by mycotoxins. Several physical, chemical, and biological techniques exist for mycotoxin decontamination or detoxification. It is a known fact that biological detoxification is highly effective and offers ecological sustainability, applicability over a wide range of mycotoxins, easiness and cost-effectiveness too. Algae and the compounds produced by algae have multiple properties like anti-fungal, anti-oxidants, antibiofilm and many more which can be exploited for many applications, including the detoxification or degradation of toxic components, including mycotoxins. Such compounds include sulphated polysaccharides, β-D-glucans, polyphenolic compounds, etc. Spirulina platensis is one such algae that has been suggested as a possible aflatoxin detoxicant. The focus of this study is on the numerous algal characteristics, particularly those derived from polysaccharides, and their potential utility in the detoxification of mycotoxins.

Introduction

The secondary metabolites known as mycotoxins are produced by toxigenic fungal strains, primarily those from the genera *Penicillium, Aspergillus, Alternaria*, and *Fusarium*. There are several different kinds of them, including patulin, zearalenone (ZEA), fumonisins, and trichothecenes. It's estimated that >400 different types of mycotoxins have been discovered and reported since 1960. These very dangerous mycotoxins are the most often found in food: aflatoxins (AF's), trichothecenes, ochra-toxins, ZEA, fumonisins, and patulin [1], [46]. Due to poor circumstances during harvest, storage, or transport, a variety of toxic fungus can create these noteworthy pollutants [2]. The majority of them possess intricate chemical structures with the precise groups that bestow the hazardous effects. AFs are the most extensively researched mycotoxin found in agricultural products and are highly harmful. The three *Aspergillus* species—*Aspergillus flavus, A. parasiticus, and A. nomius*—produce them in large quantities. According to reports, AF's can cause immunological suppression, nephron toxicity, and liver toxicity in people [3]. Aflatoxin B1 (AFB1), Aflatoxin B2 (AFB2), Aflatoxin G1 (AFG1), and Aflatoxin G2 (AFG2) are the four most well-known aflatoxins. Aflatoxin M1 (AFM1) and M2 (AFM2) are the hydroxylated metabolites of AFB1 and AFB2, respectively. AFB1 is the most dangerous of the AFs and is classified as a Group I naturally occurring carcinogen [4]. AFs are furanocoumarins linked to a coumarin that has been substituted by a cyclopentanone or a lactone and a bisdihydrodifuran or tetrahydrobisfuran [5]. The double bond in the terminal furan ring and the lactone ring of AFs are what cause their toxicity and carcinogenic activities, respectively. A schematic outlining the origins of AFs and how they affect human health is shown below (Fig. 1).

There are certain negative effects of these mycotoxins on human health. Chronic dietary intake often leads to the highest risk of AF in people. Human hepatocellular carcinomas have been linked to such dietary AF exposures, which the hepatitis B virus may exacerbate. Hepatocellular carcinomas are thought to be responsible for over 250,000 fatalities per year in China and Sub-Saharan Africa [6], where risk factors include high intakes of AF (1.4g per day) and hepatitis B [6], [7]. Aflatoxins were discovered in the tissues of children with Reye's syndrome and Kwashiorkor, and they were assumed to be a contributing component to both illnesses [8]. Reye's syndrome causes liver and kidney enlargement, brain edema, and visceral degeneration in addition to encephalopathy [8], [9]. Another probable human carcinogen is Ochratoxin A (OTA), which has been linked to upper urinary tract epithelial cancers in the Balkan region [10]. The illness is referred to as Balkan Endemic Nephropathy. Despite the severity of the issue, research has not fully revealed the mechanism or scope of OTA's human carcinogenic risk [11]. Due to these harmful effects on humans, solutions such as detoxification of these mycotoxins are necessary to be studied and applied.

Over the last few decades, a lot of research has been conducted employing physical, chemical, and biological detoxification approaches to treat AFs [12], [13]. The most popular techniques are physical ones; for instance, to lessen toxic contamination, physical adsorption is carried out using adsorbents [14]. Mycotoxins cannot be entirely adsorbed, even if adsorbent materials can diminish their bioavailability [15]. After years of progress, nanotechnology has recently been used to enhance the adsorption capacity of adsorbents such as magnetic adsorbents [16]. Physical approaches, however, have a number of drawbacks, such as restricted application, a weak detoxifying impact, and a limited status for detox products [17]. Chemical techniques call for the use of an oxidizing agent, acid, or alkali [18]. Chemicals like chlorine dioxide, which are used to disinfect toxins [19], may degrade the flavor and look of food. Chemical residues left behind from food processing may be detrimental to people [20]. Both methods are equally effective for detoxification. A schematic diagram of various methods of physical and chemical detoxification against mycotoxins is illustrated in Fig. 2. However, under the correct conditions, biological detoxification may totally detoxify samples and has great selectivity, producing innocuous metabolites [4], [18]. Biological detoxification is progressively taking over as the best detoxification strategy when compared to physical and chemical approaches.

Aflatoxin B1 is another chemical that is cytotoxic and increases the production of reactive oxygen species (ROS) and oxidative stress, both of which result in cell destruction. Microalgae have gained significant interest as a source of biomolecules with varied characteristics, such as antioxidant, anti-inflammatory, antifungal, etc., while being more well-known for biofuels. Due to its superior nutritional properties and high digestion due to the tiny quantity of carbs it contains, *Spirulina* is frequently utilized in dietary supplements. *Spirulina* includes a special combination of nutrients that include B-complex vitamins, minerals, proteins, gamma-linolenic acid, super antioxidants (such β-carotene, vitamin E, trace elements), and several undiscovered bioactive chemicals. Seaweed polysaccharides (MAP) exert multiple biological activities, possibly having a potential detoxifying effect on AFB1. The current review paper focuses on various methods of biological detoxification with a special mention on the role of algae (including macro and micro) as effective detoxicant against mycotoxins.

Section snippets

Probiotic microorganisms as detoxicants

Probiotics are described as live bacteria that, when provided in suitable proportions, impart a health benefit on the host [21]. They are present in a variety of goods, including food, medication, and dietary supplements. Probiotic microorganisms have been studied for years in relation to their biological detoxification of mycotoxins [5], [21], [22]. Mycotoxins can be eliminated primarily by one of two methods, surface adsorption or biodegradation, by probiotics, particularly lactic acid…

Green algae

There have been many micro/macroalgae and seaweeds that produce polysaccharides and sulphated polysaccharides that work as potential antioxidants. These deoxidants can be used as a detoxifying agent against mycotoxins. Significant antioxidant effects were seen in *Bryopsis plumosa* (green seaweed) sulphated polysaccharide samples. This demonstrated that sulphated polysaccharides from green algae are efficient antioxidants, much like sulphated polysaccharides from brown algae and red algae. *B.*…

Polysaccharides produced by algae

Polysaccharides are naturally occurring polymers that play a role in a number of biological functions, including cell adhesion, cell-to-cell communication, and immunological response [94], [95]. Additionally, these bioactive substances have anti-inflammatory, antioxidant, immunomodulatory, anti-cancer, and antiviral properties [94], [96]. Polysaccharides from *Chlorella* and *Spirulina*, for instance, have been mentioned as anti-obesity agents [97]. These potentials have led to the consideration of …

Bioadsorption mechanism

Large-molecular-weight substances called mycotoxin-adsorbing agents must be able to bind mycotoxins in contaminated feed without dissociating as they travel through the animal's digestive system. This allows the complex to be removed through the animal's feces. As a result, animals are not exposed to mycotoxins as much. Mineral or organic substances can be used as adsorbing agents. Their mode of action is based on intermolecular interactions (toxin-binder), which vary depending on the type of…

Current status and future perspectives

There are several new techniques being developed for the biological detoxification of mycotoxins, one of which involves the use of bacterial biofilms. Using biofilms from *Lactobacillus rhamnosus*, Nahle et al. evaluated the removal of aflatoxin M1 (AFM1) and ochratoxin A (OTA) from experimentally contaminated whole UHT milk and red grape juice, respectively. The degree of AFM1 and OTA removal from drinks was assessed using ELISA based on a number of variables. Mycotoxins may be effectively…

Conclusions

Mycotoxins' extensive contamination has received attention on a global scale. Biological degradation is thought to be the safest method for mycotoxin elimination among the several ways that have been researched. Recombinant degrading enzymes are increasingly preferred in biological detoxification with the advancement of genetic engineering technologies. A brand-new area of study still has to be done on algae, which has the ability to produce recombinant enzymes and antioxidants that can…

CRediT authorship contribution statement

Rajasri Yadavalli: Conceptualization, Methodology, Supervision, Review & editing. **Praharshita Valluru**: Writing - original draft, Data curation. **Roshni Raj**: Writing - original draft, Data curation. **Nagendranatha Reddy C**: Data curation, Methodology, Supervision, review & editing. **Bishwambhar Mishra**: Data curation, Methodology, Supervision, review & editing.…

Declaration of competing interest

The authors 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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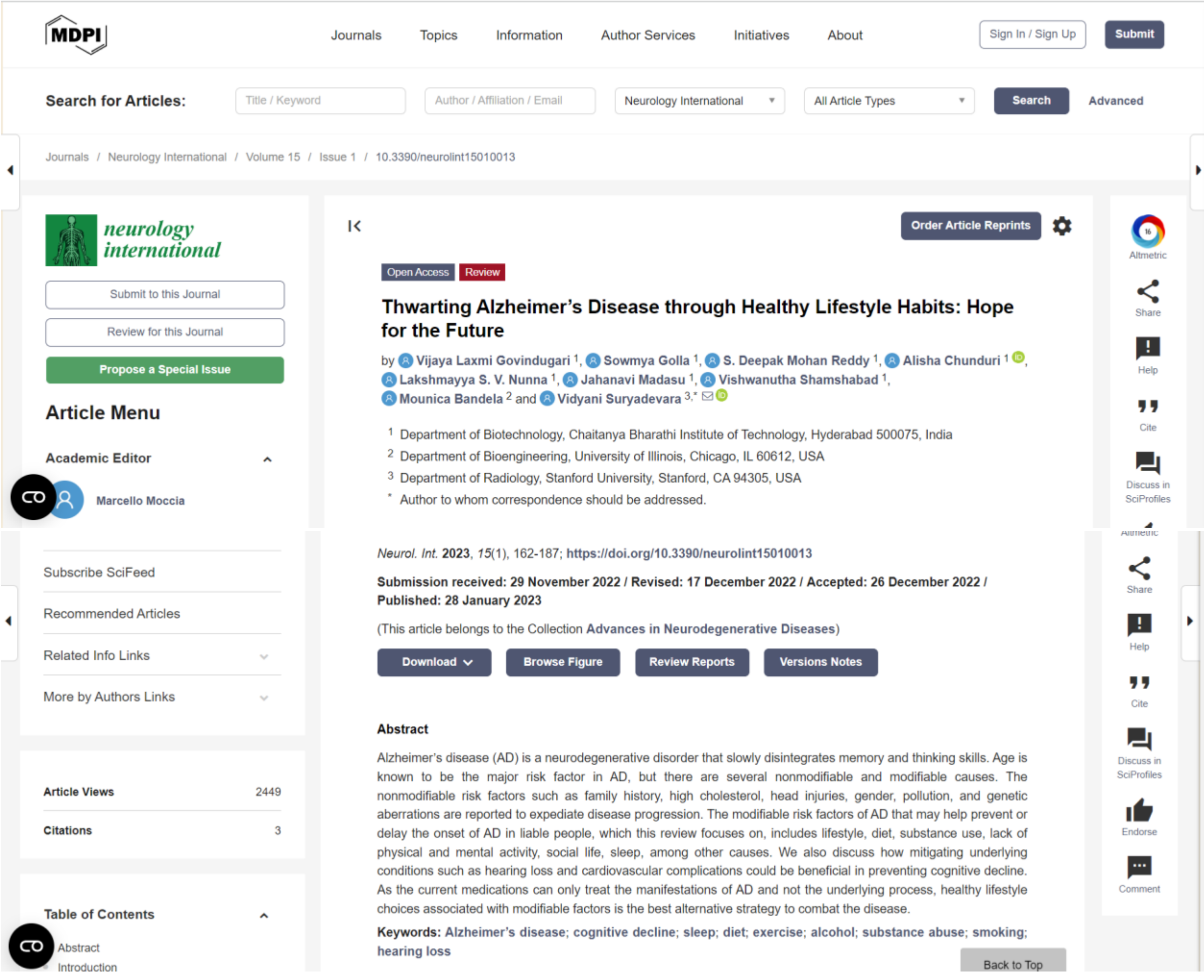
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Thwarting Alzheimer's Disease through Healthy Lifestyle Habits: Hope for the Future

by Vijaya Laxmi Govindugari [1], Sowmya Golla [1], S. Deepak Mohan Reddy [1], Alisha Chunduri [1], Lakshmayya S. V. Nunna [1], Jahanavi Madasu [1], Vishwanutha Shamshabad [1], Mounica Bandela [2] and Vidyani Suryadevara [3,*]

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(This article belongs to the Collection Advances in Neurodegenerative Diseases)

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that slowly disintegrates memory and thinking skills. Age is known to be the major risk factor in AD, but there are several nonmodifiable and modifiable causes. The nonmodifiable risk factors such as family history, high cholesterol, head injuries, gender, pollution, and genetic aberrations are reported to expediate disease progression. The modifiable risk factors of AD that may help prevent or delay the onset of AD in liable people, which this review focuses on, includes lifestyle, diet, substance use, lack of physical and mental activity, social life, sleep, among other causes. We also discuss how mitigating underlying conditions such as hearing loss and cardiovascular complications could be beneficial in preventing cognitive decline. As the current medications can only treat the manifestations of AD and not the underlying process, healthy lifestyle choices associated with modifiable factors is the best alternative strategy to combat the disease.

Keywords: Alzheimer's disease; cognitive decline; sleep; diet; exercise; alcohol; substance abuse; smoking; hearing loss

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Gut–Brain Axis, Neurodegeneration and Mental Health: A Personalized Medicine Perspective

Review article Published: 10 August 2022

Volume 62, pages 505–515, (2022) Cite this article

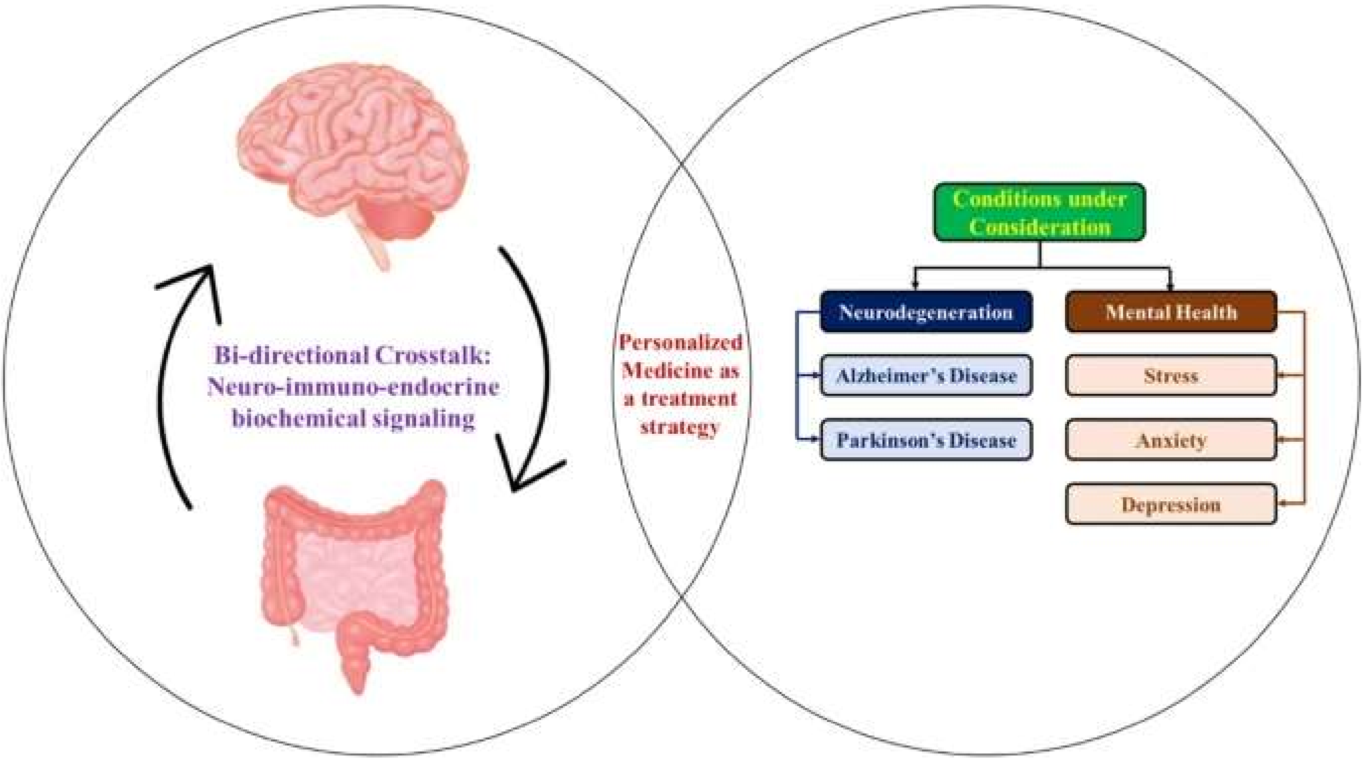
Alisha Chunduri, S. Deepak Mohan Reddy, M. Jahanavi & C. Nagendranatha Reddy

Abstract

Neurological conditions such as neurodegenerative diseases and mental health disorders are a result of multifactorial underpinnings, leading to individual-based complex phenotypes. Demystification of these multifactorial connections will promote disease diagnosis and treatment. Personalized treatment rather than a one-size-fits-all approach would enable us to cater to the unmet healthcare needs based on protein–protein and gene-environment interactions. Gut–brain axis, as the name suggests, is a two-way biochemical communication pathway between the central nervous system (CNS) and enteric nervous system (ENS), enabling a mutual influence between brain and peripheral intestinal functions. The gut microbiota is a major component of this bidirectional communication, the composition of which is varied depending on the age, and disease conditions, among other factors. Gut microbiota profile is typically unique and personalized therapeutic intervention can aid in treating or delaying neurodegeneration and mental health conditions. Besides, research on the

gut microbial influence on these conditions is gaining attention, and a better understanding of this concept can lead to identification of novel targeted therapies.

Graphical Abstract



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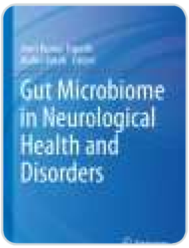

Microbiota–Gut–Brain Axis and Neurodegenerative Disorder

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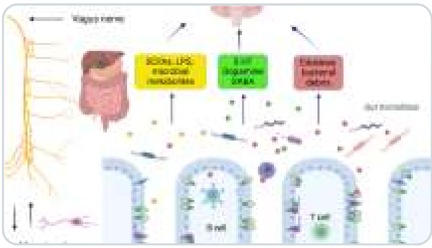

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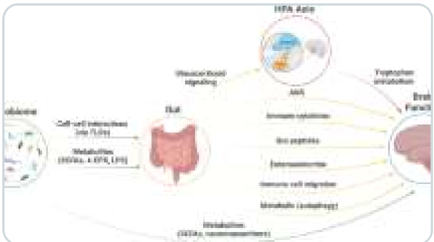

The gut microbiome and mental health: advances in research and emerging priorities

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Introduction

Physical and mental health, social activity, sleep, and food are standard key drivers that promote good quality of life. For instance, a commonly neglected factor is sleep. Chronic sleep deprivation can aggravate declining brain function in turn leading to other diseases [1]. Better dietary patterns can lead to improved cognitive abilities, as shown by the Global Council on Brain Health (GCBH) [1]. Deteriorating brain conditions include dementia, neurodegeneration, unstable mental health patterns, behavioral and neuropsychiatric disorders. Neurodegenerative diseases (ND), represent a major part of the neurological disorders with heterogeneous conditions that are caused by multiple factors including progressive neurodegeneration ultimately impairing neuronal function and leading to the death of nerve cells [2]. Alzheimer's disease (AD), and Parkinson's disease (PD) are highly prevalent and common ND having multifactorial and complex etiology [3].

Mental illness is a broad term for disruption observed in regular mental health patterns leading to behavioral abnormalities and influenced by a combination of genetics [4], environment [5], psychological and social factors hence causing different presentations of the same disease. Diagnosis of a mental health condition can be complicated because of the complex underpinnings and varying inter-individual phenotypes [6]. Diagnosis and treatment of the disorders belonging to these categories are complicated. For example, targeting different underlying causes of Alzheimer's disease like neuroinflammation, which can be reduced with the usage of drug Minocycline, primarily treats neuropsychiatric symptoms of AD [7]. Despite having the same disease, patients' exhibit varied clinical phenotypes and genotypes. Health care could be compromised when a "one-drug-fits-all" approach is used for treatment. Therefore, treatments specifically tailored for patients' needs are essential for producing better therapeutics and guide patient management. This has led to personalized way of medicine that has gained increasing importance in recent times [8]. Given the varied phenotypes of neurodegenerative and mental disorders, it would be essential to consider both protein–protein and gene-environment interactions (GxE) in the development of personalized medicine [9]. In this article, we discuss the gut–brain axis and how its disruption is interconnected to neurodegeneration, elaborating its mechanisms in AD and PD, and mental health disorders (depression, anxiety) and conditions (stress). We also emphasize the role of gut microbiota and how it can be utilized as a personalized treatment strategy for the conditions we chose to address.

Contributions of Gut–Brain Axis to Neurodegeneration and Mental Health: Disease Etiology and Treatment

Introduction to Gut–Brain Axis (GBA)

Early brain-gut interactions were shown by Pavlov in 1904, well known for his work in classic conditioning, in the cephalic phase of digestion where there was stimulation of gastric and pancreatic secretions in response to sensory signals [10]. Gut–Brain axis is bidirectional biochemical signaling or communication between the central nervous system and the enteric nervous system facilitated through neuro-immuno-endocrine pathways [11, 12]. This crosstalk between Central Nervous System (CNS) and Enteric Nervous System (ENS) is facilitated and interlinked through an autonomic nervous system (ANS) where the ANS with sympathetic (SNS) and parasympathetic (PSNS) limbs communicate the afferent signals from intestinal lumen to CNS through enteric, vagal and spinal nerves and efferent signals from CNS to intestinal wall. Communication from the brain to the intestinal cells is through neural, hormonal, and immune pathways. Immune pathways are one of the pathways of two-way communication [11].

Hypothalamic Pituitary Adrenal (HPA) Axis

HPA axis is an important part of the GBA's hormonal influence. Dysregulation of this HPA axis can affect gut microbiota and intestinal permeability [13]. It is the core stress-efferent axis and any fluctuations within the stress levels will make the hypothalamus release corticotropin-releasing factor (CRF). CRF triggers the pituitary gland to release adrenal corticotropin hormone (ACTH) which stimulates the adrenal gland to release cortisol which is a major stress hormone. Cortisol negatively affects many body systems. Studies have shown that an upsurge in psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans, with mast cells involved in the mechanism [14]. Increasing intestinal permeability would lead to an unbalanced and unintegrated passage of microorganisms and their metabolites from the lumen to the bloodstream and rest of the body causing immune system responses and inflammation. As a result of dysbiosis, leaky gut syndrome can occur [15]. Together with the environmental stressors, increased systemic proinflammatory cytokines also activate the HPA axis [13]. This is the impact of dysregulation of the HPA axis or the hormonal influence of the brain on the intestinal functional effector cells (including epithelial cells, immune cells, smooth muscle cells, interstitial cells of cajal) [11]. The intestinal function effector cells are under the effect of gut microbiota, the colonization of which begins immediately after birth.

Vagus Nerve

Vagus nerve is a chief component of the gut–brain axis, and a segment of the parasympathetic nervous system whose function is to transmit information from the inner organs, including gut, heart, and lungs to the brain, hence involved in a wide range of functions. Parasympathetic nervous system in general has a complex influence on gastrointestinal (GI) activity [16]. Vagal efferent nerves send signals from brain to gut and the afferent ones send signals from gut to the brain. Afferent vagus nerves are associated with activation or regulation of the HPA axis, electrical stimulation of afferent vagus fibers induces the production of IL-1 beta in the brain which in turn is involved in activation or regulation of HPA axis. Vagus nerve is the longest cranial nerve arising from the brainstem and extending till the gut, leading to GI innervation. An ability to modulate gut microbiota, intestinal permeability and peripheral inflammation is observed in the vagus nerve, which is partly linked to a cholinergic pathway. Drugs targeting the cholinergic system have gained interest in treatment of neurological disorders like AD [26].

An abnormal or decreased vagal tone, a clinical measure of vagus nerve, is found in conditions including anxiety, and conditions resulting from dysbiosis like Inflammatory Bowel Diseases (IBD) and irritable bowel syndrome (IBS). Studies have shown that vagus nerve stimulation will aid in restoring homeostasis in the microbiota–gut–brain axis [17]. Treatments targeting the vagus nerve are found to be effective in increasing the vagal tone and inhibiting cytokine production therefore modulating the inflammation. The vagus nerve possesses anti-inflammatory properties that can also be utilized for developing therapeutic strategies for IBS [17], depression [18], and epilepsy [19].

Gut Microbiota

Escherichia and *Enterococcus* are two of the earliest colonizing bacteria. Every human has a unique profile of gut microbial composition [20]. Various processes ranging from digestion of food to immunological responses and psychological states are a function of the gut microbiota's composition and hence, an alteration of the gut microbiota or dysbiosis can have various consequences. Gut microbiota are an important part of the gut–brain axis; they regionally interact with the intestinal walls and the ENS while also communicating with the CNS through the neuroendocrine and metabolic (metabolites released in the gut) pathways relayed through GBA. ENS development is partly modulated and mediated by gut microbiota [11, 20]. The gut microbiota research is also being extended to health benefits of other species such as poultry [21].

Modulation and protection of intestinal barrier and restoration of function of tight junctions and their integrity provenly through treatment with specific probiotics, for example, the suppression of chronic stress-mediated abnormalities of brain functions synergistically by *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 probiotic formulation which also restores tight junction barrier integrity [22]. The modulation of ENS sensory afferents takes place where the gut microbiota interacts with ENS through production of various neurotransmitters such as histamine, acetylcholine, serotonin, GABA, melatonin, and a biologically active form of catecholamine at the local level [11].

How Microbial Metabolites Modulate Brain Functions?

The major metabolites produced by gut microbiota include short-chain fatty acids (SCFAs) like acetic acid, butyric acid, and propionic acid [23]. The SCFAs also impact memory and learning processes and can even stimulate the mucosal serotonin release [23]. Other examples of GABA producing bacteria are *Lactobacillus* and *Bifidobacterium*, and serotonin producing bacteria are *Candida* and *Enterococcus* [24]. Tryptophan metabolism is an essential modulator of GBA at various levels. Metabolism of dietary substrates like amino acids by gut microbiota is an important modulatory and regulatory mechanism in tryptophan metabolism which helps in maintaining internal homeostasis. Tryptophan is a substrate for serotonin production in the brain and gut, and melatonin production in the pineal gland [25]. However, the serotonin produced in the CNS is small compared to the serotonin production in the gut which is about 90% of total body serotonin, mainly produced from enterochromaffin cells. Depression and low mood conditions have been linked with the downregulation of tryptophan metabolism [25]. Another mechanism is the effect of gut microbiota on mucosal immune activation. A balanced interaction between intestinal microbiota and mucosal immunity enables intestinal homeostasis, an imbalance of which can trigger prolonged conditions like IBD, Crohn's disease (CD) and ulcerative colitis (UC). IBD is a heterogeneous group of chronic inflammation with a multifactorial etiology influenced by microbial, genetic, and environmental interactions. Intestinal microflora manipulation and fecal microbiota transplantation have been playing an important role in effective prevention and treatment strategy respectively [26].

Neurodegenerative Disorders

Gut microbiota Dysbiosis as a Contributing Factor in Neurodegenerative Diseases

Recent research has highlighted the role of gut microbiota in healthy brain development, function, and ageing. Healthy gut microbiota can improve overall health markers in the elderly, reduce levels of systemic inflammation, maintain healthy body weight, reduce weakness, and improve life expectancy [28]. These revelations in regard to studies done on animal models provide certain helpful insights on the role of a diverse and healthy gut microbial colony that can improve brain health thereby reducing the offshoot chances of development of ND. A study suggested that mice peripherally administered with *Lactobacillus*, demonstrated anti-inflammatory and antioxidant effects on the brain [28]. The examination resulted in a severe reduction of gut microbiota and twofold reduction in neurogenesis, in mice brains when administered with several broad-spectrum antibiotics, such as ampicillin or metronidazole [27]. Due to the action of these antibiotics, a decline in neurogenesis capability was observed, which consequently was restored in mice that received the probiotic mixture VSL#3, containing *Bifidobacterium breve, Bifidobacterium longum* among others. Administration of VSL#3 probiotics showed beneficial effects on GI health, such as decreased intestinal permeability after intestinal injury. Therefore, these studies show that the gut microbiota can have a significant impact on brain neurogenesis, which is crucial in preventing a decline in age-related memory and cognitive functions [27].

The deregulation of microbiota has been recognized as one of the factors that lead to a variety of disorders and diseases, including cardiovascular disease, liver disease, autism, AD, and PD (aspects of which are mainly focused in this review). Although each of these diseases has its unique defining characteristics, they are characterized, at least in part, by chronic inflammation, which may be the result of associated microbial dysbiosis. The effects of microbial diseases on human health are not limited to peripheral diseases but can also extend to various brain diseases [27]. The mechanism of gut microbiota in the progression of AD and PD have also been shown in Table 1.

Table 1 Mechanism of Gut Microbiota in the Progression of AD and PD

Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disease caused due to the formation of senile plaques consisting of misfolded β-amyloid (Aβ) fibrils and oligomers, along with hyperphosphorylated tau protein in regions of the brain like the cerebral cortex and hippocampus [30]. Despite the fact that the first case of AD was diagnosed almost 100 years ago, there isn't any concrete therapy to cure the disease except drugs to temporarily relieve the symptoms and extend lifespan. Recent studies hint at the involvement of GBA in the pathophysiology of ND via microbial dysbiosis caused by the effects of changes in daily diet, exposure to antibiotics, and response to probiotics [29]. Research in this aspect shows the direct association between the gut microbiome dysbiosis and Aβ peptide aggregates in epithelial cells of the intestine. The excretion of various immunogenic components, lipopolysaccharides (LPS) and amyloid species by the gut microbiome into the local intestinal environment led to their polymerization and formation of insoluble fibrous protein aggregates which stimulates oxidative stress and further protein aggregation [31]. Further, parallel studies suggest the molecular mimicry by bacterial amyloid proteins of human Aβ owing to their structural overlap. This has the potential to induce an immune response by a foreign antigen against the self-antigens, sharing structural similarities, ultimately resulting in inflammatory responses towards cerebral Aβ. Bacterial species like *Lactobacillus* spp. and *Bifidobacterium* spp. inherently possess the ability to metabolize glutamate, an excitatory neurotransmitter helpful in the production of GABA, an inhibitory neurotransmitter [29]. These observations direct at thinking that altering the gut microbiota can compromise the endogenous production of GABA. This alteration of GABA results in altered signals in the brain which is known to be linked to AD thereby cognitive impairment and mood disorders. In addition, gut bacteria may also influence peripheral neuronal function through the production of short-chain fatty acids, neuromodulators developed as a result of bacterial fermentation of fiber supplemented by diet in the colon [31]. Generally, SCFAs stimulate the nervous system to release hormones like serotonin, which can affect the central nervous system's cognitive operations and processes related to memory and learning capabilities. Also, catabolism of SCFAs to ketones suggestively provides an alternative/substitute source of ATP to the brain, which can counter the disrupted glucose metabolism, progressively as reported in AD patients [31].

Parkinson's Disease (PD)

PD is the second most prevalent age-related ND, after AD. PD is characterized by progressive degeneration of dopaminergic lesions in the substantia nigra (SN) and a gradual reduction in dopamine levels, which affect both motor and non-motor functions. Patients suffering from PD show motor symptoms, such as resting tremors. While the cause of PD is yet unknown, it is believed to involve both genetic and environmental (severe head trauma) factors. Evidence suggests that the pro-inflammatory signaling molecules, like cytokines or enzymes and oxidative stress, are considered major etiological factors to neurodegeneration and dopaminergic cell death in PD. Even though there are dopamine supplementation drugs (Levodopa) for the therapy at present, it is only for temporary relief from the symptoms but does not help in the reduction of progressive degeneration [31].

Alpha-synuclein is a dynamic protein that is present in cells of the body and particularly in PD patients, higher expression of αSYN at the terminals of neurons is observed. This protein is soluble in nature and helps in regulating the dopaminergic neurons which produce the neurotransmitter dopamine. The imbalanced deposition of αSYN, followed by a β-sheet structure formation leads to compromised physiologic membrane-binding capacity, resulting in misfolded protein aggregates and further fibrils which make up the Lewy bodies dopaminergic neurons of SN (basal ganglia located in midbrain). These Lewy bodies eventually take up large space in the neurons resulting in the death and disappearance of dopaminergic cells. Similar to the pathophysiology of AD, the relation between gut microbiota and PD pathophysiology has been researched extensively. Various studies done on specific strains of probiotics like *Bacillus subtilis* have shown to inhibit the accumulation of alpha-synuclein when introduced in the gut of *Caenorhabditis elegans* model [32]. It triggered the formation of *B. subtilis* biofilm and production of nitric oxide, which protected an aging *Caenorhabditis elegans* from αSYN aggregation and also presented its reversion [32].

Gut–Brain Axis Role in Behavior, Mental Health, Psychiatry

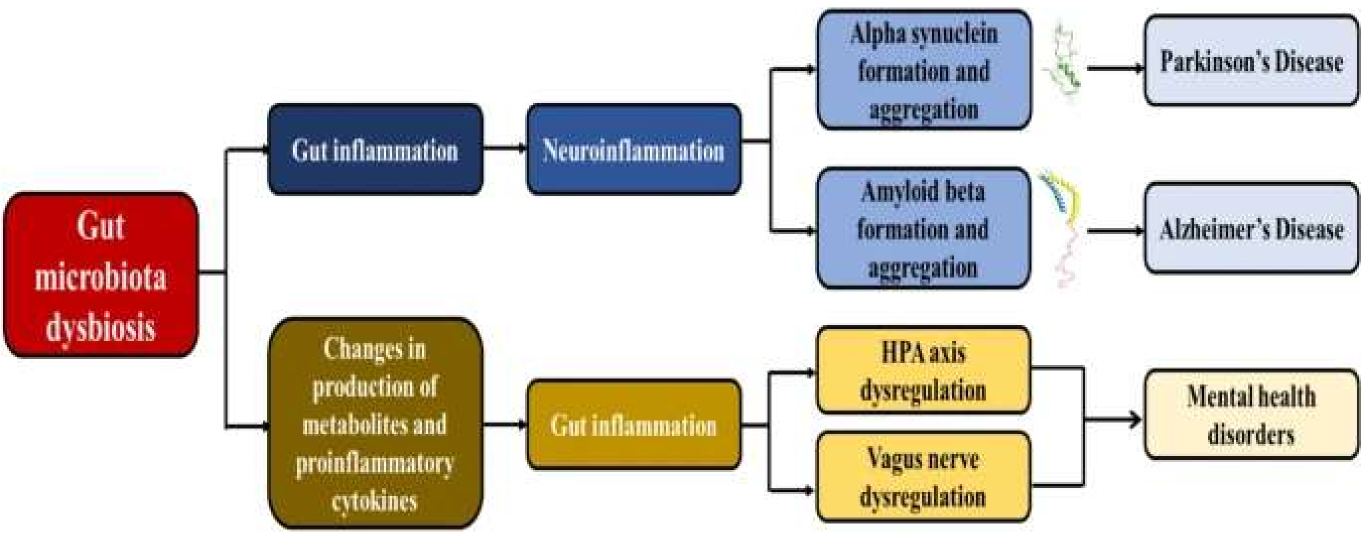
Gut microbiota are involved in secretion of major neurotransmitters like oxytocin, dopamine, GABA, acetylcholine, noradrenaline, and histamine or in providing precursors for biosynthetic pathways [24, 37]. Lactobacillus subspecies are involved in many secretions. Feeding of *Lactobacillus reuteri* from a human to mice rendered an increase in oxytocin levels and improvement in wound healing capacity, and a subsequent benefit in social behavior [38]. Bacillus subspecies *B. cereus, B. mycoides, B. subtilis* are involved in dopamine production. *Lactobacillus* and *Bifidobacterium* microbes are producers of GABA [37]. Gut microbes are involved in signaling the enterochromaffin cells to produce serotonin through tryptophan metabolism, which has been discussed in the previous section. These neurotransmitters and neuroactive molecules are involved in behavioral and neurological processes. Alterations of Brain Derived Neurotrophic Factor (BDNF) are involved in pathogenesis of various conditions like schizophrenia, depression, epilepsy [39], aging and AD [40].

BDNF levels are crucial for normal mood levels. Administration of *Lactobacillus*, *Bifidobacterium*, or probiotics such as fructo-oligosaccharide help in increasing the hippocampal and peripheral levels of BDN [41]. Chronic stress dysregulates BDNF expression both of which are part of the etiology of depression. Acute stress leads to modified cortisol levels, whereas chronic stress causes an imbalanced and dysregulated HPA axis activity [42]. The stress also alters gut microbiota composition which in turn leads to changes in HPA axis and hence mood disorders [42]. Good gut microbiota has the ability to reduce anxiety and depression levels through inhibition of cortisol increase. Probiotic-induced corticosterone level reduction is observed in normal mice, which is an indicator of the HPA axis activity [43]. Vagus nerve plays a pivotal role as the interface of GBA and gut microbiota [17]. Stress inhibits vagus nerve leading to GI conditions and gut microbial compositions. Ingestion of *Lactobacillus rhamnosus* (JB-1) by mouse model showed brain region dependent modifications of GABA expression, reduced anxiety, stress and depression. Vagus nerve stimulation (VNS) has been effectively alleviating depression, epilepsy and PTSD [44].

Inflammatory signal pathway is vital for the control of neurological functions by the intestinal microbiota. An important immune component is LPS. LPS is involved in modulating amygdala's activity, a major part of the limbic system involved in emotions [45]. Administering LPS to healthy individuals induced depression-like behaviors; and neuroinflammation in mice. LPS production happens as a result of GI imbalances and is also correlated with sickness behavior [46]. Abnormal anxiety and depression-like negative behaviors are expressed in germ-free, pathogen infected, stress or antibiotics exposed animals. Studies show the differences in emotional behavior with respect to varying gut microbiota compositions. Reversal of behavioral deficits and abnormal immune responses is seen post administration of *Bifidobacterium infantis* in the MS (maternal separation) rat, which is usually used to study early life stress. Similarly, a probiotic containing both *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reversed increased levels of intestinal permeability [22] and depressive behavior in rat models of myocardial infarction [47]. Improved social interaction, speech and language skills are also being observed after probiotic administration in these models [48].

The relation between depression and microbiota–gut–brain axis is increasingly studied for exploring the possibility of new clinical interventions. Monoamine imbalances and intestinal permeability defects in gut dysbiosis is a condition common to clinical depression, interconnecting gut microbiota and mood [43]. In stress-related psychiatric conditions and depression, there is an increased expression and production of proinflammatory cytokines. Transcription of these cytokines is influenced by gut microbiota, and the SCFA metabolites are involved in reducing or inhibiting production of proinflammatory cytokines [49]. Therefore, inflammation is a major contributor to the pathophysiology of depression. This inflammation is also involved in activating the HPA axis and reducing the neurotransmitter precursor availability [49]. In fact, COX-2 inhibitor, an anti-inflammatory drug has been shown to be favorable in treating major depression and schizophrenia [50]. Fecal microbiota transplantation (FMT) is performed with the objective to achieve a health benefit through administration or transfer of fecal matter solution from a healthy donor into the patient or recipient's intestinal tract which causes a change in intestinal microbiota composition [51]. FMT is used successfully in the treatment of *Clostridium difficile* infection. FMT enables replication of behavioral phenotypes and gut conditions of the host by the recipient. FMT from IBS-D patients to germ-free mice led to altered gut and immune function, and behavior [52]. Microbiota transfer from a high anxiety mouse model to low anxiety mouse model increased anxiety levels in the low anxiety mouse model [53]. Also, when this was performed in the opposite direction, where a low anxiety mouse model's gut microbiota is transferred into a high anxiety mouse mode; there is a reduction in anxiety levels [53]. This phenomenon has also been observed in depression [54]. FMT from depression patients to GF rats resulted in implication of conditions including depression, anxiety, anhedonia, and tryptophan alterations similar to the host [55]. A brief representation of how gut microbiota dysbiosis leads to neurodegeneration and mental health disorders is shown in Fig. 1.

Fig. 1

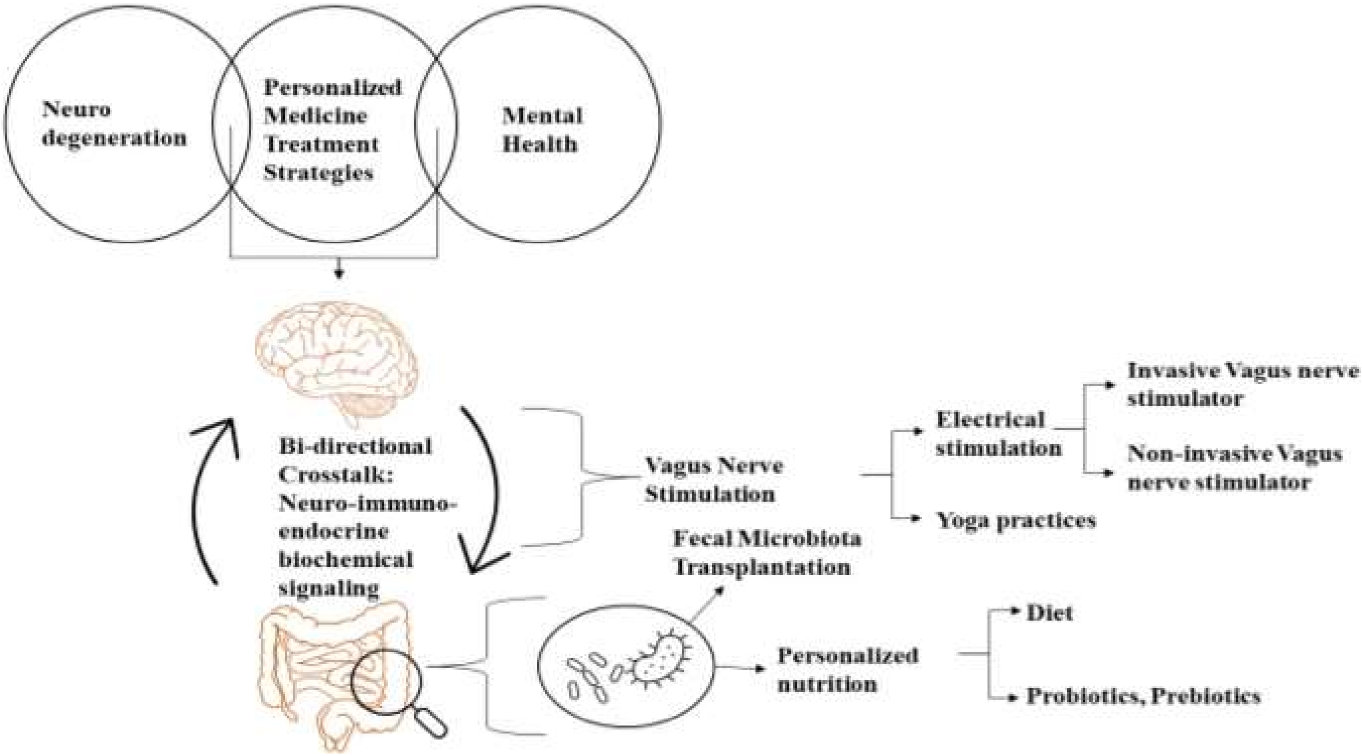


Gut microbiota dysbiosis leading to ND and mental health disorders

Potential of This Concept as a Personalized Treatment Strategy

A holistic approach, termed personalized medicine, has opened a new door in medical science approaches, and the close interrelationship between microbiome and personalized medicine seems to hold a pivotal key in the treatment of ND and mental health. Since no two persons' microbiome is found to be similar, personalized treatment is found to be an essential and a necessary method for precisely treating and thereby preventing these disorders from becoming critical or life-threatening. An approach to healthcare is to understand the complex individualized mechanisms underlying a disorder. Sometimes, a single disorder yields various phenotypes in various people, hence implying its complexity. This brings the necessity of tailoring the therapeutic interventions by taking into consideration genetics, age, medical history, and other biomarkers. Predictive technologies also play a critical role in early identification of risks of developing a disease. Understanding complex gene environment interactions models in neurodegenerative and behavioral disorders are essential for developing personalized therapeutics for these diseases [5]. Modifying the external environmental risk factors from an early age through tailored nutritional needs, exercise, or at the accurate stage with treatments like probiotics, fecal microbiota transplant (FMT), VNS, etc. should help modulate the gene environment interaction, hence achieving personalized medicine. Figure 2 represents the treatment of neurodegenerative and mental health disorders through personalized treatment of disruptions of GBA.

Fig. 2



Utilizing gut–brain axis for personalized treatment of ND and mental health disorders

In recent years, there has been an evolving appreciation for targeting GBA as a target for ND and mental health conditions. Gut is highly adaptable and modifiable for GBA-based treatments such as probiotics [15] and FMT [36, 51]; these treatments are used to recolonize the gut with healthy gut bacteria. Hence, it is evident that the use of the GBA as a target for conditions including mood disorders, and for development of personalized treatment methods could be beneficial [56]. Probiotics implementation administers one or two healthy bacterial strains to the gut [48], whereas in FMT many bacterial strains from faeces are transferred from healthy person to recipient [51]. An alternative approach for FMT is Microbial Ecosystem Therapeutics-2 (MET-2), which is currently being studied as a potential method in GAD and Major Depressive Disorder (MDD). In this approach the gut is repopulated with healthy bacteria by oral administration of lyophilized bacterial species which are initially isolated from the stool of a healthy person [57]. Prior to these treatments, the stool samples are collected from the patients. These samples are compared and analyzed for diversity and abundance of bacteria and thus the dissimilarities are recorded and the patients lacking bacterial species are administered. For this, one has to know what makes a "healthy microbiome" and use this in aforementioned personalized treatments. These treatments suggest that there is great potential for personalized treatments in mental health. Metagenomics approaches can be crucial in studying gut microbiota profile [58].

Personalizing nutrition through various diet patterns is also a beneficial strategy. A Mediterranean diet which contains large quantities of unsaturated fats, proteins, and fibers is also proved to be efficacious in preventing AD. It was also explored that across a person's life modifiable environmental factors also contribute to one-third of AD cases. These AD risk factors include diet, smoking and alcohol consumption, physical and cognitive activity, early-stage education, and social interactions at later stages [59]. Probiotics treatment has been found to reverse the PD conditions. For instance, a *bacillus* sp. has been found to convert L-tyrosine to L-DOPA, and thus it can restore the lost dopamine. FMT is also found to improve the non-GI symptoms of neurologic patients. It was found that administration of FMT increases DA and 5-HT levels, restores motor impairment, and improves gut dysbiosis [60]. Also, prebiotics and antibiotics were also found to result in restoring the gut ecosystem and improving psychological and cognitive brain processes. Evidence suggests that people who have undergone exposure to pesticides, industrial compounds like polychlorinated biphenyls, manganese and other metals, traumatic brain injury (TBI) and frequent concussions, and vitamin D deficiency have an elevated risk of developing PD. FMT could have the potential for treating AD and PD while taking into consideration their genetic and environmental factors, in the future [61].

Gut microbiota modifications are leading to negative variations in the proper functioning of the brain and hence leading to neurological conditions. The dysbiotic changes due to increase in biological age can make the nutrient signaling pathways ineffective and provoke pro-inflammatory innate immunity and other pathological conditions, thereby promoting unhealthy aging [62]. Maintaining gut microbiota diversity by personalizing nutrition through probiotics and prebiotics consumption from an early age can help avoid or delay the progression of diseases.

Conclusions and Future Prospects

We attempt to discuss the gut–brain axis, accentuating how a disruption in its components lead to ND and mental health conditions. An important step in having a good, diverse microbiota profile is the hands of lifestyle decisions, as microbiota is associated with brain. Consumption of high sugar, high fat-based diet can lead to disruption of the homeostasis of gut microbiota, thereby negatively impacting the integrity of gut and brain by modifying neurotransmitter metabolism, among other effects. Probiotics, prebiotics as seen in many cases in previous sections also supplement in maintaining gut health. *Akkermansia* is being researched as a potential treatment strategy for restoring the microbiota–gut–brain axis [63]. Manipulating gut microbiota profiles considering certain factors/biomarkers can help in personalized medicine. There are challenges surrounding the personalized medicine. The conditions that we considered in this review are multifactorial and the disruptions in gut–brain axis components is one of the contributors. Studying the unique gut microbiota profiles of patients is essential for considering this to be a personalized medicine strategy. Researchers have been investigating a number of sequencing methods with the hope of developing a novel diagnostic and therapeutic method that deciphers the relationship between the gut microbiome and neurodegenerative diseases. These include whole-genome shotgun sequencing, 16S rRNA sequencing, metatranscriptomics, metaproteomics, metabolomics, and multi-omics [64]. However, these have a number of drawbacks, such as their expense, the difficulty of assessing the sample in low abundance, and the intricacy of the data. Interpreting the data, identifying new disease biomarkers, and exploring potential therapy methods remain extremely difficult tasks. Therefore, more technological advancement is required to explore the connection between the gut microbiome and neurodegenerative disorders that aids in developing a prominent diagnostic and therapeutic approach. Although, translational significance development of such treatments in humans is still a challenge, they can possibly be a part of paradigm shift in the future treatments.

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Contributions

All authors had full access to all the contents of review paper and take responsibility for the integrity and accuracy of the text and analysis. Study concept and design: AC and CNR. Acquisition of data: AC, SDMR and JM. Analysis and interpretation of data: AC and CNR. Drafting of the manuscript: AC, SDMR, JM and CNR. Study supervision: CNR.

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Ethics declarations

Conflict of interest

The authors declare that they have no conflict of interest to this work.

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