Nutritional Neurosciences

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Geethalakshmi Sundararaman
Swarnalatha Gadde Venkata *Editors*

Role of Nutrients in Neurological Disorders

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Nutritional Neurosciences

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Foreword by Dr. Sesikeran Boindala

Neurological and neuropsychological disorders are among the most distressing and most difficult to treat. They tend to be chronic and extend for years. This leads to issues of care giving, of which nutrition is a major part. Based on information from traditional and modern medicine, there are reasons to believe that proper nutrient intakes may prevent such diseases. This book is a compilation of such information and will be of immense benefit to readers. The first chapter covers the role of nutrition in the pathogenesis of neurological disorders. Similarly, the third and fourth chapters speak of the basics of the impact of diet on neurotransmitters and best foods for the repair of brain damage. There are sections that deal with nutrition and its role in neurodegenerative diseases like Parkinson's disease, Alzheimer's, senile dementia, and other such degenerative disorders generally seen with aging. Some of the authors have reviewed the effects of herbal and traditional remedies in a range of neurological disorders as well as autism spectrum. Micronutrient deficiencies are highly prevalent in our country, and some of them are involved in the pathogenesis of neurodevelopment disorders. There is one chapter addressing this aspect. N3 and N6 PUFA and their importance in the development and functioning of the brain is given in an exclusive chapter. Recent developments on gut microbiome and the discoveries indicate that some of these bacteria generate neurotransmitter molecules in the gut, which seems to be the way the gut microbiome communicates with the brain. There could be relationship with some psychological problems and the chapter on Psychobiotics reviews the latest developments. Finally, there is one on marine derived natural products in depressive illness.

This book is very comprehensive and has broad-spectrum coverage of nutrients, nutrition, and lifestyle in a range of neurological problems. It will benefit everyone in

the field of neurology and neuropsychology. Nutritionists working with patients in hospitals or rehabilitation centers must read this book to understand the principles of nutrition support given to their patients.

Sesikeran Boindala

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Foreword by Dr. Undurti N. Das

I am pleased to write this foreword about the book entitled *Role of Nutrients in Neurological Disorders* edited by Drs. Senthilkumar Rajagopal, Saravanan Ramachandran, S. Geethalakshmi, and G. V. Swarnalatha.

The brain is considered as the final frontier of science about which we know so little despite rapid and considerable advances have been made recently. The brain is the center of all activities and seems to be the major regulator of all systems of our body. Hence, it is no wonder that understanding the physiology of the brain is important to unravel the pathophysiological aspects of neurological and psychiatric conditions both to prevent and treat them logically, and in a methodological way.

The complex structure of the brain with its 100 billion neurons and 10- to 50-fold more glial cells, consuming an outstanding 20% of the total body energy despite representing only 2% of body mass, it is no exaggeration to say that the human brain is an incredible structure performing the most complex functions. Understanding such a complex structure is naturally almost impossible, yet we are making progress slowly but steadily. In view of its incredibly complex structure and very many actions, understanding the nutritional needs of the brain is of paramount importance. Even though the brain depends on glucose as its primary source of energy, under starvation conditions, it can use fat as its metabolic fuel and still perform all its functions in a very normal fashion. This attests to the fact that the brain is an incredible organ not only in its structure and function but also in its ability to show flexibility in meeting its energy demands.

The human brain is not only rich in unsaturated fatty acids that it can obtain from our diet but also needs several minerals, trace elements, and vitamins for its normal development and function. In this context, it is noteworthy that the human brain is rich in long-chain polyunsaturated fatty acids that constitute almost 50% of its total dry weight. The high lipid content of the brain is responsible for its soft nature and high degree of flexibility. This may explain as to why synapses can be easily formed and new connections between various neurons are established with ease that ensures rapid transmission of messages across various neurons induced by various neurotransmitters in response to both internal and external messages.

Since the brain is highly evolved and endowed with complex tasks, it is quite natural that it needs to maintain its basic structure rather rigidly and limits the scope of external stimuli and nutrients to influence it both structurally and functionally. Despite these limitations, there are many dietary factors that can alter its functions. There is limited information available to support the contention that dietary factors and drugs can influence its structure though it is well known that they (dietary factors and drugs) can certainly alter neurotransmitters' formation and function. Understanding how various dietary factors alter the formation and function of neurons by virtue of their ability to influence the formation, concentrations, and function of various neurotransmitters is important to find ways and means of managing neurological and psychiatric conditions such as Alzheimer's disease, depression, anxiety, autism, Parkinson's disease, schizophrenia, migraine, headache, epilepsy, etc. Since there is very little scope to study its structure and function directly, we need to depend on several indirect methods of assessing brain's structure and function using investigations such as EEG, CT scan, MRI scan, fMRI, and measuring the concentrations of various neurotransmitters in the CSF and peripheral blood. The nature of the function of the brain is further complicated by the fact that various neurotransmitters are also formed, secreted, and released by peripheral tissues/organs such as the gut, liver, spleen, leukocytes, macrophages, and autonomic nervous system, and peripheral nerves. This suggests that there is a close interaction(s) between the brain and the rest of the body to integrate and bring cohesion in the function of various tissues/organs/systems of the body to maintain normal homeostasis.

In this book, various authors summarized their findings as to how this homeostasis is brought about and maintained by various nutrients, exercise, and lifestyle factors. Understanding the importance of these non-pharmacological/non-pharmaceutical factors in the well-being of the brain may have significant impact on the prevention and treatment of various neurological and psychiatric diseases. It is my understanding that this book will receive favorable response from one and all.

With best wishes,

Undurti N. Das

CEO-CSO, Consultant Physician &
Diabetologist, Clinical Immunologist &
Rheumatologist, Visakhapatnam,
Andhra Pradesh, India

Foreword by Dr. N. R. Jagannathan

Nutrition is an important area of research in clinics, and nutritional care has gained widespread scientific interest in the last decade. Nutritional deficit causes various metabolic disturbances and hence nutritional assessment in chronic and acute diseases has evoked considerable advances in the design, development, and clinical application of nutritional support. This is especially so in various neurological diseases and associated cognitive problems that are highly influenced by nutrition and has a major impact on healthcare. Nutritional care plays an important role during treatment and has a profound effect on patient's recovery because optimal nutritional intakes can prevent further deterioration of disorders with either traditional or modern medicine.

This book is edited by Dr. R. Senthilkumar, Dr. Saravanan Ramachandran, Dr. S. Geethalakshmi, and Dr. G. V. Swarnalatha, and it is a collection of articles by leading scientists on "Nutrition." It illustrates very elegantly the fundamentals of diet's impact on the importance and functions of nutrition in the etiology of several neurological diseases and also suggests how foods can form a part of treatment in such illness. Nutrition and its functions in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, senile dementia, and other age-related degenerative disorders are covered in this book.

The book also contains chapters that document the effects of herbal and traditional medicines in a variety of neurological illnesses including autism spectrum disorder. In a country like India, micronutrient deficiencies are most common, and these play a role in the pathophysiology of neurodevelopmental disorders. This aspect has also been dealt with in this book. Nutrition also has links with some psychiatric disorders, and this is also discussed. Finally, the use of natural sea products in the treatment of depression is presented.

In summary, I found that this volume covers a wide range of topics on nutrients, diet, and lifestyle and their relation to a variety of neurological disorders. I am sure

that this book would not only provide a comprehensive detail on the role of nutrition and its uses in various neurological diseases but would serve as a source material for those who wish to learn more about "Nutrition."

N. R. Jagannathan

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Preface

Neurodegenerative disease is a broad term for a variety of conditions which chiefly affect the central nervous system and the human brain. Such disorders are a major menace to human health. A neurodegenerative condition commonly occurs in elderly persons and is mostly age-related conditions. This condition keeps increasing in recent times and is of important concern because they are incurable by conventional treatment methods. The disease condition keeps increasing progressively causing nerve cells to deteriorate and die. Such severe degenerative conditions result in complications like dementia, Alzheimer's, ataxias, and other fatal disorders. To properly deal with such degenerative conditions and to diminish the effects, a clear understanding of the mechanism and reactions underlying these conditions is mandatory.

Several research studies show that nutrition has a bigger influence on certain disease states. Some nutrition can trigger complications while many can help cure diseases that do not have a conventional treatment method. Certain components in food have the capacity to interact with genes in a positive manner which may diminish the severity of the ailments. Clinical nutrition is a novel term which defines the management of a disease state using diet components supplied exclusively for this purpose apart from the regular intake. Aged people who cannot adapt to conventional clinical practices will easily adopt themselves to such dietary supplements without any difficulty.

This book provides enormous information about the dietary components that can be used for diminishing the disease conditions during brain damage and nervous disorders. A detailed emphasis is given to herbal drug and extracts which can react during Parkinson's, Alzheimer's, and autism. The role of micronutrients in dementia and neurological development in kids and adults is also discussed. An exclusive chapter on psychological follow-up of diabetic patients in Morocco is presented. A unique concept of Psychobiotics is also deliberated in this edition which will open up a new area of analyzing brain and nerve damage. In all the chapters, the reaction of the nutritional components with their specified targets is explained scientifically and in an effective manner.

In summary, this book deliberates on the role and action of nutrients in revitalizing the central nervous system of human beings and the mechanism of action of these dietary components in subduing the impediments at ease.

Bengaluru, Karnataka, India — Senthilkumar Rajagopal
Kelambakkam, Tamil Nadu, India — Saravanan Ramachandran
Coimbatore, Tamil Nadu, India — Geethalakshmi Sundararaman
Kurnool, Andhra Pradesh, India — Swarnalatha Gadda Venkata

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About the Editors

Senthilkumar Rajagopal is an Associate Professor/Ramalingaswami Re-entry fellow [DBT] of the Department of Biotechnology, REVA University, India. He completed his Ph.D. in Biochemistry at Annamalai University, India, and did his postdoctoral fellowship from the University of Virginia, Harvard University, and Virginia Commonwealth University. He is a recipient of Rameshwardasji Birla Smarak Kosh Endowment award from Mumbai Medical Trust, Mumbai, India, and awardee of prestigious Ramalingaswami Re-entry Fellowship from the Department of Biotechnology, Ministry of Science and Technology, Government of India. His research has addressed protein kinase C modulation on calcium channel currents. He is serving as a reviewer for many well-known peer review journals. He has also published more than 60 research articles in peer-reviewed international journals and authored or coauthored numerous books and book chapters. He is also a member of well-known scientific associations like Indian Society for Atherosclerosis Research (ISAR) (life member), Biophysical Society, Science Advisory Board (SAB), International Science congress Association (life member), Society of Biological Chemist (Life member), and Nutrition Society of India.

Saravanan Ramachandran is an Associate Professor of Marine Pharmacology at Chettinad Academy of Research and Education in Kelambakkam, Tamil Nadu, India. He has completed his Ph.D. in Marine Biotechnology from Annamalai University in India. His scientific interests are focused on understanding the effects of pharmaceuticals on marine species. He has published more than 50 research articles in journals of high repute. He also possesses two patents and has submitted 65 gene sequences to the NCBI, including three entire genomes of halophytic bacteria. He is a member of the Society for Biotechnology (India) and the International Neurotoxin Association.

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Functional Genomics, and Drug designing. She has published more than 25 research articles in international and peer-reviewed journals and has coauthored many book chapters and books. She is a lifetime member of many international scientific societies and organizations.

Swarnalatha Gadda Venkata obtained her Ph.D. in Biochemistry from the University of Mysore in India. Her Ph.D. work was conducted at Central Food Technological Research Institute (CSIR-CFTRI) Mysore, India. She has obtained a patent on "A composition and method to control rotifer infestation in microalgal cultivation systems," India. She has published a book titled "Textbook of Plant Biotechnology" and published papers in reputed international and national journals and authored or coauthored book chapters. She has more than 4 years of postgraduate teaching experience in Biochemistry and Biotechnology courses.

Part I
Neurological Disorders from Background to Interplay of Genetic, Epigenetic and Environmental Risk Factors

Chapter 1
Phytonutrients in Neurological Disorders

Vidya Murugesan, Rubalakshmi Govindraj, M. Amarnath Satheesh, and Senthilkumar Rajagopal

Abstract Phytochemicals are bioactive molecules that occur naturally in food, vegetables, plants, herbs, and fruits. Phytochemicals, unlike minerals and vitamins, are not required for cell survival, but they are critical in shielding neural cells from inflammation and oxidative stress associated with normal aging as well as acute and chronic age-related brain disorders. OCD has been associated to altered neurological function as a result of head trauma, encephalitis, aberrant birth events, and Gilles de la Tourette's disease. Obsessive-compulsive disorder (OCD) is an anxiety disorder which affects millions of people. The key features of OCD are obsessions and compulsions. The current treatments recommended are cognitive-behavioral therapy utilizing response prevention and/or pharmacotherapy. Besides phytochemicals have been studied extensively for the treatment of OCD and a wide range of anxiolytic properties were revealed. This review focusses on phytochemicals and herbal supplements with anti-OCD effects. Several medicinal plants including *Benincasa hispida*, *Cannabis sativa*, *Citrus aurantium*, *Clitoria ternatea*, *Colocasia esculenta*, *Crocus sativus*, *Curcumin*, *Echium amoenum*, *Hypericum perforatum*, *Lagenaria siceraria*, *Pyrus communis*, *Silybum marianum*, *Tabernaemontana divaricate*, *Withania somnifera*, *Valeriana officinalis*, *Cassia auriculata* and the possible mechanism in executing their anti-OCD effects are discussed.

Keywords Aging · Herbal supplements · Inflammation · Medicinal plant · Oxidative stress

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1.1 Introduction

The use of herbal medicine to treat neurological symptoms has been in practice for a long time. Although the exact mechanisms of action of herbal medications are unknown, several have been proven to have anti-inflammatory and/or antioxidant effects in a range of peripheral systems. Anti-inflammatory herbal medicine and its contents are now being proven to be an effective neuroprotector against many brain disorders, as increasing data suggests that neuroglia-derived chronic inflammatory responses play a pathogenic function in the central nervous system. Medicinal herbs' structural complexity makes them a significant source of new lead compounds for therapeutic targets found by genomes, proteomics, and high-throughput screening. The importance of phytochemicals in neuroprotective function and other related illnesses, as well as their mechanism of action and therapeutic potential, will be highlighted in this review. Obsessive-compulsive disorder (OCD) is the common mental disorder and it is diagnosed as often as asthma and diabetes (Prajapati et al. 2011a, b, c) with lifetime prevalence rate estimated approximately around 2%. Obsessions are repetitive, distressing intrusive thoughts, impulses or images. Compulsions are things that a person does to relieve the distress from obsessions. The pathophysiology includes central nervous system aberrations (in particular including dopaminergic, glutamatergic, and serotonin pathways) and genetic factors (Lochner et al. 2004). OCD impacts both professional and personal life. Plant medicines are identified to be important sources for mental disorders. Camfield et al. 2011, studied phytochemicals and medicinal plants for treating OCD and fund that a large number of plants for treating OCD act by modulation of two pathways namely serotonergic and glutamatergic pathways.

1.1.1 Plant Based Medicines for OCD

1.1.1.1 *Benincasa hispida* (Thunb.) Cogn

Benincasa hispida belongs to the family *cucurbitaceae* and is commonly called as wax-gourd, hairy melon, white pumpkin or ash pumpkin, winter melon. It has been documented for its medicinal properties and nutritional value in India and, Philippines. It is used as an important constituent of some Ayurvedic medicines like *kushmanda lehyam*, which is used for the treatment of nervous disorders and epilepsy. It is rich in triterpenes, sterols, glycosides, and phenolics (Zaini et al. 2011). *Benincasa hispida* extracts have been reported to possess anti-OCD effects. Girdha et al. (2010) have shown that the methanolic extract of *B. hispida* fruit exhibited anti-compulsive activity in marble burying behavior without affecting motor activity in mice. The results obtained from *Benincasa hispida* treatment were comparable to that of fluoxetine. The extract and juice of melon fruit possess antidepressant activities. It has been shown to possess monoamine

oxidase-inhibiting properties and increase the dopamine and norepinephrine levels (Dhingra and Joshi 2012). The anti-OCD effect elicited by the treatment of *B. hispida* extract may be attributed to improve serotonergic function.

1.1.1.2 *Cannabis sativa* L.

Cannabis sativa is from Cannabaceae family and has a long history of usage as traditional medicine in India, Persia, and China. The major active constituent present in cannabis sativa is cannabidiol (CBD), which is widely used for treating a range of neuropsychiatric disorders such as psychosis, depression, and anxiety. Many clinical studies suggest that CBD is effective in reducing some psychotic symptoms, anxiety and useful for addiction (Iffland and Grotenhermen 2017). This has been suggested to possess anti-OCD effects. CBD act by reducing the release of glutamate in neural pathways which takes part in compulsive behavior (Piomelli 2003). Investigation of CBD in humans suggests that it is safe without any adverse side effects. In a double-blind randomized clinical trial, the effect of CBD on was studied of 24 patients diagnosed with generalized social phobia. Social phobia patients were pre-treated with 600 mg of CBD 1 h before testing and simulated public speaking test was conducted to analyze the effectiveness. Research findings showed that the CBD treatment significantly reduced discomfort in speech performance, anxiety, and cognitive impairment in comparison to controls (Bergamaschi et al. 2011a, b). The effect of CBD on GABA and dopamine levels are related to its strong antioxidant activity modulates the expression of nitric oxide synthase and inhibits ROS-generating NADPH oxidases (Campos et al. 2017). Studies recommend that CBD act as an agonist at 5-HT_{1A} receptors (Casarotto et al. 2010).

1.1.1.3 *Citrus aurantium* L (Bitter Orange)

Citrus aurantium commonly known as orange blossom or bitter orange belongs to the family Rutaceae and has been used for long time for treating several health problems and is used in the "Earl Grey" tea. The active constituents present are flavonoids especially naringin, hesperidin, and alkaloids synephrine (Suryawanshi 2011). The volatile oil in bitter orange is effective against anxiety and has shown to exert anti-OCD effects (Sarris 2018).The major components in orange oil are β-myrcene (1.43%) and limonene (97.83%) and their effect on central nervous system is suggested to be through the involvement of 5-HT_{1A} receptors (Costa et al. 2013). In an in vivo study carried out in mice on marble burying test, oral administration of the fruit essential oil caused significant reduction in marble burying behavior of mice (De Moraes Pultrini et al. 2006).

1.1.1.4 *Clitoria ternatea* L

Clitoria ternatea commonly known as butterfly pea, belongs to the family Fabaceae is also known as "Sankhupushpi." The biologically active components present in *Clitoria ternatea* are phenols, alkaloids, cardiac glycosides, steroids, volatile oils, flavonoids, tannins, saponins, triterpenoids, and anthocyanins. The plant exhibits antioxidant, anticancer, antidiabetic, anti-inflammatory, and antimicrobial and central nervous system effects (Al-Snafi 2016). Parvathi and Ravishankar (2013) reported that ethanolic extract of *Clitoria ternatea* root at the dosage of 150 mg/kg and 300 mg/kg elicited antidepressant effect. Two compounds namely (Z)—9,17-octadecadienal and *n*-hexadecanoic acid isolated from *Clitoria ternatea* roots serve as potential molecules for developing inhibitors of Monoamine oxidase-A which can be used to treat psychiatric disorders such as anxiety and depression (Margret et al. 2015). An in vivo study finding revealed that the ethanolic extract of *Clitoria ternatea* could control obsessive-compulsive behavior through a significant decrease in marble burying behavior; the effect was comparable to that of fluoxetine (Shende et al. 2012).

1.1.1.5 *Colocasia esculenta* (L.) Schott

Colocasia esculenta (CE) Linn. belongs to the family Araceae which has a long history of use as a traditional medicine in various countries of the world. The herb is famous for its curative effects and has been used for the treatment of several ailments such as diarrhea, arthritis, internal hemorrhage, asthma, and neurological disorders. It has been regarded traditionally as nerve tonic (Prajapati et al. 2011a, b, c). Hydro alcoholic extract of *Colocasia esculenta* attenuated the marble burying behavior of mice in a dose-dependent manner and the effect elicited by the extract was comparable to that of antidepressant fluoxetine. The phytochemical screening of *Colocasia esculenta* extract revealed the presence of steroids, β-sitosterol, and flavonoids which may be responsible for the anti-OCD activity, may exert its activity by increasing the 5-HT concentrations in hippocampus (Kalariya et al. 2015).

1.1.1.6 *Crocus sativus* L.

Crocus sativus (saffron) belongs to the family iridaceae, commonly known as saffron. The active components of saffron are crocin (main antioxidant of saffron), picrocrocin (accountable for saffron's bitter taste), and safranal (responsible for saffron's aroma and odor). Traditionally saffron is used as a stimulant, aphrodisiac, diaphoretic, gingival sedative, nerve-sedative, antispasmodic, eupeptic, carminative, anti-catarrhal (Kashani et al. 2017). Saffron can modulate the neurotransmitters such as glutamate and dopamine in the brain (Khazdair et al. 2015). The psychoactive activities of saffron have been demonstrated in various clinical and animal research

Table 1.1 Clinical studies on the use of medicinal plants for obsessive-compulsive disorder

Scientific name	Part/extract/ phytochemical	Type of study	References
Crocus sativus	Stigma/extract	Randomized double blind	Esalatmanesh et al. (2017)
Echium amoenum	Flowers/aqueous extract	Randomized double-blind, placebo controlled, parallel group	Sayyah et al. (2009)
Hypericum perforatum	Aerial parts/extract	Open-label trial	Taylor and Kobak (2000)
	Aerial parts/ hydroalcoholic extract	Multicentral, randomized double-blind, placebo controlled, parallel group	Kobak et al. (2005)
Silybum marianum	Leaves/methanol extract	Pilot double-blind randomized trial	Sayyah et al. (2010)
Valeriana officinalis	Root/extract	Randomized double-blind, placebo controlled	Pakseresht et al. (2011)
Withania somnifera	Root/ethanol extract	Randomized double-blind, placebo controlled	Jahanbakhsh et al. (2016)

Courtesy: Ayati et al. (2020)

models. It had been shown to possess antidepressant, anxiolytic, and neuroprotective effects (Mazidi et al. 2016). A double-blind randomized study was conducted to find out the effectiveness of saffron in treating mild to moderate OCD (15 mg, 2 capsules per day) was compared with fluvoxamine. *Crocus sativus* was proved to be effective and safe as fluvoxamine. The mechanism by which saffron exerts its anti-OCD effect is unclear but it may be through the inhibition of serotonin reuptake in synapses (Esalatmanesh et al. 2017). Mohamadpour et al. (2013) studied the safety of crocin (20 mg/day for 1 month) tablets on hematological, biomedical, urinary, and hormonal parameters in pre- and post-treatment stages. Their findings suggest that they did not show any major side effects except decreased amylases, mixed white blood cells and PTT during the trial. Neuroprotective efficacy of saffron was established against glutamate-induced toxicity by Bharate et al. (2018). Table 1.1 shows the list of medicinal plants used for obsessive-compulsive disorder in clinical studies.

1.1.1.7 Curcumin

Turmeric has a long history of usage as traditional medicine to treat a wide range of diseases. The active component of turmeric is curcumin, which can affect a wide range of biological activities. They possess antioxidant, anti-inflammatory, monoaminergic, and neuroprotective effects (Lopresti 2017). Curcuminoids have a modulatory role on norepinephrine, dopamine, and serotonin in different areas of the brain and also inhibit the biogenic amines by Monoamine oxidase-A and Monoamine oxidase-B inhibition (Kulkarni and Dhir 2010). Curcumins are effective in treating psychiatric disorders such as depression and epilepsy (Jithendra et al. 2008). The antioxidant activity possessed by curcumin might be partly involved in its

neuropsychiatric activity (Ayati et al. 2020). In an in vivo study on the efficacy of curcumin on OCD, curcumin was reported to possess protective effect on OCD with slight changes on monoamine levels in the brain. In curcumin treated rats, dopamine levels were decreased and serotonin levels were increased. Curcumin treatment also reduced OCD symptoms (Chimakurthy and Murthy 2010).

1.1.1.8 *Echium amoenum*. Fisch

Echium amoenum, which belong to the family Boraginaceae, is considered to be a vital medicinal plant in Iran; the dried flower has been used as an anxiolytic and mood enhancer (Sayyah et al. 2009). Antidepressant and anxiolytic activity of the plant extract was confirmed by Sarris et al. (2011). Aqueous extract of *E .amoenum* has been reported to show anti-OCD effect by increasing the cerebrospinal fluid dopamine and serotonin (Faryadian et al. 2015). In a randomized controlled trial, 44 patients complaining of OCD received the aqueous extract of *E. amoenum* flowers. In weeks of 4 and 6, the extracts showed significant improvement than placebo in reducing anxiety, obsessive and compulsive symptoms (Sayyah et al. 2009).

1.1.1.9 *Hypericum perforatum* L

Hypericum perforatum belongs to the family hypericaceae, which is commonly known as St John's wort (SJW) and has been used as a traditional medicine for centuries to treat various ailments. It is well known for its antidepressive activity and the results are equivalent to antidepressants (Sarris et al. 2009). The anxiolytic effect of *H. perforatum* is due to the presence of flavonoids. The neurobiological effects may be due to augmented sensitization, reuptake inhibition of monoamines, and binding to receptors (Eg, 5-HT) (Camfield et al. 2011). The active components which are responsible for eliciting neurobiological effects are hypericin, pseudohypericin, and hyperforin. After 8 weeks of administering, hypericin is known to increase the 5-HT concentrations of hypothalamus, though some issues are associated with hypericin crossing the blood–brain barrier (Butterweck et al. 2002). Camfield et al. (2011) reported that the active mechanism by which the active components could exert it effects may be due to the inhibition of monoamine oxidase (MAO).

Evidence to show the efficacy of St John's wort (SJW) on OCD was carried out by Taylor and Kobak (2000). Their findings suggest that in a 12-week open-label trial the treatment of SJW (900 mg/day) showed significant improvements in OCD patients. Positive changes were observed in the first week and started increasing. The side effects reported were restless sleep and diarrhea. In another placebo-controlled trial with a sample size ($n = 60$) SJW (600–1800 mg/day) treatment did not show any significant difference when compared with placebo (Kobak et al. 2005).

1.1.1.10 *Lagenaria siceraria* (Molina)

Lagenaria siceraria (LS) belongs to the family Cucurbitaceae which is commonly called as bottle gourd and is an excellent natural fruit which possess all the essential components desired for normal human health. Traditionally LS fruits are used for their general tonic, cardioprotective, aphrodisiac, cardiotonic properties and act as a diuretic and alternate purgative (Kirtikar 2001). The phytochemical constituents responsible for eliciting the neuropharmacological effects may be steroidal or flavonoid compounds (Prajapati et al. 2011a, b, c).

In an in vivo study using mice, the methanolic extract of *L. siceraria* fruit was evaluated for its anti-OCD activity. The marble burying behavior of the mice was utilized. Research findings suggest that the extract showed anti-OCD in a dose-dependent manner and the results were comparable to that of fluoxetine. The phytochemicals present in the extract such as steroids, flavonoids, saponins may contribute to the biological activity (Prajapati et al. 2011a, b, c). The methanolic extract of Lagenaria siceraria fruits showed antidepressant activity (Prajapati et al. 2011a, b, c).

1.1.1.11 *Pyrus communis*

Pear is a juicy fruit which belongs to the family Rosaceae. It is known as "Amritphale" in Sanskrit as it widely used in human health. It is well known for its anti-pyretic, hypolipidemic, anti-inflammatory, sedative, hypoglycemic, wound healing, anti-aging, analgesic, hepatoprotective, and antimicrobial properties (Parle and Arzoo 2016). Fresh juice of pyrus communis (50 and 100%) decreased the marble burying behavior in mice and the effect elicited was comparable to fluoxetine. The mechanism by which anti-OCD effects were decreased may be attributed to the increased levels of serotonin and GABA (Arzoo and Parle 2017).

1.1.1.12 Milk Thistle (*Silybum marianum*)

Silybum marianum belongs to the family asteraceae, also known as milk thistle, is a traditional Mediterranean and Persian herbal medicine. Milk thistle extracts are reported to have anti-inflammatory (De La Puerta 1996), antioxidant, hepatoprotective (Morazzoni and Bombardelli 1995), antidiabetic (Maghrani et al. 2004), and anticancer (Zi et al. 1997). The properties of milk thistle are related to the presence of a flavonolignan complex silymarin, a significant bioactive component which has been known to possess antioxidant, anticancer, anti-inflammatory, antidepressant and sedative (Sayyah et al. 2009), immune modulator (Katiyar 2005) effects. The active flavonolignans of *S. marianum* comprises primarily silibin, silichristin, and silidianin. Other flavonoid components are taxifolin, dihydrokaempferol 2 and 3, and quercetin and also histamine, essential oils,

tyramine, carbohydrates, saponins, alkaloids, organic acid, and vitamin C, E, and K (Karen et al. 2005). Milk thistle is suggested as a potential medication for OCD and anxiety disorders (Sarris et al. 2012). Serotonin has been reported to increase serotonergic activity in brain cortex by monoamine oxidase inhibition (Solati et al. 2012). In a randomized control trial ($n = 35$) carried out between the *Solanum marianum* leaf extract (600 mg/day) versus the antidepressant drug fluoxetine in patients reported with OCD revealed that there are no significant difference between two treatments. This indicated that the effect elicited by Solanum marianum leaf extract is comparable to that of the fluoxetine in OCD symptoms and the positive effect was observed in the fifth week. Milk thistle extract administration was not associated with serious adverse effects (Sayyah et al. 2010). The anxiolytic and anti-OCD effects of milk thistle can be attributed to silymarin, which enhances serotonin concentration in the brain cortex (Camfield et al. 2011; Solati et al. 2012). This is due to the inhibitory action of silibinin on monoamine oxidase activity (Camfield et al. 2011).

1.1.1.13 *Tabernaemontana divaricata* (L).

Tabernaemontana divaricata belongs to the family Apocynaceae, possess remarkable medicinal value. The plant has been used traditionally used as a tonic, emmenagogue, purgative, and aphrodisiac, tonic to the spleen, brain, and liver. The methanloic extract exhibited in vivo antidepressant activity (Faruq et al. 2018). Phytochemical analysis revealed the presence of flavonoids, alkaloids, steroids, and terpenes. The ethanolic extract showed positive effect on generalized anxiety and OCD in mice and the results were comparable to that of fluoxetine. No adverse effects were noted with the intake of *Tabernaemontana divaricata* extract. It is assumed that the anti-OCD effect may be due to the participation of any of the phytochemical actives in serotonergic neurotransmission (Chanchal et al. 2015). Initial studies conducted with *T. divaricata* extracts are highly encouraging, clinical trials are required to prove the efficacy of *T. divaricata*.

1.1.1.14 *Withania somnifera* (L). Dunal

Withania somnifera commonly known as Ashwagandha or Indian Ginseng or Winter cherry belongs to the family Solanaceae and has a long history of usage as Ayurvedic medicine. *W. somnifera* roots are known to possess neuroprotective, anxiolytic, antidepressant, adaptogenic, and cognitive enhancing agent. It is highly valuable for stress related disorders. The neuroprotective activity could be attributed to its neurochemical alteration and nNOS downregulation of some neurotransmitter systems (Bhatnagar et al. 2009). The active components present in *W. somnifera* include alkaloids, withanolides, and sitoindosides. *W. somnifera* root extracts possess significant anti-OCD activity in marble burying behavior in mice and this could be attributed to enabling serotonergic transmission and improved serotonergic

function (Kaurav et al. 2012). In a randomized double-blind placebo-controlled trial, the root extract of *W. somnifera* (120 mg/day) was administered to OCD patients who were taking selective serotonin reuptake inhibitors. To analyze the OCD severity at baseline and at the completion of the trial the Yale-Brown obsessive-compulsive scale (Y-BOCS) was used. Treatment with *W. somnifera* was effective and regarded as safe without adverse side effects (Jahanbakhsh et al. 2016).

1.1.1.15 *Valeriana officinalis* L.

V. officinalis is a perennial plant belongs to the family Caprifoliaceae which is generally known as valerian has a long history of usage as a traditional medicine in different regions of the world. In sixteenth century the plant was used as a perfume (Mikaili et al. 2011). The active constituents of valerian are valepotriates and sesquiterpenoids (valerenic acid) (Patocka and Jakl 2010). Valepotriates are effective in the treatment of psychotic symptoms of severe anxiety. Due to its pain reliever and sedative effects, valerian is commonly used in the treatment of migraine and insomnia. Valerian extracts are highly potential in treating OCD. In a double-blind placebo-controlled study ($n = 31$), the results obtained from valerian extract treatment group was very promising when compared with placebo. The onset of the positive effect of the extract was observed on (28, 42, 56 days). In valerian treated group, somnolence was the adverse side effect noticed (Pakseresht et al. 2011). Valerian constitutes active components which exerts a wide range of neuromodulatory activities such as soporific and anxiolytic effects. The anti-OCD effect of valerian may be postulated due to the activation of adenosine receptors and through the interaction with $GABA_A$ receptors it potentiates synaptic GABAergic transmission (Muller et al. 2002; Benke et al. 2009). Valerian extracts has been reported to show potent anxiolytic effects in vivo (Neamati et al. 2014).

1.1.1.16 *Cassia auriculata* L.

Senthilkumar et al. (2002, 2003) have shown that *C auriculata* has an anti-oxidative, anti-inflammatory, anti-lipidemic and other properties and the researchers studies the flower extract of this plant a lot. Recent studies have shown that aqueous extract of flower has antidepressant activity (Mali et al. 2012). Initial studies have conducted with *C. auriculata* extracts are highly encouraging; more studies are required to prove the efficacy of *C. auriculata.*

1.2 Summary and Future Perspectives

The use of phytochemicals to improve human health has received a lot of attention in recent years because it is thought that natural substances are safer and have fewer adverse effects than synthetic medications. Phytochemicals have special medicinal properties without having a nutritional purpose in the human diet, and they can be utilized to treat certain health conditions for short or extended periods of time. The specific molecular mechanism by which the phytochemicals exert their effect still remains as a subject for investigations and it stills remains unknown, that the quanity of phytochemicals needed, duration and whether these phytochemicals are to be consumed as a supplements or not. Although the molecular mechanisms for the beneficiary effects are yet to be revealed, it is clear that phytochemicals bring health benefits via inhibiting oxidative stress, inflammatory stress signaling, stimulating neurohormetic effects to protect against neuron inflammation, and oxidative stress.

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Chapter 2
Psychobiotics in Health, Longevity, and Neurological Disorders

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Abstract Psychobiotics are an emerging class of probiotics that, when ingested in ample amounts, confer mental health benefits through interacting with gastrointestinal (GI) microbiota in patients with psychiatric problems. These mind-altering groups of probiotics modulate the functions and behavior of the central nervous system via the gut–brain axis to improve GI health and exert anxiolytic and antidepressant properties. Psychobiotics are reported to ameliorate multiple pathological hallmarks of neurodegenerative diseases and neurodevelopmental disorders. Also, the use of psychobiotics can improve motor functions, cognition, mood, and stress behavior in patients with Parkinson's and Alzheimer's disease. Interestingly, several probiotic bacteria with well-established psychotropic properties extend the mean lifespan of experimental models, suggesting their involvement in the aging process. However, in-depth scientific investigations are needed to gain a better understanding on the role of psychobiotics in the management of health and senility. Studying these new classes of probiotics could open the possibility for the development of selective and effective therapeutic strategies to improve overall health and the management of

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various human ailments. This chapter discusses the recent discoveries and developments in the exciting new field of neuromicrobiology, which explores the role of psychobiotics in health, longevity, and neurological disorders. In exploring the role of psychobiotics in health and disease, we focus specifically on mental health, depression, anxiety disorder, autism spectrum disorder, attention-deficit/hyperactivity disorder, Alzheimer's disease, and Parkinson's disease.

Keywords Probiotics · Psychobiotics · Longevity · Mental health · Neurodegenerative diseases · Neurodevelopmental disorders

2.1 Psychobiotics: A New Class of Psychotropic

Over a century ago, Nobel laureate Elie Metchnikoff proposed that health, immunity, and longevity could be enhanced by manipulating the gut microbiome with exogenously introduced host-friendly bacteria or lactic acid bacteria (LAB) termed as probiotics. According to FAO/WHO, probiotics are "live microorganisms which when administrated in adequate amounts confer health benefits on the host" (Underhill et al. 2016). Through technological advancement in omics, we realized that these microbes are an inherent part of complex multicellular communities that constitute the gastrointestinal (GI) microbiome. The microbiome contains heterogeneous symbiotic microbes that communicate with their host and with each other. Depending on their composition and abundance, these microbiotas have been directly linked to host health and disease (Sekirov et al. 2010). The gut microbiota of an individual is controlled by age, sex, genetics, and diet. The human gut contains trillions of microbes and has been reported to modulate various physiological processes, including immune response, development, metabolism, digestion, energy balance, nutrition, and central nervous system (CNS), as well as activation of the enteric nervous system (ENS). Hence this enteric microflora has been described as an organ within an organ (O'Hara and Shanahan 2006). Among the members of acquired and native inhabitants of GI microflora, certain types of bacteria that have psychotropic properties are defined as psychobiotics. Psychobiotics are a new class of probiotics which, when ingested in an adequate amount, confer mental health benefits through interaction with commensal gut microbiota (Dinan et al. 2013). Such "mind-altering" probiotics exert their beneficial effects by producing various biologically active mediators and peptides typically linked with neurotransmission. It has been well documented that several bacterial species within the human gut can produce neurotransmitters and other neuroactive molecules. Microbially derived neuroactive molecules such as serotonin, acetylcholine, catecholamine, and gamma-aminobutyric acid (GABA) have been isolated from bacteria inhabitants of the human gut. For example, *Bacillus* spp. has been reported to produce dopamine and norepinephrine; *Bifidobacterium* spp. has been reported to produce GABA; *Escherichia* spp. has been reported to produce norepinephrine and serotonin; *Enterococcus* spp. and *Streptococcus* spp. have been reported to produce serotonin; and *Lactobacillus* spp. has been reported to produce histamine and acetylcholine.

Neurotransmitters produced by microbiota induce gut epithelial cells to release molecules that in turn modulate neuronal signaling within the ENS and consequently regulate the behavior and brain functions of the host. Short-chain fatty acids and long-chain fatty acids (i.e., conjugated linoleic acid) were produced by GI microbiota with established neuroactive functions. Remarkably, neurochemical producing/releasing probiotics may be used as a delivery vehicle for neuroactive molecules. Such probiotics may have a potential therapeutic strategy in treating and preventing neurological diseases and disorders (Wall et al. 2014).

The compositions of GI microbiota evolve over time and have implications for mental health and functions. Mounting preclinical and clinical evidence shows that modifications in GI microbial diversity (dysbiosis) are directly linked with adverse health outcomes and affect CNS functions; these alterations are associated with depression, anxiety, neurodevelopmental disorders, neurodegenerative diseases, and aging (Wang and Kasper 2014). For instance, individuals with major depressive disorder exhibit lower *Lactobacillus* and *Bifidobacterium* counts (Aizawa et al. 2016). The relative abundance of GI microbiota and overall bacterial diversity was significantly lower in children with autism spectrum disorders. A recent study showed that a lower abundance of anti-inflammatory bacterial genera including *Blautia*, *Coprococcus*, and *Roseburia* were observed in fecal samples from patients with Parkinson's disease. Similarly, fewer *Bifidobacterium* was detected in the GI microbiota of individuals with Alzheimer's disease (Roy Sarkar and Banerjee 2019). Moreover, gut dysbiosis augments the risk of developing attention-deficit/hyperactivity disorder, a neurodevelopmental disorder. In addition, the standard treatment for neurological conditions may alter the GI microbiota composition, which in turn influences the response to treatment and causes several adverse side effects. The evidence of microbiota–gut–brain axis communication roots from the relationship between gut dysbiosis with functional gastrointestinal and CNS disorders. The microbiota–gut–brain axis, a bidirectional communication, concept was further supported by an interesting work of Crumeyrolle-Arias and colleagues (Crumeyrolle-Arias et al. 2014). They found that the germ-free F344 male rats exhibit a decreased social interaction compared with specific pathogen-free control rats; conversely, transplantation of a GI microbiota into germ-free rats improves deficits in social behavior. These results indicated the importance of GI microflora in CNS functions and their role in signal regulation through the gut–brain axis. In this perspective, we explore recent evidence suggesting that probiotics might be efficacious therapeutic intervention to promote signaling through the gut–brain axis and thus alleviate depression, anxiety, aging, neurological disorders.

2.2 Psychobiotics in Brain Health

Much has been explored in recent years about the gut–brain axis in the modulation of mental health. The gut microbiota (GI microbiota) and probiotics have emerged as key players in controlling this complex and multifaceted communication. The

communications between the gut–brain not only ensure gastrointestinal functions and coordination to support biological and behavioral processes but also accept feedback from the gut to exert an intense effect on stress, behavior, mood, cognition, and memory (Sherwin et al. 2016). Several groups have documented the preclinical and clinical evidence on the health-promoting, stress modulatory, antidepressant, and anxiolytic properties of mono- or multi-strain probiotic supplementation (Table 2.1). Prof. J. George Porter Phillips reported the first demonstration of the potential probiotic property of live lactic acid bacillus in improving depression symptoms in adults with melancholia with disturbance of the alimentary canal (Phillips 1910). The administration of single probiotic strain *Lactobacillus plantarum* PS128 to C57BL/6J mice exposed to early life stress resulted in changed emotional behavior, reduced depression- and anxiety-like behavior. Also, PS128 significantly enhanced dopamine levels in the prefrontal cortex of naïve adult mice and mice exposed to early life stress (ELS), whereas serotonin level was increased only in adult naïve mice compared with control mice (Liu et al. 2016b). Administration of probiotic formulation containing *L. helveticus* R0052 and *Bifidobacterium longum* R0175 significantly reduced anxiety-like behavior in rats and alleviated psychological distress in healthy Caucasian men and women (Messaoudi et al. 2011a). Similarly, another probiotic formulation Probio'Stick® containing the same probiotic strains prevents chronic stress-induced changes in the expression of hypothalamic genes involved in synaptic plasticity and hippocampal neurogenesis (Ait-Belgnaoui et al. 2014). A mono-probiotic strain *L. helveticus* NS8 exerts better anxiolytic, antidepressant, and cognition promotion effect in rats exposed to chronic restrain stress, and this effect could be mediated through the microbiota–gut–brain axis (Liang et al. 2015). Individual administration of *L. rhamnosus* strain JB-1 and *B. longum* strain 1714 decreases anxiety and depression-related behavior in mice (Bravo et al. 2011; Savignac et al. 2014). In particular, chronic administration of *L. rhamnosus* JB-1 induces region-dependent alterations in the expression of gamma-aminobutyric acid (GABA) receptor genes, including $GABA_{A\alpha1}$, $GABA_{A\alpha2}$, and $GABA_{B1b}$. Moreover, JB1 exposure directly affects physiological and behavioral responses in mice and is mediated by the vagus nerve (Bravo et al. 2011). Using another probiotic strain *B. infantis* 35624 enhanced the immune response, restored basal noradrenaline concentration in the brain stem, and restored the behavioral deficits induced by maternal separation stress in adult Sprague-Dawley upon chronic administration (Desbonnet et al. 2008, 2010). Another interesting study explored the psychobiotics potential of mono-probiotic bacteria *L. helveticus* ROO52 on wild-type and IL-10 deficient 129/SvEv mice. The administration of *L. helveticus* ROO52 prevented Western diet-induced weight gain, changes in GI microbiota, and cytokine expression in a diet- and genotype-dependent manner. In addition, ROO52 feeding also decreased anxiety-like behavior and impaired memory in mice fed with a Western diet (Ohland et al. 2013).

Consumption of a milk drink containing probiotic *L. casei* Shirota showed improved mood and cognition in healthy volunteers (Benton et al. 2007). Another study reported the mental health-promoting properties of *B. longum* strain 1714 in 2016. The authors showed that healthy male volunteers who consumed *B. longum*

Table 2.1 Selected evidence on the stress modulatory, antidepressant, and anxiolytic properties of psychobiotics

Subject	Intervention	Key findings	Reference
Preclinical evidence			
C57BL/6J mice	*L. plantarum* PS128	Changes emotional behavior, depression- and anxiety-like behavior, modulates prefrontal cortical serotonergic and dopaminergic systems	Liu et al. (2016b)
Adult specific pathogen-free (SPF) Sprague-Dawley rats	*L. helveticus* NS8	Improves chronic restraint stress-induced behavioral, cognitive, gut microbiota, and biochemical abnormalities	Liang et al. (2015)
Adult male BALB/c mice	*L. rhamnosus* JB-1	Reduces stress-induced anxiety- and depression-related behavior	Bravo et al. (2011)
BALB/c mice	*B. longum* 1714	Decreases anxiety and depression	Savignac et al. (2014)
Adult Sprague-Dawley rate	*B. infantis* 35624	Beneficially affects the neuronal system and behavioral deficits induced by maternal separation stress	Desbonnet et al. (2008, 2010)
Wild-type and IL-10 deficient 129/SvEv mice	*L. helveticus* ROO52	Reduces Western diet-induced weight gain, changes in GI microbiota, cytokine expression, and anxiety-like behavior	Ohland et al. (2013)
Male C57B/6 mice	*L. helveticus R0052* and *B. longum R0175*	Prevents stress-induced abnormal neurogenesis and brain plasticity	Ait-Belgnaoui et al. (2014)
Male Wistar rats	*L. helveticus R0052* and *B. longum R0175*	Reduces anxiety-like behavior	Messaoudi et al. (2011a)
Male C57BL/6NCrl mice	*Mycobacterium vaccae* NCTC 11659	Increases resilience to stress-related pathologies and reduces the pro-inflammatory effect	Reber et al. (2016)
Young male Sprague-Dawley rats	*L. casei* 54-2-33	Evoke early behavioral changes upon stress in HPA axis independent manner	Barrera-Bugueño et al. (2017)
BALB/c mice	*B. longum* 1714, and *B. breve* 1205	Both reduce anxiety. 1714 decreased stress-induced hyperthermia, and 1205 reduced anxiety	Savignac et al. (2014)
Male AKR mice exposed to dextran sodium sulfate	*B. longum* NCC3001	Reduces anxiety-like behavior via the vagus nerve	Bercik et al. (2011a, b)

(continued)

Table 2.1 (continued)

Subject	Intervention	Key findings	Reference
Male AKR mice infected with *Trichuris muris*	*L. rhamnosus* NCC4007 and *B. longum* NCC3001	Stabilizes anxiety behavior and brain-derived neurotrophic factor expression but did not affect cytokine or kynurenine levels	Bercik et al. (2010)
Male C57BL/6 mice exposed to social chronic defeat	*L. rhamnosus* (JB-1)	Decreases stress-induced anxiety-like behavior and prevented deficits in social interaction with conspecifics	Bharwani et al. (2017)
Male ICR mice exposed to immobilization stress	*B. adolescentis* IM38	Attenuates stress and reduces the expression of stress-related cytokines	Jang et al. (2018)
Adult male C57BL/6J mice exposed to maternal separation stress	*L. plantarum* PS128	Reduces depression- and anxiety-like symptoms and modulates prefrontal cortical serotonergic and dopaminergic systems	Liu et al. (2016b)
Female Wistar rats exposed to partial restraint stress (PRS)	*L. farciminis*	Suppresses PRS-induced hyperpermeability, endotoxemia and prevents HPA axis stress response and neuroinflammation.	Ait-Belgnaoui et al. (2012)
Specific pathogen-free Sprague-Dawley rats	*L. helveticus* NS8	Improves cognitive dysfunction, anxiety, and depression-like behavioral changes	Liang et al. (2015)
Male Sprague-Dawley rats	*B. breve, B. longum, B. infantis, L. acidophilus, L. paracasei, L. bulgaricus, L. plantarum, Streptococcus thermophilus* subsp. *thermophiles*	Improves gut dysbiosis and memory deficits	Beilharz et al. (2018)
Chronic corticosterone-treated male C57BL/6J mice	*L. paracasei* PS23	Reduces depression, improves hippocampal protein and serotonin levels, and improves fecal microflora	Wei et al. (2019)
C57BL/6J mice chronic unpredictable mild stress	*B. longum subsp. infantis* E41 and *B. breve* M2CF22M7	5-hydroxytryptophan Exert antidepressant effect partly in a 5-hydroxytryptophan dependent and microbiota-regulating manner	Tian et al. (2019)

(continued)

Table 2.1 (continued)

Subject	Intervention	Key findings	Reference
Male Swiss albino mice with chronic unpredictable mild stress or sleep deprivation stress	*L. plantarum* MTCC 9510	Prevents stress-induced behavioral despair (depression, anxiety, learning and memory, stereotypic behavior), oxidative stress markers, and inflammatory cytokines in brain and serum	Dhaliwal et al. (2018)
C3H-HeN mice	*L. brevis* SBC8803	Modulates circadian locomotion and sleep rhythms	Miyazaki et al. (2014)
Male C57BL/6J mice with subchronic and mild social defeat stress (sCSDS)	*L. helveticus* MCC1848	Ameliorates sCSDS-induced gene expression alterations in signal transduction or nervous system development	Maehata et al. (2019)
Kunming male mice	*L. kefiranofaciens* ZW3	Improves depression-like behavior, regulates stress-induced biochemical disorders in the HPA axis, immune system, and tryptophan metabolism, and modulates GI microbiota	Sun et al. (2019a, b)
Male C57BL/6 mice with chronic mild stress	*L. helveticus* R0052, *L. plantarum* R1012, and *B. longum* R0175	Attenuates stress-induced anxiety- and depressive-like behaviors and reverses the stress-induced immune changes in the hippocampus	Li et al. (2018)
Male C57BL/6 mice with chronic unpredictable mild stress	*Clostridium butyricum*	Improves stress-induced depressive-like behavior and increases serotonin and glucagon-like peptide-1 and upregulating brain-derived neurotrophic factor expression	Sun et al. (2018)
Sprague-Dawley rats with post-myocardial infarction (MI) depression	*L. helveticus* R0052 and *B. longum* R0175	Interferes with the development of post-MI depressive behavior and restores intestinal barrier integrity.	Arseneault-Bréard et al. (2012)
Sprague-Dawley rats with post-MI depression	*L. helveticus* R0052 and *B. longum* R0175	Improves post-MI depression-like behavior	Gilbert et al. (2013)

(continued)

Table 2.1 (continued)

Subject	Intervention	Key findings	Reference
Clinical evidence			
Adults with melancholia	Lactic acid bacillus	Improves depression symptoms	Phillips (1910)
Healthy adults	*L. casei* Shirota	Improves mood and cognition	Benton et al. (2007)
Healthy Caucasian men and women	*L. helveticus R0052* and *B. longum R0175*	Alleviates psychological distress	Messaoudi et al. (2011a)
Healthy women (18–55 years)	Fermented milk containing multi-strain probiotic bacteria	Alters the responsiveness of an extensive brain network	Tillisch et al. (2013)
Healthy adults	Probiotic cocktail: Ecologic®Barrier	Reduces overall cognitive reactivity to sad mood	Steenbergen et al. (2015)
Healthy fourth-year medical students exposed to academic examination stress	*L. casei* Shirota YIT 9029	Reduces stress and help maintain sleep quality	Takada et al. (2017)
Healthy adults without a current mood disorder	*B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *and L. lactis* (W19 and W58)	Reduction in overall cognitive reactivity to sad mood	Steenbergen et al. (2015)
Healthy fourth-year medical students exposed to academic examination stress	*L. casei* Shirota YIT 9029	Alters GI microbiota, relieves stress-associated responses of abdominal dysfunction	Kato-Kataoka et al. (2016)
Healthy male patients	*L. rhamnosus* JB-1	Not superior to placebo in modifying stress-related measures, HPA response, inflammation, or cognitive performance	Kelly et al. (2017)
Healthy human volunteers	*B. longum* 1714	Modulates stress, electrophysiology, and neurocognition	Allen et al. (2016)
Patients with major depressive disorder (MDD)	*L. Plantarum* 299v	Decreases kynurenine concentration and improves cognitive functions	Rudzki et al. (2019)
Patients with MDD	*L. acidophilus*, *L. casei* and *B. bifidum*	Reduces the symptoms of depression and improves the metabolic status	Akkasheh et al. (2016)
Patients with MDD and IBS	*Bacillus coagulans* MTCC 5856	Reduces depression and improve gut health	Majeed et al. (2018)
Patients with depression	*L. acidophilus*, *B. bifidum*, and *S. thermophiles*	Reduces depression and improves the quality of life	Bambling et al. (2017)
Healthy older adults (60–75 years)	*L. helveticus* IDCC3801	Improves cognition	Chung et al. (2014)

(continued)

Table 2.1 (continued)

Subject	Intervention	Key findings	Reference
Healthy human volunteers	*L. helveticus* R0052 and *B. longum* R0175	Decreases anxiety and depression	Messaoudi et al. (2011b)
Pregnant women	*L. rhamnosus* HN001	Reduces symptoms of depression and anxiety postpartum	Slykerman et al. (2017)
Adults with IBS and mild to moderate anxiety and/or depression	*B. longum* NCC3001	Reduces depression and urine methylamines and aromatic amino acids metabolites levels	Pinto-Sanchez et al. (2017)
General older adults (> 65 years)	*L. reuteri* DSM17938	Improves digestive health, no impacts on stress or anxiety	Östlund-Lagerström et al. (2015)

1714 displayed improved memory and reduced stress-related behaviors compared to those who consumed the control diet (Allen et al. 2016). As shown in the study by Reber and colleagues, heat-killed environmental bacteria *Mycobacterium vaccae* NCTC 11659 increased resistance to stress-related pathologies and reduced pro-inflammatory effect in mice through the induction of regulatory T cells and an anti-inflammatory bias (Reber et al. 2016). Apart from the mono-probiotic strains, a probiotic mixer (probiotic cocktail; contain two or more bacterial strains) containing multi-strain bacteria have a promising effect on brain health. A study by Tillisch and colleagues demonstrated the long-term administration of fermented milk products containing multi-strain probiotic mixer (*B. animalis* subsp. *lactis*, *Streptococcus thermophiles*, *L. bulgaricus*, and *Lactococcus lactis* subsp. *lactis*) on healthy women volunteers. The clinical data from healthy individuals suggest that the administration of probiotic mixers can alter the responsiveness of an extensive brain network (Tillisch et al. 2013). Notably, the administration of Ecologic®Barrier, a multispecies probiotic intervention containing *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, and *L. lactis* (W19 and W58), to healthy adults resulted in significantly reduced cognitive reactivity to sad mood. In other words, the probiotic intervention reduced aggressive and ruminative thoughts in response to sad moods (Steenbergen et al. 2015).

Mounting evidence indicated that the GI microbiota influences stress-related behaviors, including stress, depression, and anxiety. It has been demonstrated that GI microbiota influences the development of behavior and alters the neurochemical changes in the brain of germ-free (GF) mice, and GF rat exhibits an increased anxiety-like behavior (Crumeyrolle-Arias et al. 2014; Neufeld et al. 2011). Bercik and colleagues described a crucial role of GI microbiota in stress-related behavior in mice. Transfer of stress-prone microbiota from BALB/c mice to GF Swiss Webster (SW) mice has increased the anxiety-related behavioral changes. However, the transfer of microbiota from SW mice to GF BALB/c mice increased the exploratory behavior and hippocampal levels of the brain-derived neurotrophic factor and

reduced anxiety-related behavioral alterations compared to normal BALB/c mice (Bercik et al. 2011a, b). These findings suggest the direct role of microbiota on the influences of brain chemistry and behavior. In addition, GF mice monocolonized with probiotic *L. plantarum* PS128 exhibit better locomotion activity when compared to that of control GF mice. The behavioral changes were further associated with increased serotonin, dopamine, and their metabolites in the striatum of GF mice (Liu et al. 2016a). In 2004, Sudo and colleagues described the vital relationship between probiotics and the hypothalamic–pituitary–adrenal (HPA) axis. The GF mice displayed an exaggerated HPA stress response, and it could be reversed by reconstitution with *B. infantis*. When compared to specific pathogen-free (SPF) mice, GF mice also showed reduced expression of a brain-derived neurotrophic factor in the cortex and hippocampus (Sudo et al. 2004). Multiple studies confirmed the connection between GI microbiome and stress responsiveness, including reports that prenatal or adulthood stress exposure can change the GI microbiota composition of an organism which in turn helps to shape the stress responsiveness (Bharwani et al. 2016; De Palma et al. 2014; Golubeva et al. 2015; Jašarević et al. 2015). Recently, investigators have utilized the fecal microbiota transplantation (FMT) approach to explore the influence of microbiota on stress-related behavioral alterations. In one study, the investigators showed that male Wister rats exposed to chronic mild stress (CMS) and FMT of CMS-induced donor to health animals showed behavioral changes and increased the IL-6, IL-7, and carbonyl protein levels. Intestinally, FMT of healthy animals effectively reduced the brain oxidative stress and inflammation and improved the behavioral abnormalities (Marcondes Ávila et al. 2020). Similarly, successful transplantation of GI microbiota from resistant to susceptible mice resulted in delayed colonization and death caused by enteric bacteria (Willing et al. 2011). A clinical study showed that FMT on depressed patients to GF rats could induce anhedonia and anxiety-like behaviors in addition to altered tryptophan metabolism (Kelly et al. 2016). Microbiota transfer can effectively eliminate superoxide and nitric oxide production in necrotizing enterocolitis mice through modulating S-glutathionylation of endothelial nitric oxide synthase. Furthermore, FMT also suppresses apoptosis and inflammation in the colon, alters the GI microbial composition, and modulates oxidative stress (Li et al. 2017). Li et al. conducted an interesting study in 2019 to determine whether GI microbiota is a decisive factor in depression- and anxiety-like behavior in mice. It has been shown that healthy recipients who were colonized with GI microbiota from chronic unpredictable mild stress-induced mice had a higher degree of depression- and anxiety-like behavior compared to the controls, and significant elevation in tumor necrosis factor-alpha (TNF-α), interferon-γ (IFN-γ), and indoleamine 2,3-dioxygenase 1 (IDO1) in the hippocampus has also been observed (Li et al. 2019).

It has been well documented that dietary supplementation has a direct effect on GI microbiota. David and colleagues showed that supplementation of docosahexaenoic acid (DHA) in socially isolated mice reduces depression and anxiety-related behavioral changes, and the protective effect was mediated by sex-specific GI microbiota (Davis et al. 2017). Likewise, long-term DHA/Eicosapentaenoic acid

supplementation alters the GI microbiota composition of early life stressed and neurodevelopmentally normal animals (Pusceddu et al. 2015). The stress reversal and stress-protective effects of probiotics have also been demonstrated. For example, in a preclinical study, the administration of *L. helveticus* NS8 adult SPF Sprague-Dawley rats showed an improved chronic restraint stress-induced cognitive dysfunction, anxiety, and depression-like behavioral changes, which is similar to and better than that of citalopram, a selective serotonin reuptake inhibitor (Liang et al. 2015). Similarly, partial restraint stress-induced animals supplemented with *L. farciminis* suppressed hyperpermeability and endotoxemia, and prevented HPA axis stress response and neuroinflammation. Also, oral *L. farciminis* administration increases stress-reactivity and stress-induced hyperpermeability (Ait-Belgnaoui et al. 2012). In a clinical trial, a total of 81 patients were assigned to receive probiotics (*L. helveticus* and *B. longum*) in addition to prebiotic (galactooligosaccharide) or placebo for 2 months. No significant changes in the patient's body mass index were recorded; however, *L. rhamnosus* can reduce stress-related behavior and corticosterone release in patients (Kazemi et al. 2020). Similarly, short-term exposure to *L. gasseri* CP2305 improves clinical symptoms and stress-related symptoms in individuals with irritable bowel syndrome (IBS) and healthy young adults, respectively. Nishida and colleagues demonstrated the long-term exposure to heat-inactivated CP2305 in 60 healthy Japanese young adult students preparing for the national examination for medical practitioners for 6 months. Continuous intake of CP2305 reduced sleep disturbances, and anxiety relative to placebo was accompanied by stress-induced elevation of *Streptococcus* spp., stress-induced decline of *Bifidobacterium* spp., and improved mental state of healthy adults under stressful conditions (Nishida et al. 2019). Moya-Perez et al. evaluated the effect of *B. pseudocatenulatum* CEC7765 in a murine model of chronic stress induced by maternal separation. Male breast-fed pups of C57BI/6J were subjected or not to maternal separation and supplemented with CEC7765 or placebo until postnatal period 21 and followed-up until postnatal 41. It was found that CEC7765 supplementation reduced maternal stress-induced stress response of the HPA axis, intestinal inflammation, anxiety, and intestinal hypercatecholaminergic activity (Moya-Pérez et al. 2017). Oral administration of *B. adolescentis* IM38 showed an anxiolytic-like effect on mice treated with immobilization stress and attenuated stress through modulation of the benzodiazepine site on the $GABA_A$ receptor and reduced the expression of stress-related cytokines (Jang et al. 2018). Several clinical trials are currently investigating the brain health-promoting effects of psychobiotics and are summarized in Table 2.2.

2.3 Psychobiotics in Aging and Longevity

Aging is an inevitable natural phenomenon characterized by progressive functional deteriorations at the molecular to the organismal levels that constitute a critical risk factor for various life-limiting diseases (Fontana et al. 2010). Multiple cellular and molecular declines have been identified to be responsible for aging, including

Table 2.2 Clinical trials investigating psychobiotics on brain health

Subject details	Intervention	Location of the study	ClinicalTrials.gov identifier	Outcome measures
$N = 92$; age group: 18–30 years	*L. rhamnosus* GG (ATCC 53103) *Saccharomyces boulardii* (CNCM I-1079)	Poland	NCT03427515 (completed)	Primary: Performance under examination stress Secondary: Anxiety, cortisol, pulse rate, and metanephrine level
$N = 70$; age group: 19–35 years	Probiotic supplement	Sweden	NCT03284905 (completed)	Primary: Reduction of the cortisol level during acute stress
$N = 75$; age group: 18 years and older	The probiotic cocktail contains 7 probiotic strains	Canada	NCT02035878 (unknown)	Primary: Depression, anxiety, and feelings related to stress
$N = 9$; age group: 9–13 years	*L. rhamnosus* GG (Culturelle®)	USA	NCT02711800 (completed)	Primary: Abdominal pain and anxiety symptoms Secondary: Changes in the microbiome, cortisol, and heart rate.
$N = 60$; age group: 18–65 years	A multi-strain probiotic product (refer: Vivomixx® or Visbiome)	China	NCT04006977 (not yet recruiting)	Primary: Reduction of anxiety and depression Secondary: Clinical response and remission, endoscopic remission/response, changes in fecal microbiota, and adverse events
$N = 39$; age group: 18–35 years	Bifihappy (*L. fermentum*, *L. rhamnosus*, *L. plantarum*, and *B. longum*)	Italy	NCT03539263 (completed)	Primary: Changes in psychological behavior Secondary: Evaluation of mood and personality
$N = 66$; age group: 30–60 years	PROBIOSTICK®	France	NCT00807157 (completed)	Stress and anxiety of people sensible to daily stress
$N = 60$; age group: 18–65 years	*L. plantarum* 299v	Poland	NCT02469545 (completed)	Primary: Evaluation of psychometric parameters Secondary: Cognitive function and biochemical analysis
$N = 108$; age group: 18–65 years	Probio'Stick (containing *L. helveticus* and *B. longum*)	Canada	NCT03277586 (recruiting)	Primary: Mood Secondary: Anxiety, cognition, anhedonia, blood plasma, stool microbiome, and fMRI

(continued)

Table 2.2 (continued)

Subject details	Intervention	Location of the study	ClinicalTrials.gov identifier	Outcome measures
$N = 120$; age group: 18–45 years	*L. paracasei* (Lpc-37)	Germany	NCT03494725 (completed)	Primary: Changes in heart rate Secondary: Physiological, behavioral, and biological parameters
$N = 40$; age group: 18–55 years	*B. longum* 35624® and *B. longum* 1714™	Ireland	NCT04422327 (completed)	Primary: Changes in anxiety and depression Secondary: IBS-related symptoms, sleep quality, cognition, and other relevant parameters
$N = 60$; age group: 18–40 years	Vivomixx® powder	Germany	NCT03478527 (recruiting)	Primary: Changes in hippocampal volume, functional brain activation, depression, spatial navigation, IL-6, IL-1β, TNF-α, BDNF, and verbal learning Other: Changes in oxytocin, processing speed, cognitive emotion regulation, and sleepiness
$N = 64$; age group: 18–65 years	*L. helveticus* R0052 and *B. longum* R0175	Canada	NCT02334644 (recruiting)	Primary: Yale brown obsessive-compulsive and clinical global impression Secondary: Other obsessive-compulsive disorder parameters
$N = 40$; age group: 20–65 years	*L. plantarum* PS128	Taiwan	NCT03237078 (unknown)	Primary: Changes in hs-CRP, TNF-α, IL-6, and IL-10 Secondary: Changes in depression, GI microbiota, GI permeability and inflammation, and TLPs
$N = 40$; age group: 18–65 years	*L. helveticus*	Brazil	NCT04333277 (recruiting)	Primary: Change in the severity of the depressive symptoms Secondary: Changes in the microbiota, serum levels of biomarkers, and perception of stress
$N = 10$; age group: 18–65 years	Probio'Stick	Canada	NCT02838043 (completed)	Primary: Mood Secondary: Anxiety, cognition, sleep, and levels of inflammatory markers

(continued)

Table 2.2 (continued)

Subject details	Intervention	Location of the study	ClinicalTrials.gov identifier	Outcome measures
$N = 60$; age group: 18–55 years	Bio-Kult, probiotic capsule	United Kingdom	NCT03801655 (recruiting)	Influences on emotional and cognitive processing in participants with low mood
$N = 60$; age group: 20–65 years	*L. plantarum* PS128	Taiwan	NCT04199845 (recruiting)	Primary: Severity of depression Secondary: Changes in severity of depression, gut permeability, inflammation markers, and gut microbiota

genomic instability, telomere attrition, epigenetic changes, mitochondrial dysfunction, loss of protein homeostasis, stem cell exhaustion, deregulated nutrient sensing, and altered intercellular communication (López-Otín et al. 2013). The aging hallmarks are interconnected, and the perturbation of one can affect others as well. In the context of aging, these changes could affect the overall physiological functions as well as the GI microbiota composition and abundance, which can be potentially ameliorated by probiotic interventions (Biagi et al. 2013). Indeed, aging-induced changes in the composition of GI microbiota and immune function can favor the development of several pathogens and increase the vulnerability to gastrointestinal diseases, which in turn affects the enormous number of health-promoting bacteria inhabiting the gut (Ghosh et al. 2020; Guarner and Malagelada 2003). At this stage, the administration of probiotics exerts several health-promoting benefits for the host by protecting them against microbial infections, counteracting gastrointestinal diseases, enhancing the immune system, improving overall metabolic functions, and extending organismal lifespan (Aureli et al. 2011; Sanders et al. 2019).

In general, a series of in vitro and in vivo experiments are carried out to select new probiotic strains. The in vitro experiments have undeniable advantages and provide vital information about probiotic strains, including their tolerance to acid, bile, and other gastric enzymes, adhesion to GI cells, persistence in the gut, and pathogenic behavior. However, complementary in vivo analysis is mandatory for a better understanding of their potential probiotic properties and their mechanism of action, but also of safety measures (Papadimitriou et al. 2015). Regarding the in vivo experiments, the preclinical studies involve laboratory animals like mice and rats or clinical trials on the human population. Although in vivo experiments are essential to determine the effectiveness of probiotics, these studies have been time-consuming, expensive, arduous to implement, and required ethical and legal considerations (Lacroix et al. 2015). Currently, in vivo methods for the fast, less expensive, reliable, and high-throughput analysis of collection using complex experimental models are very limited. The use of mammalian models such as mice and rats in the early phase of research is not possible considering their cost reasons, infrastructure facilities, and ethical issues. Therefore, alternative model(s) with a

simplified, less expensive, and extensively close homology are needed to identify probiotic strains from a wide range of microbial communities. To this respect, the soil nematode *Caenorhabditis elegans* has become a powerful animal model for studying host–probiotic interactions to counteract aging and extend lifespan. *C. elegans* is the most widely used model organism for almost all aspects of biology. Its advantages include ease of maintenance, transparent anatomy, short life cycle and lifespan, higher progeny production, fully sequenced genome, and the absence of ethical issues. Importantly, it has highly conserved biochemical pathways and a large number of genetic resources. In particular, many mutants and transgenic reporter strains available in *Caenorhabditis* Genetic Center (CGC, University of Minnesota, USA) can help to study the mechanism of host–probiotic interaction more in detail. Also, RNA based reverse genetic approach (RNA interference/RNAi) has become a major tool in several aspects of biology since its discovery in *C. elegans* and a collection of feeding *E. coli* strain that expresses target gene dsRNA (RNAi) also available at Source BioScience and Horizon Discovery Ltd., to the scientific community. It is important that a large amount of data on the entire biology of *C. elegans* such as WormBook, WormBase, WormAtlas, OpenWorm, and WormWiring are freely available for researchers across the world.

Focusing on lactic acid-producing bacteria (LAB), several lactobacilli strains increase the mean lifespan of wild-type *C. elegans* under standard conditions compared to worms fed with the standard dietary source *E. coli* OP50. Most of the bacterial species known to extend the lifespan of *C. elegans* belong to the genera *Bifidobacterium*, *Lactobacillus,* and *Weissella*, which are commonly found in fermented food materials and in the GI tract of humans and animals, and thus generally recognized as safe (GRAS) (Roselli et al. 2019). In addition, members of other bacterial species, including *Bacillus licheniformis*, *B. subtilis*, *Butyricicoccus pullicaecorum*, *Clostridium butyricum*, *Enterococcus faecalis*, *E. faecium*, *Megasphaera elsdenii*, and *Propionibacterium freudenreichii* can have documented longevity-promoting and immune-modulatory benefits. Four bifidobacteria strains (*B. animalis* subsp. *lactis*, *B. breve*, *B. infantis*, *B. longum*, *B. longum*), 18 lactobacilli strains (*Lactobacillus acidophilus* NCFM, *Lactobacillus* spp. Lb21*, L. casei* LAB9, *L. fermentum* JDFM216, *L. fermentum* MBC2, *L. fermentum* LA12, *L. fermentum* U21, *L. fermentum* BGHV110, *L. gasseri* SBT2055, *L. gastricus* BTM7, *L. helveticus* NBRC15019, *L. plantarum*, *L. plantarum* CJLP133, *L. plantarum* dy-1, *L. rhamnosus* CNCM I-3690, *L. rhamnosus* Lcr35, *L. salivarius* FDB89, *L. zeae* LB1) and three Weissella strains (*W. koreensis*, *W. cibaria*, *W. confusa*) have shown to increase the mean lifespan of wild-type worms from 14% to 50% under standard culture conditions or infected with human pathogens (Table 2.3). Few other studies also indicated that *Bifidobacterium* and *Lactobacillus* species grown under anaerobic conditions increased the lifespan of nematodes. These probiotic strains can able to exert anti-aging effects in *C. elegans* by acting on multiple intracellular signaling pathways, such as insulin/insulin-like growth factor-1 (IIS), p38 mitogen-activated protein kinase (p38 MAPK), transforming growth factor-β (TGF-β), nuclear hormone receptor (NHR), AMP-activated protein kinase (AMPK), and dietary restriction (Table 2.3). Several probiotic bacteria listed in

Table 2.3 Life-promoting and immune-modulating ability of selected probiotic bacteria and their mechanism of action in *C. elegans*

Probiotic strain	Mechanism of action	Reference
B. licheniformis	Serotonin signaling	Park et al. (2015)
B. subtilis	DAF-2/DAF-16/HSF-1 signaling	Donato et al. (2017), Gusarov et al. (2013), Smolentseva et al. (2017)
B. animalis subsp. *lactis* CECT 8145	IIS pathway	Martorell et al. (2016)
B. breve UCC2003	Unknown	Christiaen et al. (2014)
B. infantis	p38 MAPK pathway Toll-like receptor	Komura et al. (2013), Sun et al. (2019a, b)
B. longum BB68 *B. longum* BR-108	TIR-1/JNK-1/DAF-16 signaling IIS pathway	Sugawara and Sakamoto (2018), Zhao et al. (2017)
Butyricicoccus pullicaecorum KCTC 15070	TGF-β pathway	Kwon et al. (2018)
Clostridium butyricum MIYAIRI 588	IIS pathway	Kato et al. (2018)
Enterococcus faecalis MMH594 *E. faecalis* Symbioflor®	p38 MAPK and β-catenin Unknown	Yuen and Ausubel (2018), Neuhaus et al. (2017)
E. faecium L11	p38 MAPK and TGF-β	Sim et al. (2018)
Megasphaera elsdenii KCTC 5187	TGF-β pathway	Kwon et al. (2018)
Lactobacillus acidophilus NCFM	p38 MAPK and β-catenin	Kim and Mylonakis (2012)
Lactobacillus spp. Lb21	TGF-β signaling	Mørch et al. (2021)
L. casei LAB9	TLR mediated RACK-1 dependent p38 MAPK pathway	Kamaladevi and Balamurugan (2016)
L. fermentum JDFM216 *L. fermentum* MBC2 *L. fermentum* LA12, U21 *L. fermentum* BGHV110	NHR and p38 MAPK pathway IIS pathway Unknown HLH-30/TFEB-mediated autophagy	Dinić et al. (2021), Lee et al. (2011), Marsova et al. (2020), Park et al. (2018, 2020), Schifano et al. (2019)
L. gasseri SBT2055	p38 MAPK pathway	Nakagawa et al. (2016)
L. gastricus BTM7	p38 MAPK pathway	Kavita et al. (2020)
L. helveticus NBRC15019	Unknown	Ikeda et al. (2007)
L. plantarum *L. plantarum* CJLP133 *L. plantarum* dy-1	JNK-1/DAF-16 pathway Unknown IIS pathway	Ikeda et al. (2007), Lee et al. (2011), Zhao et al. (2020)
L. rhamnosus CNCM I-3690 *L. rhamnosus* Lcr35	IIS pathway	Grompone et al. (2012), Poupet et al. (2019)

(continued)

Table 2.3 (continued)

Probiotic strain	Mechanism of action	Reference
L. salivarius FDB89	Dietary restriction	Zhao et al. (2013)
L. zeae LB1	p38 MAPK pathway	Zhou et al. (2014)
Propionibacterium freudenreichii	p38 MAPK pathway	Kwon et al. (2016)
Pediococcus acidilactici P25	Innate immunity, longevity, and MAPK pathway	Tan et al. (2020)
Stenotrophomonas CPCC 101271	Unknown	Han et al. (2021)
W. koreensis KACC 11853 and *W. cibaria* KACC 11845	JNK-1/DAF-16 and AMPK pathway	Lee et al. (2015)
W. confusa CGMCC 19,308	Upregulates *col-*, *gst-*, *sod-*, and immune-related genes	Wang et al. (2021)

Table 2.3 enhance the lifespan, healthspan, and immune response of *C. elegans* under normal/infected conditions through multiple cellular signaling pathways and have well-established psychotropic properties. Few of them have also been shown to extend the organismal lifespan, but their psychotropic properties are still unexplored. Since the molecular mechanisms regulated by probiotics in *C. elegans* appear to be conserved across species, this suggests that they could also exert a similar effect on humans, which is an important issue that needs to be validated in the future. Indeed, probiotic supplementation is often suggested to reverse or slow the age-associated changes in GI microbiota composition and immune functions in aged populations. Nevertheless, in-depth scientific investigations are required to get insight into the longevity-promoting ability of probiotics in mammals.

2.4 Psychobiotics in Neurodevelopmental Disorders

2.4.1 Autism Spectrum Disorder (ASD)

ASD is a group of neurodevelopmental disabilities associated with a range of communication and behavioral deficits. People with ASD show alteration in brain development and have difficulty with communication and interaction, changes in social development, repetitive behavior, and restricted interests (Bell 1994). Apart from the influence of genetic changes, the causes of ASD are not well documented. Individuals with autism frequently experience gastrointestinal disturbances, including diarrhea and constipation (Coury et al. 2012). It has been established that probiotic supplementation could improve the GI symptoms and even reduce ASD-associated symptoms in individuals with ASD. Mounting preclinical and

clinical evidence indicated a link between the GI microbiota composition and ASD. More than 60% of patients with ASD have been found to have GI disturbance, signifying the possible role of the gut–brain axis in ASD (Dinan and Cryan 2015). A study performed by Mayer et al. pointed out the relationship between intestinal microbiota and ASD. They found that the microbiota of children with ASD is more diverse than healthy children without ASD (Mayer et al. 2014). Oral administrations of human commensal gut bacterium *Bacteroides fragilis* with a maternal immune-activated mouse model showed increased gut permeability, altered microbial composition, and ameliorated several behavioral abnormalities of ASD (Hsiao et al. 2013). Administration of probiotic cocktail of *B. bifidum*, *B. longum*, *L. acidophilus, L. casei*, *L. delbrueckii*, and *L. rhamnosus* to children with ASD significantly reduced severe constipation and diarrhea (Sichel 2013). These results highlight the potential of probiotic interventions for the treatment and management of GI microbiota-mediated neurodevelopmental disorders.

A randomized, double-blind, placebo-controlled study investigated the effect of mono-probiotic supplementation (*L. plantarum* PS128) on 7–15 years old boys with ASD in Taiwan. The results showed that *L. plantarum* PS128 ameliorated several behavioral symptoms of ASD, including opposition and rule braking, hyperactivity, inattention, and impulsivity. In addition, early life exposure of *L. plantarum* PS128 displayed better activity than children who received supplementation at older ages (Liu et al. 2019). Another two-staged, randomized, double-blind, placebo-controlled, parallel-group study investigated the synergistic effect between oxytocin, a neuropeptide, and probiotic *L. reuteri* supplementation. Throughout the study period (6 months), 60 individuals diagnosed with ASD were randomly assigned to receive either oral *L. reuteri* supplement or placebo in the first stage. On stage two, all participants will receive intranasal oxytocin spray. The primary outcomes of this trial are social communication and behavior assessment. The secondary outcomes are neuroendocrine biomarkers in blood, structural and functional MRI, blood volume, pulse, heart rate, peripheral skin temperature, skin electrodermal activity, blood oxygen saturation, 16 s metagenomic sequencing of the microbiome, eye behavior, and emotional response. This pilot study will provide direct evidence on the potential efficacy of mono-probiotic supplementation therapy and dual probiotic+oxytocin therapy for treating core symptoms of ASD (Kong et al. 2020). Parracho et al. reported the double-blind, placebo-controlled, crossover study in which they investigated the effects of probiotic *L. plantarum* WCFS1 on individuals with ASD in the United Kingdom. A trial completed with 17 patients and *L. plantarum* WCFS1 improved ASD-related communication and behavior deficits. In addition, continuous administration of *L. plantarum* WCFS1 for 3 weeks alters the GI microbiota in patients with ASD (Parracho et al. 2010). A recent clinical trial investigated the efficacy of applied behavioral analysis (ABA) training with probiotic intervention on children with ASD. When compared with ABA training alone, children supplemented with probiotics along with ABA training reduced the behavioral and emotional deficits of ASD children with GI distress (Niu et al. 2019).

Besides the use of mono-probiotic supplementation against ASD-related symptoms, multi-strains of probiotics were also reported. Supplementation of probiotic

B. bifidum, *B. infantis,* and *L. helveticus* during pregnancy prevents the ASD behavior in the offspring of the maternal immune-activated mouse. Oral administration of these probiotic strains with prebiotics (fructooligosaccharides and maltodextrin) for 3 weeks decreases the frequency of ASD and alleviates the IL-6 and IL-7a production in offspring (Wang et al. 2019). A recent study demonstrated the effect of a probiotic cocktail containing *Bifidobacteria* and *Lactobacilli* strain (ProtexinR) against autistic-like behavior in hamsters induced by clindamycin and propionic acid. Supplementation of these probiotic strains ameliorated ASD symptoms and glutamate toxicity by decreasing the excitatory glutamate and restoring the depleted Mg^{2+} and GABA neurotransmitters (El-Ansary et al. 2018). A randomized, double-blind study investigated the effect of probiotic cocktail Vivomixx® on inflammatory and GI biomarkers, GI disturbances, behavioral and developmental profiles, and neurophysiological features in preschoolers with ASD with or without GI symptoms (Santocchi et al. 2016). Subjects were divided into four groups (25 children in each group): GI symptoms and probiotics (group-1), GI Symptoms and placebo (group-2), non-GI symptoms, and probiotics (group-3), and non-GI symptoms and placebo (group-4). Subjects were provided with two packets a day in the first month of treatment and one packet a day for additional 5 months. Vivomixx® contains 450 billion lyophilized bacterial cells belonging to eight probiotic bacterial strains, viz., *B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *L. acidophilus* DSM 24735, *L. plantarum* DSM 24730, *L. paracasei* DSM 24733, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, and *S. thermophilus* DSM 24731. This study could provide a comprehensive and multifaceted characterization of patients with ASD. Moreover, this work will also provide solid evidence on the role of probiotic cocktails on GI function, and behavioral and neurophysiological parameters of ASD favor the development of non-pharmacological and relatively risk-free treatments for the management of ASD-related neurodevelopmental disorders. The effect of another product containing the same probiotic strains as in Vivomixx®, Visbiome Extra Strength, was investigated on children ($N = 13$; age group: 3–12 years) with ASD, anxiety, and GI symptoms. Subjects were randomized into either Visbiome or placebo for 8 weeks, followed by a 3-week washout. The preliminary findings of this crossover trial showed that Visbiome improved the GI and pain symptoms by altering GI microbiome composition and related metabolites (Arnold et al. 2019). An open-label trial was conducted to evaluate the efficacy and tolerability of probiotic cocktail in 30 Egyptian cohorts of children from 5 to 9 years old with ASD and GI symptoms. Individuals were analyzed for GI and ASD symptoms before and after 3 months of supplementation of probiotic cocktail. The probiotic formula contains three bacterial strains namely *L. acidophilus*, *L. rhamnosus,* and *B. longum*, and each gram of cocktail contains 100×10^6 colony forming units. The results of the trial indicated that the probiotic supplementation significantly reduced the body weight, and severity of ASD and GI symptoms in children (Shaaban et al. 2018). In Table 2.4, we summarized ongoing clinical trials investigating the effect of psychobiotics on the ASD and associated deficits.

Table 2.4 Clinical trials investigating the effects of mono- or multi-strains probiotics on individuals with ASD

Subject details	Intervention	Location of the study	ClinicalTrials.gov Identifier	Outcome measures
$N = 100$; age group: 2–18 years	*L. rhamnosus*—ATCC 21052, *L. plantarum*—ATCC 8014, and *B. longum* subsp. *infantis*-ATCC 1570	India	NCT04939974 (not yet recruiting)	Changes in childhood autism rating scale at 24 weeks
$N = 1000$; age group: 2.5–75 years	Customized probiotics (Flore)	USA	NCT04655326 (recruiting)	Parent global impressions of autism, social responsiveness, and GI symptoms
$N = 82$; age group: 3–16 years	Vivomixx® (probiotic cocktail)	United Kingdom	NCT03369431 (recruiting)	Measures the behavior and GI function
$N = 13$; age group: 3–12 years	Visbiome extra strength (probiotic cocktail)	USA	NCT02903030 (completed)	Improves ASD and GI symptoms
$N = 85$; age group:18–72 years	Vivomixx® (probiotic cocktail)	Italy	NCT02708901 (completed)	Inflammatory and GI biomarkers, GI disturbances, behavioral and developmental profiles, and neurophysiological features
$N = 29$; age group: 4–15 years	*B. animalis* subsp. *lactis* BB-12 and *L. rhamnosus* GG	USA	NCT02674984 (completed)	Evaluates the safety and tolerability of the probiotic combination
$N = 70$; age group: 4–16 years	*B. animalis* subsp. *lactis* BB-12 and *L. rhamnosus* GG	USA	NCT03514784 (recruiting)	Measuring the adverse events of probiotic supplementation
$N = 80$; age group: 18 months–8 years	*L. reuteri* DSM 17938 + *L. reuteri* ATCC PTA 6475	Taiwan	NCT04293783 (recruiting)	Changes in ASD symptomatology and microbiome profile
$N = 250$; age group: 30 months–7 years	*L. plantarum* PS128	Taiwan	NCT03982290 (recruiting)	Behavioral assessment, GI symptoms, and microbiota composition
$N = 80$; age group: 2–5 years	*L. plantarum,* PS128	China	NCT04942522 (enrolling by invitation)	Changes in ASD-related behavior, GI symptoms, cytokines, and type, number, and structural composition of GI microbiota

2.4.2 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a childhood-onset brain disorder with impairing symptoms of hyperactivity, inattention, and impulsivity. People with ADHD are at risk for a wide range of mental and functional impairments, although several details about the pathophysiology of ADHD are quite ambiguous. It has been demonstrated that an imbalance in the gut microbial community (dysbiosis) has a negative effect on cognition, behavior, and neurodevelopment (Borgo et al. 2017; Sharon et al. 2019; Strati et al. 2016). Related to this, dysbiosis has been consistently found in patients with ASD (Finegold et al. 2010), and a pilot study found a difference in several GI microbiota between healthy and ADHD subjects (Petra et al. 2015). In particular, higher *Bifidobacterium* genus and lower *Firmicutes* genus were found in individuals with ADHD than in healthy children. The increase in the *Bifidobacterium* genus relating to decreased ventral striatal functional magnetic resonance imagining responses during reward anticipation (Petra et al. 2015). Another pilot study investigates the effect of broad-spectrum micronutrients on fecal microbiome contents in children who are diagnosed with ADHD. As a result, micronutrient administration improved overall function, attention, emotional regulation aggregation. In addition, post-micronutrient treatment increased the frequency of species from *Collinsella* and reduced the *Bifidobacterium* abundance (Stevens et al. 2019). A clinical study showed that 75 infants who have received *L. rhamnosus* GG (ATCC 53103) during the first 6 months of life exhibited a reduced risk of developing ADHD (Pärtty et al. 2015). In addition, probiotic *L. rhamnosus* supplementation prevents learning and memory dysfunction in mice infected with *Citrobacter rodentium* (Gareau et al. 2011). As shown in one case study, food supplement fortified with *L. acidophilus* improved self-control and attention in children (Harding et al. 2003). A synergistic combination of probiotic and prebiotic microbes, synbiotic formulation, can revert dysbiosis and improve brain functions, cognition behavior, and mood (Tillisch et al. 2013). Besides, a recent study has shown that early life oral administration with *Lactobacillus* potentially reduced the prevalence and incidence of both ADHD and ASD in children (Yousefi et al. 2019). However, the exact mechanisms by which probiotics exert their activity remain largely unclear. A recent study suggests that the anti-inflammatory and immunomodulatory properties of these probiotics specifically target T-helper type 1 and T-helper 17 cell lineages (Mardani et al. 2019). According to Kumperscak and colleagues, children and adolescents with ADHD who received *L. rhamnosus* GG supplementation exhibited a better health-related quality of life than their peers who received a placebo. In particular, *L. rhamnosus* GG supplemented group showed enhanced serum cytokines IL-6, IL-7, and TNF-α (Kumperscak et al. 2020). Chou et al. discovered that certain types of *Lactobacillus* spp. showed protection against central nervous system deficits. Preterm babies who received probiotic *L. reuteri* and *L. rhamnosus* for 6 weeks resulted in significantly reduced neurological aberrations in compression with that of the group fed with *L. acidophilus* and *B. infantis* (Chou et al. 2010). In Table 2.5, we summarized the relationship between psychobiotics and ADHD. An ongoing double-blind, placebo-

Table 2.5 Effect of probiotic strains on the management of ADHD

Subject details	Intervention	Duration	Observation	Reference
Children ($N = 10$)	*L. acidophilus*	6 months	Improves attention and self-control	Harding et al. (2003)
Infant ($N = 75$)	*L. rhamnosus* GG	6 months	Reduces risk of the development of ADHD, and *Bifidobacterium* composition in feces	Pärtty et al. (2015)
Female (24-year-old)	Olive leaf extract and probiotics	2 months	Improves mood and energy levels, and low *Candida* infection	Rucklidge (2013)

controlled clinical trial (NCT02908802) is being conducted to explore the beneficial effect of probiotic supplementation on students with ADHD. The preliminary outcome will be evaluated on symptoms of attention deficits after 6 months of continuous probiotic intake. Another randomized, open-label clinical trial will be initiated with 40 patients to assess the effect of *L. fermentum* and *L. delbruekii* (Lacteal forte) on the management of ADHD (NCT04167995). In Table 2.6, we summarized the ongoing clinical trials investigating the effects of probiotics on individuals diagnosed with ADHD.

2.5 Psychobiotics in Neurodegenerative Diseases

2.5.1 Alzheimer's Disease (AD)

AD is a progressive neurodegeneration, the most common form of dementia, affecting more than 50 million people worldwide. The two major hallmark pathologies of AD are β-amyloid (Aβ) plaque deposition and neurofibrillary tangles of hyperphosphorylated tau (Jagust 2018; Xin et al. 2018). Aβ peptides are produced by amyloid precursor protein (APP) and are associated with oxidative damage and neuroinflammation in the brain, resulting in the loss of neurons and disease progression. In recent years, attempts have been devoted to correcting imbalances in the microbiome–gut–brain axis with psychobiotics that release neuroactive substances. When the APP/PS1 transgenic mice practiced exercising and were treated with probiotics (*B. longum* and *L. acidophilus* lysates), they reduced the number of Aβ plaques in the hippocampus and decelerated the progress of AD as well (Abraham et al. 2019). The probiotic cocktail of eight strains of lactic acid-producing bacteria (VSL#3 containing *L. plantarum, L. delbrueckii* subsp. *bulgaricus, L. paracasei, L. acidophilus, B. breve, B. longum, B. infantis,* and *S. salivarius* subsp. *thermophilus*.) feeding considerably altered the enterotype and reduced the aberrant intestinal permeability, intestinal inflammation, serum eicosanoids, and bile acid levels of $App^{NL\text{-}G\text{-}F}$ mice rather than wild-type (C57BL/6) mice. However, the

Table 2.6 Clinical trials investigating the effects of mono- or multi-strains probiotics on people with ADHD

Subject details	Intervention	Location of the study	ClinicalTrials.gov identifier	Outcome measures
$N = 80$; age group: 6–16 years	*L. fermentum* and *L. delbruekii* (lacteal forte)	Egypt	NCT04167995 (recruiting)	Fourteen subscales of symptoms, including the opposition, cognitive problems, inattention, and hyperactivity, will be measured
$N = 45$; age group: 19–30 years	Dietary probiotic supplements	Israel	NCT02908802 (active, not recruiting)	The reduced symptoms of attention deficit will be measured by the MOXO test after 6 months of exposure
$N = 180$; age group: 18–65 years	*Pediococcus pentosaceus*, *L. paracasei* subsp. *paracasei*, and *L. plantarum*	Spain	NCT03495375 (not yet recruiting)	Change in ADHD symptoms
$N = 100$; age group: 6–14 years	*L. helveticus* R0052 and *B. longum* R0175	Canada	NCT02545634 (unknown)	ADHD-related disruptive behavior, and changes in cortisol, word pairs memory, visual memory, and total omission and commission errors on the continuous performance task
$N = 40$; age group: 6–11 years	Probiotic cocktail – 7 strains (*L. casei* PXN 37, *L. rhamnosus* PXN 54, *S. thermophilus* PXN 66, *B. breve* PXN 25, *L. acidophilus* PXN 35, *B. longum* PXN 30, *L. bulgaricus* PXN 39)	Iran	NCT04333394 (not yet recruiting)	ADHD-associated symptoms and severity
$N = 320$; age group: Child, adult, and older adults	Probiotic mixture	Taiwan	NCT03858816 (recruiting)	The incidence rate of death or ADHD
$N = 150$; age group: Child, 4–16 years	*B. bifidum* 688	Taiwan	NCT04958460 (active, not recruiting)	Inhibits the proportion of *Sutterella* and improves ADHD symptoms

probiotic treatment did not affect Aβ accumulation, cytokines, gliosis, and memory function in App^{NL-G-F} mice (Kaur et al. 2020). A triple transgenic mouse model of AD (3x-Tg AD mice) fed with another probiotic formulation SLAB51 contains nine live bacterial strains, viz., *S. thermophilus*, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, and *L. brevis* altered the intestinal microbiota structure, positively interfered with inflammatory cytokines, and reduced cognitive decline and Aβ aggregates. Moreover, SLAB51 administration exhibited partial restoration of impaired neuronal proteolytic pathways and activation of the SIRT1 Pathway (Bonfili et al. 2017, 2018). Administration of *B. breve* A1 in ddY-AD mice prevented cognitive impairment and the hippocampal expressions of inflammation and immune-reactive genes induced by Aβ (Kobayashi et al. 2017). Amyloid genesis and memory deficiency in AD is caused by the administration of lipopolysaccharide (LPS found in the wall of all gram-negative bacteria), which contributes to increased neuroinflammation and damage to the blood–brain barrier. This lipopolysaccharide-induced neuroinflammation and memory impairment in ICR mice was attenuated by the administration of lactic acid bacteria fermented cow's milk (CM-LAB). CM-LAB offers neuroprotection via restoration of the cholinergic neurotransmission and attenuation of neuroinflammation. The attenuation of neuroinflammation was mediated by inhibition of AChE and antioxidative activities (Musa et al. 2017). Oral administration of prebiotic-chitosan oligosaccharides inhibited oxidative stress by decreasing MDA and 8-OHdG levels coupled with increasing GSH-Px and SOD activities and suppressing the neuroinflammation by decreasing the release of IL-1β and TNF-α in $A\beta_{1-42}$-induced rats (Jia et al. 2016). In addition, the recent study suggests that supplementation of *Lactobacillus* and *Bifidobacterium* strains improved learning in $A\beta_{1-42}$-induced rats through presynaptic neurotransmitter release via presynaptic mechanisms (Rezaeiasl et al. 2019). It was also described that the combination of *L. helveticus* R0052 and *B. longum* R0175 decreased the levels of pro-inflammatory cytokines in the serum and hippocampus of LPS-induced rats (Mohammadi et al. 2019). Aβ can reduce the binding affinity of insulin receptors and cause insulin signaling impairment, leading to insulin resistance. Since the insulin signaling cascades have a neuroprotective role in the CNS, the disruption of the insulin signaling cascade can induce AD. Intake of *Lactobacilli* and *Bifidobacteria* strains prevents Aβ-induced memory deficit and decreases insulin resistance markers in $A\beta_{1-42}$ injected rats (Athari Nik Azm et al. 2017, 2018). Besides, the anti-Alzheimer properties of *L. plantarum* MTCC1325 were tested against D-Galactose-induced AD rates. The results revealed that improved behavioral activity and learning skills in rats through an elevation in the cholinergic neurotransmitter in the hippocampus and cerebral cortex regions of the brain (Nimgampalle 2017). In Table 2.7, we summarized the effect of psychobiotics against AD and its associated pathologies.

Table 2.7 Selected evidence for the AD-inhibiting potential of mono- and multi-strain probiotics

Subject	Intervention	Key findings	Reference
App^{NL-G-F} mice	VSL#3	Decreases intestinal inflammation and gut permeability with minimal effect on Aβ, cytokine, or gliosis levels in the brain	Kaur et al. (2020)
3xTg-AD mice	SLAB51 probiotic formulation	Partially restores the ubiquitin-proteasome system and autophagy and improves cognitive function by reducing Aβ load	Bonfili et al. (2017)
3xTg-AD mice	SLAB51 probiotic formulation	Reactivates the SIRT1 pathway, increases the activity of antioxidant enzymes, decreases protein and lipid oxidation, restores the basal level of cleaved PARP, OGG1, and 8-OHdG	Bonfili et al. (2018)
ddY-AD mice	*B. breve* A1	Ameliorates the cognitive decline and suppresses the expressions of inflammation and immune-reactive genes induced by Aβ	Kobayashi et al. (2017)
ICR mice	Fermented cow's milk containing *L. fermentum* (LAB9, LAB10) (CM-LAB9) or *L. casei* (LABPC)	Increases antioxidants (SOD, GSH, GPx), reduced levels of NO, MDA, AChE, and pro-inflammatory cytokines	Musa et al. (2017)
$A\beta_{1-42}$-induced rats	Prebiotic-chitosan Oligosaccharide	Reduces learning and memory deficits and ameliorates neuronal apoptosis via inhibition of oxidative stress and neuroinflammatory responses	Jia et al. (2016)
$A\beta_{1-42}$-induced rats	A cocktail containing *L. acidophilus, B. bifidum,* and *B. longum*	Improves learning, increases paired-pulse facilitation (PPF) ratios following LTP induction, decreases serum levels of total cholesterol, triglyceride, and very-low-density lipoprotein-cholesterol	Rezaeiasl et al. (2019)
$A\beta_{1-42}$-induced rats	Probiotics powder containing *L. acidophilus* 1688FL431-16LA02, *L. fermentum* ME3, *B. lactis* 1195SL609-16BS01, and *B. longum* 1152SL593-16BL03	Improves spatial memory, reduces Aβ plaque, and decreases MDA and SOD levels	Athari Nik Azm et al. (2018)
$A\beta_{1-42}$-induced rats	Probiotics powder containing *L. acidophilus, L. fermentum, B. lactis,* and *B. longum*	Decreases insulin level and HOMA-IR index, serum TG level was not altered	Athari Nik Azm et al. (2017)

(continued)

Table 2.7 (continued)

Subject	Intervention	Key findings	Reference
LPS-induced rats	Probiotic mixture containing *L. helveticus* R0052 and *B. longum* R0175	Decreases the level of TNF-α and IL1-b, and also reduces the decremental effect of LPS on memory through brain-derived neurotrophic factor protein expression	Mohammadi et al. (2019)
D-galactose induced rats	*L. plantarum* MTCC1325	Increases cognitive behavior restored ACh and histopathological abnormalities	Nimgampalle (2017)
Wistar rats	Probiotic capsule	Improves spatial performance positively affects antioxidant/oxidant biomarkers and restores attenuated LTP	Rezaei Asl et al. (2019)
AD patients	Probiotic milk containing *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum*	Positively influence cognitive function and some metabolic statuses in the AD patients but did not significantly affect oxidative stress and inflammation	Akbari et al. (2016)
AD patients	A probiotic capsule containing *L. fermentum*, *L. plantarum*, *B. lactis, L. acidophilus, B. bifidum,* and *B. longum*	Probiotic treatment did not affect the cognitive test and the serum level of cytokines (TNF-α, IL-6, and IL-10), total antioxidant capacity, GSH, NO, MDA, and 8-OHdG	Agahi et al. (2018)
AD patients	OMNi-BiOTiC® STRESS repair; *L. casei* W56*, L. lactis* W19*, L. acidophilus* W22*, B. lactis* W52*, L. paracasei* W20*, L. plantarum* W62*, B. lactis* W51*, B. bifidum* W23, and *L. salivarius* W24	Declines fecal zonulin, increased *Faecalibacterium prausnitzii* and serum kynurenine, serum tryptophan, phenylalanine, and tyrosine were not altered	Leblhuber et al. (2018)
Patients with mild cognitive impairment (MCI)	*B. breve* A1	Improves cognitive function	Kobayashi et al. (2019a)
Patients with MCI	*B. breve* A1	Increases neuropsychological test scores and no significant adverse effects caused by *B. breve* A1	Kobayashi et al. (2019b)

2.5.2 Parkinson's Disease (PD)

Parkinson's disease (PD, MIM168600) is a complex neurological condition that can be seen in elderly people from all geographical regions and is characterized as a movement disorder. The neuronal loss in pars compacta of the substantia nigra and a

typical aggregation of α-synuclein inside the brain tissues are the two pathological hallmarks of neurodegeneration in PD. Also, PD is commonly associated with some common nonmotor symptoms, including impaired gastric motility, constipation, and elevated α-synuclein aggregation in the intestine (Aarsland et al. 2017; Fasano et al. 2015; Shannon et al. 2012). In addition to several pathophysiological hallmarks, individuals with PD also exhibit increased colonic inflammation and intestinal permeability (Devos et al. 2013). Physicians often recommend dopamine supplementation for treating PD, but currently, no effective therapies are available that delay PD-associated neurodegeneration, and the exact mechanism that causes this disease remains poorly defined. Several links between the GI microbiota and PD have been proposed. For example, the fecal microbiota of patients with PD displayed an enhanced *Enterobacteriaceae* and a reduced *Prevotellaceae* abundance compared to healthy individuals. Moreover, it was found that the abundance of *Enterobacteriaceae* was directly related to motor impairments in PD patients (Scheperjans et al. 2015). Sampson and colleagues recently explored the involvement of GI microbiota in the onset and progression of PD and associated functional deficits in mice model that overexpresses α-synuclein. They found that GI microbiota is required for the pathological events linked with α-synuclein, microglial activation, and motor deficits. Importantly, microbial re-colonization promotes the pathophysiology of PD in adult animals and oral administration of short-chain fatty acids, specific microbial metabolites, to GF mice sufficient to promote motor symptoms and neuroinflammation. Interestingly, colonization of GI microbiota from patients with PD in mice expressing α-synuclein exacerbated physical impairments compared to mice received microbiome from healthy human donors (Sampson et al. 2016). These findings reveal the critical involvement of the microbiome in the regulation of movement disorder, at least in part, and suggest that modulation of gut dysbiosis may provide an effective treatment to slow or even halt the progression of PD and related diseases.

Few studies highlighted the value of probiotics for improving PD and its associated functional deficits in experimental models and human trials. It was demonstrated that probiotic supplementation alters the onset and progression of the disease by regulating the PD-associated changes in microbiota composition, improving GI function, modulating intestinal permeability, and neuroinflammation in the enteric nervous system. However, preclinical and clinical evidence on the beneficial effect of probiotic strains against neurodegeneration associated with PD are still very limited (Ma et al. 2019; Mertsalmi et al. 2017; Perez-Pardo et al. 2017). The first clinical trial was conducted in 2011 and demonstrated that patients with PD suffering from chronic constipation taking a fermented milk drink containing *L. casei* Shirota for 6 weeks improved the stool consistency and reduced bloating, abdominal pain, and sensation of incomplete emptying (Cassani et al. 2011). In a randomized, double-blind, placebo-controlled trial, the patients with PD were assigned to take either placebo or a probiotic cocktail containing *L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* (8×10^9 CFU/day) for 3 months. The results showed that consumption of the probiotic cocktail decreased Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), high-sensitivity

C-reactive protein, and malondialdehyde levels but also enhanced glutathione levels. Remarkably, the consumption of probiotics resulted in a significant increase in insulin sensitivity and reduction in insulin levels and insulin resistance in PD patients compared to the placebo (Akkasheh et al. 2016). Borzabadi et al. conducted a clinical trial in 2018 with the same probiotic cocktail on the expression of genes related to inflammation, insulin, and lipid in patients ($n = 50$ individuals) with PD. They have observed that probiotic intake for 3 months downregulated the expression of IL-1, IL-7, and TNF-α and upregulated the TGF-β and peroxisome proliferator-activated receptor gamma (PPAR-γ) in peripheral blood mononuclear cells (PBMC) of PD patients compared with placebo. However, probiotic supplementation did not obviously alter the low-density lipoprotein receptor (LDLR) and vascular endothelial growth factor (VEGF) in PBMC of patients with PD (Borzabadi et al. 2018). In another clinical trial, the PD patients administered with a probiotic tablet containing *L. acidophilus* and *B. infantis* have been shown capable of reducing GI nonmotor symptoms such as abdominal pain and bloating as much as with trimebutine, a medication for irritable bowel syndrome and other gastrointestinal disorders (Georgescu et al. 2016). It has been shown that the PD patients with Rome III-functional constipation who took fermented milk containing multiple probiotic strains, including *S. salivarius* subsp. *thermophilus*, *E. faecium*, *L. rhamnosus* GG, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, *B. breve*, and *B. animalis* subsp. *lactis* increased the number of complete bowel movements than the placebo (Barichella et al. 2016).

A randomized, double-blind, placebo-controlled clinical study currently being investigating the effect of probiotic capsules containing *B. lactis* on PD patients with constipation. Individuals will be randomly assigned to take either probiotic capsules or placebo capsules (containing maltodextrin) for 4 weeks. The investigators will examine the average number of bowel openings per week based on the stool diary in the primary outcome. In addition, they will measure the average stool consistency, the total score of a constipation severity (based on ROME IV criteria for functional constipation), and patient assessment of constipation quality of life (PAC-QOL; i.e., physical and psychosocial discomfort, worries/concerns, and patient's satisfaction) as secondary outcomes (ClinicalTrials.gov Identifier: NCT03377322). Another open-label pilot study was conducted investigating the effect of short-term supplementation (3 months) of *L. plantarum* strain PS128 (30 billion CFU/capsule/day) on the Parkinsonian symptoms in PD. Motor and nonmotor scores were measured as primary and secondary outcomes, respectively, using standard protocols (ClinicalTrials.gov Identifier: NCT03566589). An ongoing randomized, triple-blind, placebo-controlled study is being started to explore the effect of a multi-strain probiotic cocktail (Ecologic® BARRIER 849) for treating anxiety in patients with PD. The cocktail contains probiotic bacteria (2.5 × 10^9 CFU/g) *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lc. lactis* W19, and *Lc. lactis* W58. Another cocktail contains maize starch, maltodextrin, vegetable protein, and potassium chloride, magnesium sulfate, and manganese sulfate will be served as a placebo. The participants (72 patients with PD between 40 and 80 years) will be assigned to intake oral

probiotic or placebo cocktail in a powdered form for 12 weeks. Persistent anxiety, episodic anxiety, and avoidance behavior will be measured as primary outcomes according to Parkinson's anxiety scale. Assessment of depression (Beck Depression Inventory), quality of life (PAC-QOL), the severity of fatigue (Fatigue Severity Scale), cognitive impairment (Montreal Cognitive Assessment), and motor/nonmotor symptoms (MDS-UPDRS) will be considered as secondary outcomes (ClinicalTrials.gov Identifier: NCT03968133). Table 2.8 summarizes ongoing clinical trials investigating mono- and multi-strain probiotic strains against PD and its associated declines. Few in vitro evidence also demonstrated the PD inhibitory potential of probiotics. For example, a novel probiotic bacterium, *Bacillus* sp. JPJ can produce 99.4% levodopa (L-DOPA) from L-tyrosine buffer containing 1 mg/mL cells (Surwase and Jadhav 2011). Based on the severity of symptoms, L-DOPA is typically prescribed to PD patients with other antiparkinsonian drugs. In one study, the in vitro effect of six probiotic bacterial strains (*L. salivarius* LS01 DSM 22775, *L. plantarum* LP01 LMG P-21021, *L. acidophilus* LA02 DSM 21717, *L. rhamnosus* LR06 DSM 21981, *B. animalis* subsp. *lactis* BS01 LMG P-21384, *B. breve* BR03 DSM 16604) in PBMC isolated from patients with PD was presented against healthy controls. The investigators of this study measured the in vitro release of the major anti-inflammatory (IL-4 and IL-10) and pro-inflammatory (TNF-α and IL-17A) cytokines from PBMC in addition to the intracellular ROS production. They found that all probiotic strains tested were capable of inhibiting ROS production and inflammatory cytokines. In particular, *L. salivarius* LS01 and *L. acidophilus* LA02 significantly increased anti-inflammatory and reduced pro-inflammatory cytokines. Also, most probiotic strains antagonize the growth of potential human pathogenic bacteria such as *E. coli* and *Klebsiella pneumonia* and determine restoration of membrane integrity (Magistrelli et al. 2019).

Recently, Goya and colleagues demonstrated the protective effect of probiotic bacteria *B. subtilis* strain PXN21 against PD and its associated pathologies in the *C. elegans* model for PD expressing human α-synuclein in body wall muscle cells (NL5901 [*pkIs2386*(*unc-54p::α-synuclein::YFP*)]). The authors found that *B. subtilis* inhibits the aggregation of α-synuclein and clears preformed aggregates in NL5901 worms. The aggregation inhibition by *B. subtilis* is also driven by the production of nitric oxide and biofilm formation. Furthermore, spores of *B. subtilis* inhibit the protein accumulation in *C. elegans* partially via the dietary restriction (DR) mechanism. In contrast, the vegetative cells of *B. subtilis* protect via activating an evolutionary conserved DAF-16/FOXO signaling in a DR-independent mechanism. Interestingly, several host metabolic pathways are differentially regulated by *B. subtilis* in worms, including the sphingolipid metabolism pathway. In particular, *B. subtilis* feeding upregulates *lagr-1* (ortholog of human ceramide synthase CERS1) and *asm-3* (an ortholog of human acid sphingomyelinase, SMPD1), and downregulates *sptl-3* (an ortholog of a serine palmitoyltransferase, SPTLC2) in *C. elegans* PD model (Goya et al. 2020). These three sphingolipid metabolic pathway genes are proposed to modify α-synuclein pathology in PD (Alecu and Bennett 2019; Lin et al. 2019).

Table 2.8 Clinical studies investigating the effects of mono- or multi-strain probiotic interventions on patients with AD and PD

Disease	Subject details	Interventions	Location of the study	ClinicalTrials.gov identifier	Outcome measures
AD	$N = 90$; age group: 55 years and older	*Bifidobacterium*	China	NCT03991195 (recruiting)	Primary: Assessment of cognitive, auditory verbal learning, and changes in GI microbial diversity Secondary: Changes in brain network
PD	$N = 70$; age group: 18–80 years	Probiotic cocktail (*E. faecium*, *L. rhamnosus*, *L. acidophilus*, and *L. plantarum*)	United Kingdom	NCT04140760 (recruiting)	Primary: Patient experience and existence Secondary: Microbiome, MDS-UPDRS, sleep quality, and gastrointestinal disorders measurement
PD	$N = 72$; age group: 40–80 years	Probiotic cocktail: Ecologic® BARRIER 849	Canada	NCT03968133 (not yet recruiting)	Primary: Anxiety Secondary: Assessment of depression, PAC-QOL, the severity of fatigue, cognitive impairment, and MDS-UPDRS
PD	$N = 48$; age group: 18 years–older	Probiotic cocktail: *Lactobacillus* spp. and *Bifidobacterium* spp.	Malaysia	NCT04451096 (completed)	Primary: Changes in the presence of constipation symptoms Secondary: Whole gut transit time, quality of life (PDQ39-SI), MDS-UPDRS, and nonmotor symptoms
PD	$N = 72$; age group:40–85 years	*B. lactis*	Malaysia	NCT03377322 (completed)	Primary: Average bowel opening Secondary: Average stool consistency, the total score of a constipation severity, and patient assessment of constipation quality of life
PD	$N = 30$; age group: 40–80 years	*L. plantarum* PS128	Taiwan	NCT03566589 (completed)	Primary: MDS-UPDRS Secondary: Change in nonmotor symptoms and patient global impression of change

(continued)

Table 2.8 (continued)

Disease	Subject details	Interventions	Location of the study	ClinicalTrials.gov identifier	Outcome measures
PD	$N = 6$; age group: 40–80 years	*L. plantarum* PS128	Taiwan	NCT04389762 (completed)	Primary: MDS-UPDRS, UPDRS III scores Secondary: Measurement of nonmotor symptoms, change in the patient global impression of change, and Parkinson's experience
PD	$N = 30$; age group: 18–75 years	*L. casei* DG (Enterolactis duo®)	Italy	NCT04293159 (recruiting)	Primary: Satisfaction and improvement with therapy and neuropsychological function Secondary: MDS-UPDRS and constipation symptoms

2.6 Conclusions

Several clinical studies provide promising evidence of how psychobiotics can help to improve mood and behavior, reduce stress, strengthen memory, and manage anxiety, suggesting that these strains may be used in the near future to treat stress- and depression-related behavior, neurological disorders, and other mental health issues by using them in the form of nutritional supplement. Although we are still in the initial stage of understanding the complex interaction between psychobiotics and the brain, we know that specific native and exogenously introduced bacteria can secrete neuroactive molecules that could directly alter brain functions. However, only cultivable bacterial strains have been investigated for their in vitro and in vivo psychotropic properties, and a very limited number of bacterial strains have been explored till now. Competition and interaction can occur in the human gut because of its complex microbial ecosystem, which has not yet been studied. In addition, a suitable in vivo model system with relatively inexpensive and genetic similarity is urgently needed to investigate the longevity-promoting effect of psychobiotics. In this perspective, the nematode *C. elegans* can be used as a powerful in vivo screening platform to understand how psychobiotics interact with the host to modulate healthspan, lifespan, and immunostimulation and what potential mechanisms are involved in these processes. Several probiotic strains with established psychotropic properties have been shown to extend the lifespan of the host by activating conserved stress- and aging-associated signaling pathways, while other key regulators have yet to be identified and characterized. Since the molecular mechanisms

regulated by probiotics in *C. elegans* appear to be conserved across species, suggesting that they may also exert a similar effect on humans, which is an important issue that needs to be validated in the future.

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Chapter 3
Nutritional, Dietary, and Lifestyle Approaches for Prevention and Management of Alzheimer's Disease

Supta Sarkar and Madhubalaji Chegu Krishnamurthi

Abstract Neurodegenerative disorders have grabbed global attention as it resulted in morbidity and disability worldwide. Neurodegenerative diseases pertaining to the central nervous system are heterogeneous disorders characterized by the progressive degeneration of its structure and function. Alzheimer's disease is one of the most frequently occurring neurodegenerative disorders and is the major cause of dementia. Worldwide 50 million people are suffering from dementia (among 60–70% belongs to Alzheimer's disease), and it is increasing at the rate of ten million new cases per year. There is a vast evidence for possible dietary risk factors in the development of Alzheimer's disease and cognitive decline with age. Therefore, diet and nutrition are essential in modulating the risk of Alzheimer's disease. Epidemiological evidence demonstrates a protective role of dietary supplementation of antioxidants, polyunsaturated fatty acids, B complex vitamins, essential elements, and polyphenols, which could protect the brain from oxidative and inflammatory damage. Furthermore, consumption of fish, fruits, vegetables, coffee, and light-to-moderate alcohol reduces the risk of Alzheimer's disease. Adherence to a healthy diet and the dietary patterns like the Mediterranean diet or DASH diet are associated with a lower risk of Alzheimer's disease. This chapter focused on the epidemiological evidence linking many nutrients, foods, and dietary habits to Alzheimer's disease.

Keywords Alzheimer's disease · Nutrition · Diet · Dietary pattern · Dietary recommendation

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3.1 Introduction

Alzheimer's disease is a neurodegenerative and progressive disorder characterized by deterioration in intellect, affecting memory, thought, language, reasoning, learning, orientation, comprehension, judgment, as well as behavior and impairment of everyday activities (Abate et al. 2017). Alzheimer's disease, primarily causing dementia worldwide, accounts for 50–60% of all cases (Morris 2009). The global prevalence of dementia is expected to double every 20 years, and it will be more than 80 million people by 2040 (Morris 2009) and the estimate of Alzheimer's disease cases is projected to reach 106.8 million worldwide by 2050; hence, it is a growing public health issue with a global socioeconomic burden (Hu et al. 2013).

Alzheimer's disease has a complex, multifactorial neuropathophysiology involving the deposition of extracellular 4 kDa peptide amyloid beta (Aβ) plaques and somatodendritic makeup of hyperphosphorylated tau protein-producing intraneuronal neurofibrillary tangles, which are both associated with synaptic and neuronal loss and neuroanatomic dysfunctions, including those involving cholinergic transmission (Swaminathan and Jicha 2014; Kamphuis and Wurtman 2009; Bazan et al. 2011). Besides these critical pathological characteristics of Alzheimer's disease, there is ample evidence that increased oxidative stress, abnormalities in mitochondrial dysfunction and the development of cellular energy, and chronic inflammatory responses lead to the degenerative cascade of this complex disease (Swaminathan and Jicha 2014). Alzheimer's disease is broadly divided into two primary forms: early onset and late-onset. The uncommon early onset form of Alzheimer's disease (about 1% of all cases of Alzheimer's disease) is characterized by autosomal-dominant genetic mutations, symptoms starting before age 60, and genetically induced Aβ overproduction (Mosconi and McHugh 2015). Less than 1% of Alzheimer's cases are caused by particular mutations in three genes for amyloid precursor protein (APP), presenilin-1, and presenilin-2, all associated with Aβ metabolism (Abate et al. 2017). At a cellular level, dysfunction in the processing of βAPP results in an overabundance of the 42 amino acid Aβ42 peptide oligomer, which initially impairs synaptic function. Aβ42 triggers damaging signals (accompanied by early apoptosis) and changes in gene expression, which emulate neurodegeneration and Alzheimer's disease characteristics. Neuroinflammatory degeneration related to Aβ42 is an essential contributory factor to the neuropathology of Alzheimer's disease (Bazan et al. 2011). On the other hand, the most common form of late-onset Alzheimer's disease (onset after 60 years of age), which accounts for >99% of the total population of Alzheimer's disease, is a multifactorial disease of unknown origin most likely to develop from the complex interaction between genetic and environmental factors (Mosconi and McHugh 2015). Late-onset Alzheimer's disease has been correlated with several risk factors, including demographics (i.e., old age, female gender, low education), ancestry or inheritance (i.e., family history of first-degree, epsilon 4 allele of the apolipoprotein E gene [APOE? 4]), medical status (i.e., hypertension, cardiovascular disease), cognitive status (i.e., objective and subjective cognitive decline), environmental factors (i.e., pollutants,

environmental toxins), and lifestyle factors (poor diet, low physical or social activities, chronic stress) (Mosconi and McHugh 2015).

At present, there is no cure for Alzheimer's disease, and the existing therapies only momentarily alleviate the symptoms (Sindi et al. 2015; Kamphuis and Wurtman 2009). The prevailing medical therapies improve the transmission of acetylcholine and other neurotransmitters, along with various multidisciplinary strategies which focus on improving the quality of life and reducing symptom burden (Swaminathan and Jicha 2014). There are two major challenges concerning Alzheimer's disease: the delay in diagnosis and the lack of neuroprotective or curative pharmacological treatment. In fact, Alzheimer's disease is only recognized in the later stage when cognitive performance begins to decline (Abate et al. 2017). The G8 Dementia Summit and World Health Organization (WHO) have identified dementia and Alzheimer's disease prevention as a major public health concern (WHO 2012; G8 Dementia Summit Declaration 2013). Thus, there is a strong unmet need for effective prevention and therapeutic strategies. Furthermore, evidence showed the potential role of nutrition in such strategies is rapidly gaining interest (Kamphuis and Wurtman 2009).

Diet and nutrition have been increasingly recognized as the potential factors influencing the susceptibility of Alzheimer's disease by preventing or delaying cognitive decline (Mosconi and McHugh 2015; Kamphuis and Wurtman 2009). Thus, a potential role for nutrition in the prevention and management of Alzheimer's disease seems likely. A growing body of literature, from preclinical to epidemiological, provides evidence of dietary and nutrient trends associated with Alzheimer's disease risk biomarkers, suggesting that dietary nutrients may modulate the risk of Alzheimer's and cognitive function. Nutrients effect on the deposition of Aβ and associated neuronal damage even several years before the potential onset of symptoms (Mosconi and McHugh 2015). Several nutrients such as monounsaturated and ω-3 fatty acids, antioxidants, vitamins, and polyphenols have been documented to minimize the risk of Alzheimer's disease, whereas saturated fat intake, high-calorie intake, and excessive alcohol intake have been identified as risk factors (Hu et al. 2013). The combined effect of dietary fats with the level of plasma cholesterol is of great importance due to the role of cholesterol involved in both Aβ production and deposition. Besides, the protein APOE?4, which is a known genetic risk factor for Alzheimer's disease is the key cholesterol transporter in the brain (Abate et al. 2017).

This chapter will discuss the impact of nutrition, diet, and dietary pattern on Alzheimer's disease, the most common cause of dementia. Dietary and lifestyle approaches for prevention and management of Alzheimer's disease will also be focused in the later section.

3.1.1 Risk Factors

Several factors are contributing to the risk of Alzheimer's disease (Fig. 3.1), including older age, genetic factors (particularly the presence of the allele APOEε4), family

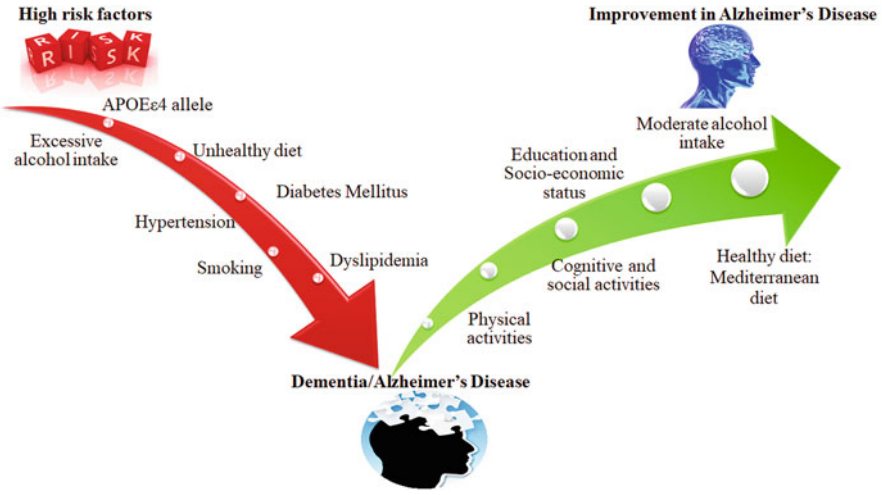

Fig. 3.1 Risk factors associated with Alzheimer's disease

history, obesity, diabetes mellitus, hypertension, and hypercholesterolemia, cardiovascular problems, lifestyle factors like dietary pattern, excessive alcohol consumption, smoking; a history of head injury, anxiety, stress, depression, and also low physical activity (Sindi et al. 2015; Barnard et al. 2014; Morris 2009). A vast amount of studies have also suggested that dietary and lifestyle factors may influence risk, raising the possibility that preventive strategies with diet may be effective (Barnard et al. 2014).

3.2 Role of Nutrients in Prevention and Management of Alzheimer's Disease

The "precautionary principle" is applied in toxicology under circumstances where there is significant ground for concern about the health effects on exposure and where available evidence precludes a thorough risk evaluation (European Commission 2000). A similar approach may be extended to nutrition and other lifestyle-related exposures, particularly in conditions such as Alzheimer's disease, where there may be a long period of latency between exposure and the disease manifestation (Barnard et al. 2014). A nutritional and dietary approach to prevent or slow the progression of Alzheimer's disease can be a promising strategy and thus has been widely explored (Abate et al. 2017). It is well known today that certain dietary nutrients, including polyunsaturated fatty acids (PUFA), vitamins, essential elements, and polyphenolic compounds, may significantly affect the aging of the brain, contributing to enhanced memory and motor skills. All of these compounds have powerful antioxidant and anti-inflammatory activity (Abate et al. 2017; Hu et al. 2013) and have the ability to enhance cognition. However, it is not limited to

their antioxidant properties, since they often involve particular complex molecular and cellular processes that promote brain plasticity (Abate et al. 2017). In this section, we will discuss different nutrients which play a role in the prevention or management of Alzheimer's disease.

3.2.1 Antioxidants

Multiple studies have shown that Alzheimer's disease involves oxidative and inflammatory activities, but it is not clear if such processes are a cause or consequence of the disease or both (Morris 2009). Oxidative stress and the inflammatory mechanism eventually contribute to a disruption of the functioning and signaling of neuronal cells, leading to neuronal cell death (Morris 2009; Gustafson et al. 2015). Oxidative stress occurs when the intracellular capacity to expel free radicals is surpassed, resulting in changes in DNA, lipids, polysaccharides, and proteins, as well as changes in the homeostatic redox balance. A common and early characteristic of Alzheimer's pathology is oxidative stress. Some of the pathogenic factors, such as oxidative damage, accelerated amyloidogenic APP processing, mitochondrial dysfunction, and Aβ accumulation, are observed at synaptic terminals of the brains of Alzheimer's disease patients and animal models, which are associated with synaptic dysfunction. This is crucial because synaptic disruption is a key factor in cognitive impairment during aging and Alzheimer's disease progression (Gustafson et al. 2015). The antioxidant, which offers the most protection, is still debatable. Some antioxidants ideally target cytosolic oxidative stress pathways, while others typically function as mitochondrial cofactors that can reduce the intrinsic mechanisms of oxidative stress (Swaminathan and Jicha 2014). There are several potential sites of activity and complex antioxidant-influenced cellular pathways. The hypothesis that antioxidant therapy can prevent or delay the Alzheimer's disease progression has led to many studies suggesting potential risks and advantages of antioxidant therapy for the treatment of Alzheimer's disease (Swaminathan and Jicha 2014). Antioxidants such as vitamins E and C constitute the body's innate defense mechanisms to combat oxidative stress (Morris 2009).

In animal models, dietary supplement studies with antioxidants exhibited better learning attainment and memory retention. At death, the brains of the antioxidant-fed animal models unveiled less neuronal cell loss and less evidence of oxidative damage and inflammation (Morris 2009). Thus, dietary nutrients with antioxidant properties may have positive effects in Alzheimer's disease and those at risk for the disease by reducing oxidative stress, particularly when used in combination (Gustafson et al. 2015). It has been shown that the dietary intake of antioxidants in foods is superior to supplements in human studies on cognition and risk of developing Alzheimer's disease (Zandi et al. 2004; Morris et al. 2002). Several nutrients, particularly vitamin C, vitamin E, and carotenoids, and non-nutrient food ingredients such as polyphenols and anthocyanins, have direct antioxidant activity. Furthermore, some essential elements such as selenium, zinc, and copper serve as cofactors for

proteins or enzymes with antioxidative potential (Scarmeas et al. 2018). Thus, the intake of dietary antioxidants could have an effect on the development of cognitive impairment.

3.2.2 Dietary Fat

Changes in fatty acid composition and levels have important implications on neuronal integrity during aging and for the development of Alzheimer's disease (Morris and Tangney 2014; Gustafson et al. 2015).

3.2.3 Saturated Fat and Trans Fat

Several studies, although not all, have suggested an association between intake of saturated or trans fats with Alzheimer's disease (Barnard et al. 2014; Morris and Tangney 2014; Hu et al. 2013). The Chicago Health and Aging Project has shown that the population with higher saturated fat intake had twice the risk of developing the disease (Morris et al. 2003). A moderate intake of saturated fatty acids has been associated with an increased risk of Alzheimer's disease and dementia, especially among APOEε4 carriers (Laitinen et al. 2006). Trans-fatty acid can also potentially increase the risk of Alzheimer's or trigger an earlier occurrence of the disease by increasing Aβ production through increasing amyloidogenic processing and by decreasing APP through non-amyloidogenic processing (Hu et al. 2013). Additional evidence of probabilistic associations between saturated or trans fat intake and Alzheimer's risk stems from the fact that the APOEε4 allele, which is strongly correlated to Alzheimer's disease, produces a protein that plays a crucial role in the transportation of cholesterol. Also, the observational studies indicate that consumption of high-fat foods and increased blood cholesterol concentrations may contribute to Aβ production or its aggregation in the brain tissues (Barnard et al. 2014).

3.2.4 Monounsaturated fatty acid (MUFA)

Monounsaturated fatty acids (MUFAs) and their derivatives have anti-inflammatory effects (Borniquel et al. 2010). Intake of higher monounsaturated fatty acid was associated with better cognitive function, while higher saturated fatty acid was linked with worse cognitive function (Hu et al. 2013).

3.2.5 *Polyunsaturated Fatty Acid (PUFA)*

Numerous studies have investigated the effects of PUFAs in preventing or slowing Alzheimer's disease, while elevated intake of PUFA might be beneficial to Alzheimer's disease (Hu et al. 2013). The ability of PUFA to avoid neuronal loss and cognitive impairment derives from the evidence that PUFAs are vital components of neuronal cell membranes, retaining membrane fluidity necessary for neural network connectivity of the synaptic vesicle fusion and neurotransmitter (Joseph et al. 2009). Long-term ω-3 supplementation to the animal models showed that a decreased ω-6/ω-3 ratio reduced Aβ, prevented neuronal failure and increased cognitive function in Alzheimer's (Abate et al. 2017).

The ω-3 long-chain PUFAs (ω-3 LC-PUFA's), which are primarily docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), control the excitability of the neuronal membrane and enhance the capacity for neuronal transmission, thus improving memory and learning (Abate et al. 2017). In addition, ω-3 LC-PUFA's modulate the inflammatory processes by functioning in several different ways at the level of the immune system with respect to (1) controlling the expression of cytokines and chemokines, (2) decreasing prostaglandins and eicosanoids, and (3) inducing proresolutive factors, resolvins, and protectins which are involved in inflammation resolution (Abate et al. 2017). Interestingly, Freund Levi et al. (2014) reported that ω-3 LC-PUFAs rich diet significantly improved the levels of DHA in the brain, and indicating that supplementation of ω-3 LC-PUFA's like DHA and EPA might directly impact neuroinflammatory pathways. Thus LC-PUFA's may hold promise for the prevention and treatment of Alzheimer's disease (Morris 2009). Furthermore, studies demonstrated that DHA has effects in reducing Aβ production (Abate et al. 2017). The major mechanism involved in the DHA-induced reduction of Aβ may be due to multiple implications: changes in the structure of lipid raft, alterations in the processing of APP, and induction of anti-amyloidogenic chaperones for APP (Abate et al. 2017). In comparison to the pro-inflammatory effect of other members of the ω-6 PUFA family (Bazan et al. 2011), ω-3 DHA exhibits anti-inflammatory and inflammatory mitigating properties. Supplementation of dietary ω-3 polyunsaturated fatty acids has been reported to influence gene expression that could affect inflammatory processes (Hu et al. 2013). Metabolic trials have shown that diets with a high ratio of saturated to polyunsaturated or monounsaturated fats contribute to poor plasma cholesterol profile, which may play a central role in Alzheimer's disease due to its involvement in both the generation and deposition of Aβ (Morris 2009). The most important genetic risk factor for Alzheimer's disease is the APOEε4, which is predominantly responsible for regulating cholesterol transport in the brain. Diet-induced hypercholesterolemia accelerates Aβ deposition in the brain, whereas a diet rich with unsaturated fat exhibits superior memory and learning (Morris 2009). The primary role of lipids in maintaining neuronal integrity has clear insinuations for dietary impact in Alzheimer's disease prevention and management.

3.2.6 Carbohydrate

It has been indicated that type 2 diabetes mellitus patients are at elevated risk of developing Alzheimer's disease (Williams et al. 2010). The common mechanism has been proposed to be the deficient brain insulin signaling pathway. With increased exposure to glucose, several proteins in neurons are prone to glycation, which is an important contributor to Alzheimer's disease (Hu et al. 2013). Therefore, a high dietary intake of carbohydrates may be detrimental to Alzheimer's. However, sufficient information is not available to establish the association between a high carbohydrate diet and Alzheimer's disease. A prospective study by Luchsinger et al. (2007) indicated that carbohydrate content in food was not associated with a higher risk of the disease.

3.2.7 Vitamins

Vitamins are strong antioxidants. Their potential to maintain healthy cognition and inhibit cognitive decline is heightened by the fact that the brain is highly susceptible to damage from oxidative stress. The brain is a major oxygen metabolizer, accounting for 20% of the body's consumption, and has relatively weak antioxidant protective mechanisms. It also contains a large amount of prooxidants such as polyunsaturated peroxidizable fatty acids, along with high iron levels. Accumulation of free radicals in the brain environment leads to a steady decline in cognitive abilities, intensifying dementia (Abate et al. 2017). Studies have revealed that antioxidants protect the brain from oxidative and inflammatory damages (Morris 2009).

3.2.8 Vitamin B Complex

Because of their involvement with neuronal metabolic pathways, most of the B complex vitamins are directly or indirectly linked with neuronal health. Such vitamin deficiency has been directly associated with the development of specific neurological disorders (Swaminathan and Jicha 2014). Reportedly, vitamin B_6 reduces oxidative stress in Alzheimer's disease (Hashim et al. 2011). Several studies have indicated that elevated levels of serum homocysteine and lower folate and B_{12} levels are linked with increased risk of Alzheimer's disease, as it is observed that level of homocysteine to be significantly higher in Alzheimer's disease patients (Morris et al. 2003; Morris 2012; Nilforooshan et al. 2011). Older individuals with higher homocysteine levels appear to have lower vitamin B status and lower cognition (Abate et al. 2017). B vitamins can contribute to Alzheimer's by hindering oxidative stress and diminishing homocysteine concentrations (Hu et al. 2013). Increased dietary folate

intake has been reported to reduce Alzheimer's disease risk (Corrada et al. 2005). Nonetheless, few studies confirmed that vitamin B did not play a significant role in cognitive or neuropsychological functions (Kwok et al. 2011). The reasons for this inconsistency might be due to differences in study design, dissimilar pathological conditions of the patients, and the varied measurements of the results.

3.2.9 Vitamin C

Vitamin C has been shown to reduce the development of Aβ oligomers and oxidative stress (Murakami et al. 2011). Prospective observational studies have indicated that the combined use of vitamin C and vitamin E for at least 3 years has been associated with a decrease in Alzheimer's disease prevalence and incidence (Zandi et al. 2004). However, there are contradictory studies on the impact of vitamin C supplementation on Alzheimer's disease (Devore et al. 2010). Overall, however, there is ample evidence ensuring healthy levels of vitamin C may have a protective effect against Alzheimer's disease, thus avoiding vitamin C deficiency from a normal healthy diet is likely to be more advantageous than taking supplements (Harrison 2012).

3.2.10 Vitamin E

Vitamin E is a lipid-soluble potent chain-breaking antioxidant that has been found to confer neuroprotection by inhibiting oxidative and scavenging Aβ-associated free radicals (Hu et al. 2013). Vitamin E is perhaps the most extensively investigated vitamin for its role in protecting membrane phospholipids against peroxidation (Gustafson et al. 2015). Supplementation of vitamin E for patients with moderate Alzheimer's disease showed that it delayed the progression of the disease and therefore reduced the likelihood of institutionalization (Zandi et al. 2004). The Chicago Health and Aging Project found higher vitamin E intake from food sources to be correlated with decreased incidences of Alzheimer's disease (Morris et al. 2005) and dementia (Devore et al. 2010). The level of evidence for dietary tocopherols is high, with a low intake showing deleterious impact (Gustafson et al. 2015). The best evidence for antioxidant defense against Alzheimer's disease is a high intake of vitamin E in the diet. Thus, for the dietary management of Alzheimer's disease, vitamin E should be obtained from foods rather than taken as supplements (Barnard et al. 2014).

3.2.11 Vitamin D

Vitamin D may have little role in Aβ mechanisms, and its potential link with Alzheimer's disease may include pathways such as antioxidative, anti-inflammatory, vascular, or metabolic pathways (Hu et al. 2013). Observational studies provide vast evidence that a low concentration of vitamin D is a risk factor for developing Alzheimer's disease (Abate et al. 2017). Furthermore, as Alzheimer's disease patients have a lower levels of serum vitamin D which was associated with cognitive decline (Annweiler et al. 2013). Five months of vitamin D_3 supplementation improved learning and memory (Landel et al. 2016), which has been demonstrated in animal models of Alzheimer's disease. Vitamin D supplementation has also reported inducing expression of immune and inflammatory response proteins, neurotransmitter activity, and endothelial and vascular processes with a substantial decrease in amyloid plaques and astrogliosis. Thus, the guidelines of the Endocrine Society for keeping vitamin D_3 concentrations above 75 nmol/L should be considered to minimize the risk of Alzheimer's disease (Grant 2016).

3.2.12 Vitamin A

Vitamin A and β-carotene could be key molecules for the prevention of Alzheimer's disease and its therapy due to their ability to inhibit both Aβ oligomerization and fibrils formation (Hu et al. 2013). In an in vitro study, Takasaki et al. (2011) demonstrated a possible correlation between vitamin A, β-carotene, and Alzheimer's disease with apropos to anti-Aβ oligomerization. Furthermore, low serum and plasma concentrations of vitamin A and β-carotene have been indicated in Alzheimer's disease patients, whereas a higher β-carotene plasma level was associated with better memory performance (Hu et al. 2013). However, more clinical studies are required to establish the potential benefit of vitamin A supplementation in Alzheimer's disease patients.

3.3 Minerals

Minerals too play an important role in the pathophysiology of Alzheimer's disease when consumed in excess or scanty.

3.3.1 Selenium

Selenium is one of the essential micronutrients in humans and is reported to have antioxidant properties. However, it is toxic at higher doses (Rayman 2000). Selenium plays an important role in antioxidative defense and inflammatory disease (Hu et al. 2013). A significantly lower level of plasma selenium has been reported in Alzheimer's disease patients (Cardoso et al. 2010). Several supplementation trials have demonstrated intervention of selenium improved cognition (Chandra 2001; Cornelli 2010; Scheltens et al. 2010); however, the effect of selenium supplementation in Alzheimer's disease requires validation.

3.3.2 Copper

Copper is essential for life, but it is also toxic when consumed in excess. High circulating serum copper has been reported in Alzheimer's disease patients, which are associated with high risk (Squitti 2012; Ventriglia et al. 2012). Thus, copper dysfunction is thought to play a role in Alzheimer's pathology (Hu et al. 2013). Even though a prospective, randomized supplementary trial showed that oral copper supplementation did not affect the progression of Alzheimer's disease(Kessler et al. 2008), some studies have indicated that excessive intake of iron and copper may contribute to cognitive problems (Brewer 2009, 2012; Stankiewicz and Brass 2009). Individuals with a high dietary intake of saturated fat in conjunction with high copper were reported to have cognitive decline (Loef and Walach 2012).

3.3.3 Iron

Iron facilitates oxidative stress in Alzheimer's disease, and disparity in iron homeostasis may be a potential risk for the disease (Hu et al. 2013). Irrespective of baseline iron status, its supplementation has been reported to improve attention and concentration in older children and adults (Falkingham et al. 2010). However, excessive dietary intake of iron, along with high saturated fat, should be avoided in the elderly (Loef and Walach 2012).

3.3.4 Zinc

In Alzheimer's disease patients, cognition loss has been associated with zinc deficiency (Hu et al. 2013). Animal supplementation trial revealed intervention of zinc

had reduced both Aβ and tau pathologies in Alzheimer's disease models (Corona et al. 2010). However, limited data is available for clinical studies.

3.3.5 Aluminum

Like many other minerals Aluminum's role in Alzheimer's disease also remains controversial. Some researchers have reported aluminum's as neurotoxic when present in large amounts in the body (Barnard et al. 2014) but aluminum has been found in the brains of individuals with Alzheimer's disease (Crapper et al. 1976). Prevalence of Alzheimer's was also found to be higher in areas of the United Kingdom and France where water from tap contained higher aluminum concentrations (Barnard et al. 2014). However, due to limited data, its role in Alzheimer's disease risk cannot be ascertained.

3.3.6 Polyphenols

Polyphenols are phytonutrients present in many fruits and vegetables. The advantageous role of dietary polyphenols has been proposed as a potential functional food to prevent memory weakening. Their effects may be not only due to their properties of antioxidant and anti-inflammation but also due to their ability in modulating enzyme activity and regulating intracellular signaling pathways and gene expression (Choi et al. 2012; Obrenovich et al. 2010). Polyphenols, particularly flavonoids, has the potential to modulate those neuronal signaling cascades, improving memory and learning (Abate et al. 2017). Polyphenol supplementation can play a role in the prevention by inhibiting Aβ oligomer formation as well as destabilizing preformed Aβoligomers (Ono et al. 2003) and thereby attenuating cognitive deterioration (Hartman et al. 2006; Ho et al. 2009). The phenolic curcumin also has a potential role in the prevention and treatment of Alzheimer's disease. Curcumin, a bioactive yellow-pigmented component of *Curcuma longa*, (commonly called turmeric in India) has potent anti-inflammatory, antioxidant, and anticancer properties (Abate et al. 2017). An animal study showed that curcumin reduced pro-inflammatory cytokines, oxidative damage, Aβ production, and ameliorating cognitive deficits (Frautschy et al. 2001). In addition, it has been reported that curcumin decreased the oxidation of lipoprotein and the formation of free radicals in Alzheimer's disease and in other neurodegenerative disorders (Kim et al. 2005). However, further studies are necessary to demonstrate the effects of polyphenols in delaying or prevention of Alzheimer's disease.

While there are many new medical treatment approaches for Alzheimer's disease, the most important advantages of these nutritional interventions are their safety, especially when in the form of diets, utility, low cost in comparison to supplements, and suitability for prevention.

3.4 Role of Diet in Prevention and Management of Alzheimer's Disease

Nutrients are not consumed individually in isolation. In the case of diet, different nutrients are consumed in combination. Thus, recognizing the role of diet in the prevention and management of Alzheimer's disease is more important. Understanding dietary patterns rather than individual nutrients or food groups, might help in better to understanding of the role of diet in amelioration of diseases. This section will discuss the role of different food components and diet patterns for prevention or slowing Alzheimer's disease.

3.4.1 Role of Food Components in the Prevention and Management of Alzheimer's Disease

3.4.1.1 Fish

Epidemiological studies indicate that fish consumption has a protective effect against cognitive decline, which can reduce the risk of dementia and Alzheimer's disease (Scarmeas et al. 2018; Huang et al. 2005; Morris et al. 2005). The positive factor is thought to be associated with ω-3 LCPUFA's like EPA and DHA (Hu et al. 2013). Several studies indicated that higher blood ω-3 level is associated with reduced cognitive decline.

3.4.1.2 Fruits and Vegetables

Frequent consumption of fruits and vegetables in medium or great proportion might reduce the risk of Alzheimer's disease and dementia (Scarmeas et al. 2018; Barberger-Gateau et al. 2007; Hughes et al. 2010). Fruits and vegetables are enriched with micronutrients like antioxidants, bioactive compounds such as vitamins, minerals, and polyphenols which are important to the brain and also have low or no saturated or trans fats (Morris et al. 2006), which might be linked with their higher intake and lower Alzheimer's disease incidence. Slower rates of cognitive decline and decreased risk of dementia have been detected in individuals who consume more vegetables and fruits (Scarmeas et al. 2018). Benefits were reported to be greater on higher consumption of vegetables over fruits (Morris et al. 2006). Many foods of plant sources are rich in several B vitamins. Vitamin B_{12}, folate and vitamin B_6 act as cofactors for the methylation of homocysteine, which is reported to be associated with a higher risk of cognitive impairment at elevated serum homocysteine levels (Morris 2012; Smith et al. 2010; Barnard et al. 2014).

3.4.1.3 Dairy and Dairy Products

A lower milk or dairy product consumption has been identified to be associated with reduced cognitive function. Dairy consisting of vitamin D, phosphorus, and magnesium may reduce the risk of cognitive impairment by decreasing vascular alterations and structural changes in the brain that occur with cognitive decline (Hu et al. 2013). In respect to fat intake from milk products, it has been found that moderate intake of unsaturated fats decreased the risk of Alzheimer's, while saturated fat was associated with an increased risk of the disease at midlife (Laitinen et al. 2006). Lower incidence of vascular dementia was reported in individuals aged 30 years or older who consume milk every day in comparison to those who consume milk less than four times a week (Yamada et al. 2003). Another study by Ozawa et al. (2014) found that the incidence of Alzheimer's disease and dementia was reduced in participants aged 60 years or older who reported high consumption of milk and dairy products.

3.4.1.4 Tea and Coffee

Tea and coffee are the most common sources of not only caffeine but also other biologically active compounds, including catechins, L-theanine, polyphenols, and other compounds (Wang and Ho 2009; Song et al. 2012). Several neuropharmacological activities have been suggested for tea and coffee ingredients, including antioxidant, anti-inflammatory, and neuroprotective effects (Islam et al. 2018; Song et al. 2012). Therefore, tea and coffee were relevant contributors to Alzheimer's disease, which were associated with decreased risk. Studies reported that coffee consumption is negatively associated with the risk of Alzheimer's disease (Scarmeas et al. 2018), whereas drinking tea was associated with lower risks of cognitive impairment and decline (Feng et al. 2010; Ng et al. 2008). But it has been found to be beneficial with mild to moderate consumption only (about three cups per day) (Scarmeas et al. 2018). In general, consumption of tea or coffee may have a protective impact on cognitive decline, although few studies report no association. Therefore, further prospective studies for evaluating the association of tea and coffee with Alzheimer's disease are strongly required.

3.4.1.5 Alcohol

Epidemiological evidence indicates that light-to-moderate consumption of alcoholic beverages was associated with a reduced risk of Alzheimer's disease, particularly among APOEε4 non-carriers (Panza et al. 2009). Resveratrol and other polyphenols in red wine have been found to reduce plaque formation and to protect against neurotoxicity caused by Aβ (Ho et al. 2009, 2013). Moderate consumption of beer was thought to be a protective factor for Alzheimer's disease due to the toits content of bioavailable silicon (González-Muñoz et al. 2008). Therefore, alcohol intake was

proposed to have a beneficial effect on Alzheimer's disease. However, heavy drinking (>2 drinks), in conjunction with heavy smoking and APOEε4, was associated with poor cognitive outcomes and an earlier onset of Alzheimer's disease (Harwood et al. 2010).

3.4.2 Role of Dietary Pattern and Diet in Prevention and Management of Alzheimer's Disease

A dietary pattern is the consumption of a combination of several food components that exert an overall effect of diet on human health. The majority of epidemiological studies of diet and Alzheimer's disease have focused on detecting associations between adherence to a specific diet, dietary patterns and the risk of reducing Alzheimer's disease. This section has discussed the effect of healthy or unhealthy dietary patterns and diets such as the Mediterranean and DASH diet on Alzheimer's disease.

3.4.2.1 Healthy Dietary Pattern

A healthy dietary pattern is characterized with the consumption of whole grains, breakfast cereal, fruits, vegetables, fresh dairy products, fish, vegetable fat, nuts, and tea (Kesse-Guyot et al. 2012). Reports have shown that the highest adherence to a healthy diet had a better cognitive performance (Kesse-Guyot et al. 2012; Samieri et al. 2008) and was associated with a decreased risk of Alzheimer's disease (Eskelinen et al. 2009).

3.4.2.2 Western Dietary Pattern

A Western dietary pattern is characterized by higher consumption of red and processed meats, refined grains, sweets, high-fat dairy products, butter, potatoes, high-fat gravy, and low intakes of fruits and vegetables (Li et al. 2017). A high-fat Western dietary pattern may contribute to the development of Alzheimer's disease by impacting Aβ deposition and inducing oxidative stress (Hu et al. 2013).

3.4.2.3 Mediterranean Diet

Mediterranean diet is the most extensively studied dietary pattern. The Mediterranean diet is a typical diet consumed in the Mediterranean region, which is plant focused and is characterized by a high intake of vegetables, fruits, cereals, legumes, bread, potatoes; high intake of MUFA, PUFA with nuts and olive oil, whereas low

intake of saturated fatty acids; a moderately high intake of fish; a low intake of red meat and poultry; a low-to-moderate intake of milk products; and a regular moderate intake of alcohol. Several recent systematic studies, reviews, and meta-analysis showed that higher adherence to a Mediterranean diet was favorably associated with slower cognitive decline and reduced risk of progression from mild cognitive impairment to Alzheimer's disease, and also reduced mortality in Alzheimer's disease patients (Tangney et al. 2014; Scarmeas et al. 2006; Mosconi and McHugh 2015). Superior adherence to the Mediterranean diet has been reported to not only reduce the risk of Alzheimer's disease but also for stroke, depression, and other neurodegenerative diseases (Sofi et al. 2010; Psaltopoulou et al. 2013). The body of evidence confirmed that a Mediterranean diet which includes a higher intake of MUFA, ω-3 polyunsaturated fatty acids, high levels of antioxidants from fruit and vegetables, fish, and low-to-moderate alcohol consumption might be protective against Alzheimer's disease (Panza et al. 2009, 2014; Barberger-Gateau et al. 2007; Huang et al. 2005; Morris et al. 2003). The role of nutrients in these foods in Alzheimer's disease is explained in the previous section.

3.4.2.4 DASH Diet

The Dietary Approaches to Stop Hypertension, commonly known as the DASH diet, is characterized by high consumption of whole grains, fruits and vegetables, fish, poultry, low-fat milk products, and nuts; while limiting the intake of sodium, red meat, sweets, desserts, and sweetened beverages (Hankey 2012; Panza et al. 2014). DASH diet is generally recommended for the therapeutic requirement of people suffering from hypertension. But since hypertension is associated with increased risk for Alzheimer's disease, it is plausible that the DASH diet could reduce the risk of Alzheimer's disease. Studies reported a higher correlation between the DASH diet with greater cognitive improvements (Smith et al. 2010) and lower dementia incidence risk (Norton et al. 2012).

Epidemiological studies indicated a beneficial effect of adherence to certain healthy dietary patterns such as the Mediterranean diet or DASH diet on slower cognitive decline and lower risk of developing dementia, including Alzheimer's disease (Scarmeas et al. 2006; Tangney et al. 2014; Smith et al. 2010). This evidence showed that diets and dietary patterns have a significant association with the risk for Alzheimer's disease. Therefore, a healthy diet should be one of the most important interventions for the prevention or management of Alzheimer's disease.

3.5 General Dietary and Lifestyle Approaches for Prevention and Management of Alzheimer's Disease

The role and importance of different nutrients, food components, diet, and dietary patterns have been explained in the previous sections. Based on all this information, in this section, a few general dietary and lifestyle approaches are discussed which can be taken into consideration for the prevention and management of Alzheimer's disease. Although it must be noted that the conditions or degree of the disease might vary from individual to individual; and therefore, one must be careful while making any changes in the diet or before taking any supplements. Any change must be done under the direction of a physician and dietitian after taking suggested biochemical or clinical tests to understand the changes in different biochemical parameters and their correlation with comorbidities.

1. Overweight or obesity is associated with a decline in cognitive ability, brain atrophy, white matter changes, and disturbances of blood–brain barrier integrity. It is also associated with a higher risk of Alzheimer's disease and other dementias in late life, although conflicting results have also been reported (Gustafson et al. 2015). However, maintaining a healthy weight or BMI is always advisable for all individuals across all populations.
2. Epidemiological studies have revealed a negative relationship between caloric intake and the risk of Alzheimer's disease (Luchsinger et al. 2002; Mattson et al. 2002). Animal studies confirmed that restricting caloric intake about 30–40% from normal levels can markedly slow the pathogenesis of Alzheimer's disease (Halagappa et al. 2007). Thus, a calorific restriction may reduce the risk of Alzheimer's disease occurrence or progression.
3. The contribution of different food processing and cooking methods is often poorly considered. Food processing, cooking, and storing methods can often contribute not only to the degradation of heat-labile micronutrients, such as folates, vitamin C, and thiamine but also can lead to the formation of toxins. High temperatures, mostly for long duration while food processing and cooking, bring about different biochemical reactions and the formation of a toxic secondary substance called Advanced Glycation End-products (AGEs). AGEs are also continuously formed in the body as a part of normal metabolism under hyperglycemic and oxidative stress conditions. Receptors of AGE (RAGE) were found to act as a cell surface receptor for Aβ and promote the circulation of Aβ across the brain. Also, RAGE plays a role in the pathogenesis of many chronic diseases, such as diabetes, hypertension, cardiovascular diseases, which are identified as risk factors for Alzheimer's disease, indicating that it might be ultimately leading to Alzheimer's disease etiology (Abate et al. 2017). Therefore, it is advised to cook food at a low temperature, preferably by boiling, steaming, or poaching.
4. Intake of food rich in saturated or trans fats should be minimized. Saturated fat is primarily found in dairy products, meats, and certain fats and oils (lard, butter,

Table 3.1 List of nutrients showing protective effect in Alzheimer's disease and their dietary sources

Nutrients	Dietary sources
MUFA	Olive oil, groundnut oil, canola oil, sunflower oil, sesame oil; almonds, cashews, pistachios, and hazelnuts
ω-3 PUFA	Fish like salmon, mackerel, sardines, herring; chia seeds, flax seeds, soybean, and walnut
Vitamin E	Almonds, soybean, safflower, sunflower seeds, vegetable oils, margarine, fatty fish (e.g., sardines, salmon, herring, swordfish, and trout), whole grain cereals, egg yolk, green leafy vegetables like spinach; mangoes, papayas, avocadoes, apples, tomatoes, and red capsicum
Vitamin D	Fish (especially fatty fish) and fish liver, full-fat dairy products (or fortified low-fat), egg yolk, meat, and meat products
Vitamin A	Yellow or orange vegetables (sweet potatoes, carrots, and pumpkins), dark leafy vegetables (spinach, broccoli, and endives), and yellow or orange fruits (apricots, peaches, mangoes, and melons)
Vitamin C	Fruits like berries, citrus fruits, kiwis, litchi, and papayas; vegetables like Brussels sprouts, cauliflowers, cabbages, sweet peppers, and tomatoes
Vitamin B_6	Fish, meat, chicken liver, drumstick leaves, sunflower seeds, safflower seeds, walnut, soybean, tofu, carrot, egg, and spinach
Folate	Dark green leafy vegetables like spinach, lettuce, kale, broccoli, cauliflower, beets, asparagus, beans, peas, capsicum, cantaloupe, avocado, lentils, rajma, and citrus fruits
Vitamin B_{12}	Meat, fish, poultry, milk, *spirulina*
Polyphenols	Fruits (mainly citrus fruits, bananas, and berries), vegetables (parsley and onions), tea (black and brewed), spice like turmeric

margarine, coconut, and palm oils). Trans fats, often labeled as "partially hydrogenated oils," are found in many snacks and fried foods, which are listed on the nutrition label of the food package.

5. More of MUFA and ω-3 PUFA should be included in the diet. Dietary sources of MUFA and ω-3 PUFA are mentioned in Table 3.1.
6. The inclusion of vegetables and fruits should be given more importance as they are rich in nutrients like antioxidants, vitamins, and polyphenols which play an important role in Alzheimer's and have shown to prevent or slow the development of Alzheimer's disease.
7. Nutrients such as vitamins, antioxidants, polyphenols from different food sources should be included in the diet as they have a protective role in Alzheimer's disease. Studies have also proved that nutrients like vitamins E should come from foods sources that are more effective than supplements. It must be noted that vitamin B_{12} is found naturally only in animal foods. Thus, vegetarians are often at risk of vitamin B_{12} deficiency (Madhubalaji et al. 2019), and hence they must pay more attention to prevent such deficiencies. Different nutrients which play a role in Alzheimer's disease and their sources are mentioned in Table 3.1.

8. A lower incidence of cognitive impairment and vascular dementia has been reported in individuals who consumed milk every day. Hence, it is advised to drink a glass of milk every day to prevent the risk of Alzheimer's disease.
9. Studies have shown that brisk walking for 40 min three times per week reduces brain degeneration and enhances memory and other cognitive functions (Hotting and Roder 2013). Individuals exercising regularly are at low risk of developing Alzheimer's disease and also exercising in midlife was found to prevent developing dementia at old age (Barnard et al. 2014). Furthermore, low physical activity has long been associated with the risk of Alzheimer's disease (Mosconi and McHugh 2015; Barnard et al. 2014; Sindi et al. 2015). Thus, moderate regular exercise of about 40 min each day for at least three times a week is highly recommended.
10. Several studies have suggested that individuals who are more mentally active have reduced risk for cognitive deficits later in life (Curlik and Shors 2013; Hotting and Roder 2013; Barnard et al. 2014). Therefore, regular mental activity that promotes new learning should be followed for about 30 min per day, four to five times per week.
11. Cognitive impairment in older adults has been associated with sleep disturbances (Blackwell et al. 2011; Lim et al. 2013). Thus maintaining a sleep routine of approximately 7–8 h for most individuals is advised.
12. Consumption of alcohol has been reported to reduce the risk of Alzheimer's disease, but only when taken in a low-to-moderate level. However, one must remember that indulging in heavy drinking and smoking will lead to cognitive decline and early onset of Alzheimer's disease.

3.6 Perspective

A growing number of epidemiological studies have indicated that nutrition and diet play a major role in the prevention, development, and management of Alzheimer's disease. It also suggests that nutrition is an important modifiable risk factor for cognitive dysfunction and Alzheimer's. The existing evidence suggests that certain nutrients like unsaturated fatty acids, particularly MUFA, ω-3 PUFA; vitamins, particularly vitamin E, vitamin D, vitamin C, folate; polyphenols have a potential role in improving cognitive function or in Alzheimer's disease. Superior adherence to a healthy diet which includes higher consumption of more vegetables and fruits, fish, whole grains, unsaturated fats, and a lower intake of saturated fats, processed foods like in Mediterranean diet and DASH diet have shown beneficial effects for Alzheimer's disease prevention and management. However, sufficient information is not available to recommend daily allowance for specific nutrients required for individuals with Alzheimer's disease or its prevention. Hence, more dose-dependent studies are required to establish the same. There are also some contradictory studies available for the role of minerals such as selenium, copper, aluminum, iron.

Therefore, evaluation and validity of the interventional trials must be done, which also create an opportunity for more research in this field.

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Chapter 4
Qualitative and Analytical Treatment of Nonlinear Dynamical Systems in Neurological Diseases

Venkata Sundaranand Putcha and Sudeep Katakol

Abstract The study of nervous system and neurological diseases attracted the attention of scientists working in medical sciences and quick progress in present times than that of previous, only because of simulated models, computational power, and advances in experimental methods. There is a considerable increase in the neurological disorders (Alzheimer's disease, Parkinson's disease, headaches, stroke, amyotrophic lateral sclerosis epilepsy, and seizures, etc.) cases over the past quarter century. Neurological disorders (NDs) are the leading cause of death and disability in the world today. In general combination of experimental and theoretical (mathematical) approaches are used to investigate the complex and dynamic interactions within a biological system or process in systems biology. In systems biology, a mathematical model is used to study the biological, chemical, and physical processes within living organisms by integrating genetics, signal transduction, biochemistry, and cell biology.

These mathematical models are of immense use in understanding the mechanisms behind the gene regulation and also in the identification of pathways that reveal the root causes for diseases. It is always easy to solve a linear dynamic model by using high-performance computing (HPC) cluster but it is still hard to construct solutions of nonlinear dynamic model. Most of the time it is much more difficult to find an analytical solution than a numerical solution of a nonlinear dynamic model even by utilizing the high-performance computing and some state-of-the-art symbolic computation software such as MATLAB, Mathematica, Maple, Axiom, Scilab, FriCAS, and so on. This chapter deals with analytic, qualitative, qualitative, and numerical treatment of nonlinear dynamical systems. This chapter present linearization, various notions qualitative properties, analytical methods, and numerical methods to handle

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nonlinear dynamical systems. The presented results and methods are illustrated and explained by numerical examples.

Keywords Nonlinear differential equation · Stability · Qualitative properties · Neurological diseases and numerical solutions

4.1 Introduction

The cases of neurological disorders in recent times are alarming in countries with an increasing percentage of the aged population since average life span increased because of the advances of medical care. It is always a challenge to understand how sensory information is fed to organism and how the brain integrates and uses the information received by organisms and how the output of the processed information contributes in taking meaningful decisions and behaviors by the organism to permit it to function and blossom in its ecosystem. This has been motivating scientists all over the world to construct mathematical models which explain observed evolution phenomena to understand the cumbersome dynamics of the brain function.

Neurological modeling does not deal directly with neural objects and neural functions. Neurological modeling deals with the mathematical objects, functions, and operations which are expressed as analogues of neural processes. These neurological mathematical models do not contain all information about brain and its functions, but only what we think are the most relevant for the problem of consideration. Neurological modeling helps to understand the rationale of our thinking about neurological functions and to prevent us from making scientific fallacies that may not be true or only true under certain constraints. We need a *model* that describes the dynamical behavior of the latent phenomena which can be described by ordinary differential equations (partial differential equations) or difference equations since most processes are time continuous, but some are inherently time discrete. A model is envisaged initially with a set of experimental observations or measurements. The aim of this model is to provide a set of relationships, equations or rules that are framed to describe, verify, and validate the initial experimental observations and also produces the desired characteristics, outputs or measurements of experiments because of the correlation between the data and the underlying dynamic molecular, cellular, and systems mechanisms embedded in the model. In general, a neurological system *interacts with its environment* through ***inputs***, which *affect* the system behavior and ***outputs***, which *give information* about the system behavior. The basic purpose of a model is for estimation and prediction. The accuracy of a model depends on the stability of the system. Stability can be achieved by controlling the system dynamic of the constructed model. This can be measured by qualitative properties such as controllability, observability, reachability, and realizability. Therefore, it is mandatory to study the qualitative properties of dynamical systems so as to achieve model precession by adopting various analytical and numerical schemes for solving the models.

Differential equations are necessary tools in scientific modeling of physical, biological and engineering problems where change happens continuously. The development of differential equations is classified into two streams.

One is referred to as the quantitative theory. In this the aim is to construct exact solutions (or closed form solutions) or approximate solutions. In many practical scenarios it is not possible to construct closed form solutions, one has to go for approximate solution. The other called qualitative theory is an endeavor to acquire information about the behavior of class of differential equations without finding an exact or approximate solution.

Many of the real-world problems are represented by the systems of nonlinear differential equations in an abstract form and mathematicians, engineers, physicists, and biologists developed interest in systems. Therefore, it is of great interest to construct mathematical models on neurological diseases (Achdou et al. 2013; Guckenheimer and Holmes 2002; Banwarth-Kuhn and Sindi 2020; Tewari et al. 2016; Bakshi et al. 2019) and find their approximate analytical solutions. In general construction of analytic approximations of nonlinear problems with strong nonlinearity is not so easy and solutions are constructed by a technique corresponding to the type of nonlinearity. The fundamental concepts of dynamical systems required for researchers working in Neurological Sciences are presented in Wilson (1999).

There are many numerical methods to solve nonlinear system of differential equations, a functional form of solution of differential equation which is essential to study the system behavior can be constructed by homotopy approach. It is always difficult to obtain approximate analytical solutions of system of nonlinear differential equations with strong nonlinearity. In the literature, solution expressions of a nonlinear problem are determined by the type of nonlinear equations and the used analytic technique, but the physical parameters influence the region of convergence of the solution series. A powerful analytic method to handle nonlinear problems was proposed by Liao in his Ph.D. thesis (Liao 1992). Liao clearly explained the HAM in (Liao 2003). In recent years, many authors Sami Bataineh et al. (2008), Fernt'andez (2009), Faghidian et al. (2011), Liao (2005), Zoua et al. (2008), Rafei et al. (2007), and Liu (2011) employed this method to solve many types of nonlinear problems arise in economics, science, and engineering. Some interesting results on qualitative properties of dynamical systems were established by Anand (2009), Putcha (1995), Rompicharla et al. (2019, 2020), Murty et al. (2009, 2013). Readers who would like to construct models by considering chaos can refer Hirsch et al. (2004) for understanding chaos and dynamical systems

4.2 Mathematical Methods

This section presents basic concepts of differential equations, system of differential equations, handling nonlinearity through linearization, qualitative treatments like various stabilities, and Lyapunov functions.

4.2.1 Basic Concepts

One can refer Arnold (1983), Boyce and DiPrima (1997), Coddington (1989) and Coddington and Levinson (1955) for basic concepts for understanding ordinary differential equations. A normed linear space S in which, for each vector X there corresponds a real number denoted by $\|X\|$ and has the following properties:

(i) $\|X\| \geq 0$ and $\|X\| = 0$ if and only if $X = 0$
(ii) $\|X + Y\| \leq \|X\| + \|Y\| \quad \forall\ X, Y \in S$
(iii) $\|\alpha X\| = |\alpha|\|X\|$ for any scalar α.

Let S be a normed linear space with norm denoted by $\|\cdot\|$. A sequence of elements $\{y_n\}$ of S is a Cauchy sequence if for every $\varepsilon > 0$, there exist an integer N such that $\|y_m - y_n\| < \varepsilon \quad \forall\ m, n \geq N$. S is a complete normed linear space if every Cauchy sequence in S converged to a limit point in S, i.e. if to every Cauchy sequence there corresponds a unique number $y \in S$ such that $\|y_n - y\| \to 0$ as $n \to 0$. Let $T : S \to S$ we say that T is a contraction mapping, if there exists a number $\alpha(0 < \alpha < 1)$ such that $\forall\ x, y \in S$, $\|T_X - T_Y\| < \alpha\|X - Y\|$. A Banach space is a complete vector space B with a norm. Let T be a contraction mapping from a closed subset S of a Banach space E into S. Then there exists a unique $z \in S$ such that $T(z) = z$. (This theorem is called Banach fixed point or contraction mapping theorem or contraction mapping principle). Let f be function defined for (t, x) in a set S. A function f is said to satisfy Lipschitz condition on S, if there exists a real constant $K > 0$ such that $|f(t, x_1) - f(t, x_2)| \leq K|x_1 - x_2|$ for all (t, x_1), (t, x_2) in S. The constant K for which the above inequality holds, is called the Lipschitz constant of f.

Most of the problems in biological sciences are described a systems of ordinary differential equations of first order. Initial value problem (IVP) is a differential equation or a partial differential equation with the value of the solution specified at one point. Boundary value problem (BVP) is a differential equation or a partial differential equation with the value of the solution specified at more than one point. If the solution is specified at two points, it is called a two-point BVP and at n points is called n point BVP.

A general form of IVP associated with nonlinear ordinary differential equations is given by

$$\frac{dx}{dt} = \dot{x} = f(x), \quad x \in R, \quad x(0) = x_0 \tag{4.1}$$

where R is the set of all real numbers.

$$\frac{dX}{dt} = \dot{X} = f(X); \quad X \in R^n; \quad x(0) = x_0 \tag{4.2}$$

where x_0 is an initial condition, and

$$f(X) = \begin{pmatrix} f_1(x_1, \ldots, x_n) \\ . \\ . \\ . \\ f_n(x_1, \ldots, x_n) \end{pmatrix}, \quad X = \begin{pmatrix} x_1 \\ . \\ . \\ . \\ x_n \end{pmatrix}. \tag{4.3}$$

Equation (4.3) is called an IVP associated System of differential equations. The time-dependent quantities $x_j = x_j(t)$ are called *state variables* and they evolve in an n-dimensional *state space*, which are in Euclidean space R^n. The functions $f_j(x)$ depend upon *parameters* $u = (u_1, \ldots, u_k)$ in which case we may write $f(x, u)$ or $f_u(x)$, to indicate the different status of x and u. The parameters are taken as constant while solving (4.2) since they may change on their own and change on a slower scale than x. The function $f(x)$ (or $f(x, u)$ or $f_u(x)$) defines vector field on R^n.

A general nonlinear scalar system is represented by $\dot{x} = f(x, t)$. The solution of this equation is given by

$$X(t, X_0) = \varphi_t(X_0) \quad \text{or} \quad \varphi_t : R^n \to R^n, \tag{4.4}$$

at least for short times t, provided that the functions $f_j(x)$ (or, collectively, $f(x)$) are smooth. This follows from assembling the unique solutions of (4.2) for each initial condition $X(0) = X_0$, which exist for finite time intervals around $t = 0$. We are interested in finding solutions corresponding to different of initial conditions. Depending upon the nonlinear function $f(x, t)$, sometimes it is possible to find solutions expressed in terms of known popular functions. Points of equilibria can be found by solving $f(x, t) = 0$.

4.2.2 Linearization and Solving Linear Systems of ODEs

Suppose that $X = X^e$ is an equilibrium or fixed point, i.e., $f(X^e) = 0 \left(\Leftrightarrow f_j\left(x_1^e, \ldots, x_n^e\right) = 0, \ 1 \le j \le n\right)$. Therefore, if $X_0 = X^e$, we assume that $X(t) = X^e$. Let $X(t) = X^e + \xi(t)$, where $\xi(t) = (\xi_1, \ldots, \xi_n)$ is a small perturbation: $|\xi(t)| \ll 1$ By substituting into (4.2) and expanding f in a vector-valued Taylor series expansion of function of two variables to obtain

$$\dot{X}^e + \dot{\xi} = f(X^e + \xi) = f(X^e) + Df(X^e)\xi + O\left(|\xi|^2\right). \tag{4.5}$$

In (4.5) $Df(X^e)$ denotes the $n \times n$ Jacobian matrix of partial derivatives $\left[\frac{\partial f_i}{\partial x_j}\right]$ evaluated at the fixed point X^e, and the "Big Oh" notation $O(|\xi|^2)$ characterizes the magnitude of quadratic and higher order terms in the components $\xi_1, \ldots, \xi_n$. Specifically, $g(\xi) = O(|\xi|^p)$ means that, for each component g_i

$$\lim_{|\xi|\to 0} \frac{g_i(\xi)}{|\xi|^p} \leq k < \infty, \quad \text{where} \quad |\,\xi\,| = \sqrt{\sum_{i=1}^{n} {\xi_i}^2} \tag{4.6}$$

More generally, $g(x) = O(|\,h(x)|\,)$ as $x \to x_0$ means that the quotient $g(x)/h(x)$ is bounded as $x \to x_0$. (In some of the problems Sin x can be approximated by x or $(x - x^3/3)$, i.e., $\sin x \sim x$ or $\sin x \sim (x - x^3/3)$). For small value of $|\xi|$, the contribution of first-order term $f(X^e)\xi$ in Eq. (4.5) much more to the R.H.S when compared to that of the higher powers of ξ. Since $\dot{X}^e$ and $f(X^e)$ vanish and small term $O(|\xi|^2)$, can be ignored and we obtain the linear system

$$\dot{\xi} = Df(X^e)\xi \tag{4.7}$$

The constant-coefficient linear system of ordinary differential equations (4.7) is called the linearization of (4.2) at X^e. The general solution of any linear system of the form

$$\dot{y} = By \tag{4.8}$$

where B is an $n \times n$ matrix and $y = (y_1, \ldots, y_n)$ is an n-vector, can be obtained by the eigenvalues and eigenvectors of B. If V_i, $i = 1, 2, \ldots, n$ are n linearly independent eigenvectors of the matrix B corresponding to the eigenvalues, λ_i, then an $n \times n$ fundamental solution matrix $X^e(t)$ can be constructed by writing $V_i e^{\lambda_i t}$ as its columns. If complex eigenvalues, $\lambda_\pm = \alpha \pm i\beta$ occur, then X^e can still be constructed by taking adjacent columns as $e^{\alpha t}[u\,\mathrm{Cos}\,(\beta t) - w\,\mathrm{Sin}\,(\beta t)]$ and $e^{\alpha t}[w\,\mathrm{Cos}\,(\beta t) + u\,\mathrm{Sin}\,(\beta t)]$, where $v = u \pm iw$ is the complex conjugate pair of eigenvectors belonging to $\lambda_\pm$. The solution of (4.8) with initial condition $y(0) = y_0$ is given by

$$y(t) = \phi(t)y_0, \quad \text{where} \quad \phi(t) = X^e(t)[X^e(0)]^{-1} \tag{4.9}$$

Whatever may be the order of the columns of $X^e(t)$.

This fundamental solution matrix $\phi^e(t)$ which satisfies $\phi(0) = I$, is called the flow map for (4.8). It is an explicit expression that gives the forward evolution of vector field. Fundamental solution matrix defines a flow map that propagates solutions in the state space R^n.

4.2.3 Stability of Solutions of ODEs

In this section definitions of Lyapunov function and qualitative properties of solution of ODEs along with properties of Lyapunov function are presented. This section also present basic theorems on application of Lyapunov functions, procedure for the construction of Lyapunov functions and characterization of various stabilities by

using Lyapunov functions. Stabilities of pathogen models Brown (1984) and prey predator models Srinivas (1989) were studied. Putcha (2014) studied qualitative properties of repetitive discrete dynamical systems by using Linear Matric Inequality (LMI) approach.

Definition 2.1 (Lyapunov Stability) X^e is a stable fixed point of (4.2) if for every neighborhood U containing X^e there is a neighborhood $V \subseteq U$ such that every solution $X(t)$ of (4.2) starting in $V(x(0) \in V)$ remains in U for all $t \geq 0$. If X^e is not stable, then it is unstable.

Definition 2.2 (Asymptotic Stability) X^e is asymptotically stable if it is stable and additionally V can be chosen such that $|X(t) - X^e| \to 0$ as $t \to \infty$ for all $X(0) \in V$.

A fixed point is called neutrally stable if it is Lyapunov stable but not asymptotically stable.

Proposition 2.1 If X^e is a fixed point of $\dot{X} = f(X)$ and all the eigenvalues of $Df(X^e)$ have strictly negative real parts, then X^e is asymptotically stable. If at least one eigenvalue has strictly positive real part, then X^e is unstable.

Consider a system of differential equations

$$\dot{X} = f(t, X) \tag{4.10}$$

where X is an n-vector and $f(t, X)$ is an n-vector function which is defined on a region $\Omega \subset I \times R^n$ (where I is an interval, a subset of R) and continuous in (t_0, X_0) so that for each (t_0, X_0) there is a solution $X(t, t_0, X_0)$ satisfying

$$X(t_0, t_0, X_0 = X_0) \tag{4.11}$$

and

$$X(t, t_0, X_0) = X \tag{4.12}$$

Let f be smooth enough to assure the existence of a solution, i.e. f is continuous and satisfies Lipschitz. Smoothness of f guarantees the existence of a unique solution for Eq. (4.10). Let this be Eq. (4.12). Suppose that C is a class of solutions of Eq. (4.10) and $X_0(t)$ is an element of C, then by setting $X = Y + X_0(t)$ together with the continuity of $f(t, X)$, Eq. (4.2) becomes

$$\dot{Y} = f(t, Y + X_0(t)) - f(t, X_0(t)) \tag{4.13}$$

Let $G(t, Y) = f(t, Y + X_0(t)) - f(t, X_0(t))$ then $G(t, 0) \equiv 0$. The zero solution $Y(t) \equiv 0$ of Eq. (4.13) corresponds to $X_0(t)$.

One can easily observe that exploring the stability, boundedness and periodicity of zero solution of equation (4.13) is equivalent to exploring the stability, boundedness and periodicity of $X_0(t)$ of equation (4.10). Therefore, we can assume that

$f(t, 0) \equiv 0$ and the following definitions will hold for solutions $X_0(t) \equiv 0$ of the equation (4.10).

Definition 2.3 The zero solution of Eq. (4.10) is stable, if given $\varepsilon > 0$ and $t_0 \in I$, there exists a $\delta(t_0, \epsilon) > 0$, such that whenever $|X_0| < \delta(t_0, \varepsilon)$, $|X(t, t_0, X_0)| < \varepsilon \; \forall \;\; t \geq t_0$.

Definition 2.4 The zero solution of Eq. (4.10) is uniformly stable, if it is stable and the δ in the definition (4.10) above is independent of t_0.

Definition 2.5 The zero solution of Eq. (4.10) is asymptotically stable, if itis stable and in addition, there exists an $\alpha \in [t_1, t_2], \quad t_0 \leq t_1 \leq t_2 \leq t$ such that if $|X_0| < \delta(t_0, \alpha)$, we have $X(t, t_0, X_0) \to 0$ as $t \to \infty$.

Definition 2.6 The zero solution of Eq. (4.10) is uniformly asymptotically stable, if it is uniformly stable and if there is a $\delta > 0$ and $T(\varepsilon)$, such that whenever $|X_0| < \delta$ we have $|X(t, t_0, X_0)| < \varepsilon$ for all $t \geq t_0 + T(\varepsilon)$.

Remark 2.1 It follows from the definitions that stability is the prerequisite for uniform stability, asymptotic stability or uniform asymptotic stability.

Definition 2.7 A solution $X(t, t_0, X_0)$ of Eq. (4.10) is bounded if there exists a $\beta > 0$, such that $|X(t, t_0, X_0)| < \varepsilon$ for all $t \geq t_0$ where β may depend on each solution.

Definition 2.8 A solution $X(t)$ of Eq. (4.10) is periodic if for some $\omega > 0$ is the least possible vale such that, $X(t + \omega) = X(t)$; ω is called the period of X.

4.2.4 Lyapunov Functions

In his doctoral thesis Lyapunov (1992) dealt with stability by two distinct methods; called first and second methods of Lyapunov. The system's time response (i.e., the solution of the differential equations) is the prerequisite for the first method and this method is applicable to some limited cases. The Lyapunov second method popularly known as direct method does not require the knowledge system's time response. This method has great application potential and is applied to a wide range of problems. Construction of a scalar function is the vital part of this method and the derivative of this constructed function characterizes various stabilities. The properties of the scalar function V and $\dot{V}$ determines the stability behavior of the system. We now define the Lyapunov function which is used to determine the stability and asymptotic stability.

Definition 2.9 A Lyapunov function V defined as $V : I \times R^n \to R$ is a real function of real variables $X(X \in R^n)$; t with the conditions that $t \geq T$ and $|x_i| < H$. T and H are real constants of which T can be supposed to be as large as we wish and H as small as we wish but not zero having the following properties:

(i) Continuity: $V(t, X)$ is continuous and single valued under the condition $t \geq T$ and $|x_i| < H$ and $V\,(t.\,0) \equiv 0$;

(ii) $V(t, X)$ is positive definite;
(iii) $\dot{V} = \frac{\partial V}{\partial x_1}\dot{x}_1 + \frac{\partial V}{\partial x_2}\dot{x}_2 + \frac{\partial V}{\partial x_3}\dot{x}_3 + \ldots + \frac{\partial V}{\partial x_n}\dot{x}_n$, representing the total derivative with respect to t is negative definite.

Definition 2.10 (A Complete Lyapunov Function) A Lyapunov function V defined as $V : I \times R^n \to R$ is said to be complete if for $X \in R^n$

(i) $V(t, X) \geq 0$,
(ii) $V(t, X) = 0$; if and only if $X = 0$ and
(iii) $\dot{V}\big|_{(2,1,1)}(t, X) \leq -c \mid X \mid$ where c is any positive constant and $|X|$ given by

$$|X| = \left(\sum_{i=1}^{n} x_i^2\right)^{1/2} \to \infty$$

It is incomplete if (iii) is not satisfied.

By verifying the above properties of V and $\dot{V}$ one can study the qualitative behavior of the system. Stability of the system cannot be determined if the necessary conditions are not satisfied. Lyapunov function is problem specific and new function is to be constructed for each problem and there is no general approach or method for the construction. Experience, ingenuity, and good fortune will propel the analyst to choose appropriate V.

We present some standard theorems on stability and boundedness of Lyapunov second method which are having application relevance. The proofs of these theorems can be understood from all the standard books and all are inspired by the general problem of the stability of motion of Lyapunov (1992).

The right hand side (RHS) of the equation $\dot{X} = f(t, X)$ can be written in the following ways:

$$f(t, X) = A(t)X \tag{4.14}$$

and

$$f(t, X) = A(t)X + P(t) \tag{4.15}$$

where $A(t)$ is an $n \times n$ matrix of unknown coefficients, $P : R \to R^n$ is a continuous function. The equation (4.15) is the non-homogeneous equation and (4.14) is the corresponding homogeneous equation. Suppose that $f(t, 0) \equiv 0$ for all t, then the following theorem is true.

Theorem 2.1 [Lyapunov Theorem (Lyapunov 1992)] If the differential equations of undisturbed motion (the steady state of a system before pertubations are introduced) are such that it is possible to find a definite function V, of which the derivative $\dot{V}$ is a function of fixed sign, which is opposite to that of V or reduces identically to zero, the undisturbed motion is Stable.

Various simplified versions of Theorem 2.1 gives the following theorems.

Theorem 2.2 Assume that there exists a function $V(t, X)$ defined for $t \geq 0$; $|X| < \delta_0$ (δ_0 is a positive constant) continuous with the following properties:

(i) $V(t, 0) \equiv 0$,
(ii) $V(t, X,) \geq a(|X|)$,
where $a(r)$ is continuous monotonically increasing and $a(0) = 0$,
(iii) $\dot{V}(t, X,) \leq 0$
then the solution $X(t) \equiv 0$ (zero solution) of Eq. (4.10) is stable.

Theorem 2.3 Suppose conditions (i) and (iii) of Theorem 2.2 hold, and if we replace condition (ii) with (iv) $a(|X|) \leq V(t, X) \leq b(|X|)$, $a(r)$ and $b(r)$ being continuous monotone increasing functions and $a(0) = b(0) = 0$, then the zero solution of Eq. (4.10) is uniformly stable.

Theorem 2.4 Under the assumptions of the Theorem 2.3, if (v) $\dot{V}(t, X) \leq -c(|X|)$ where $c(r)$ is continuous on $[0, \delta_0]$ and positive definite, and if $f(t, X)$ is bounded, then the zero solution of Eq. (4.10) is asymptotically stable.

Theorem 2.5 Under the same assumptions of Theorem 2.2 with condition (v) of Theorem 2.4, then the zero solution of Eq. (4.10) is uniformly asymptotically stable.

Theorem 2.6 If $\dot{V}(t, X,) \leq -cV(t, X)$, where $c > 0$ is a constant under the same assumptions as in Theorem 2.3, then the zero solution of Eq. (4.10) is also uniformly asymptotically stable.

The application of Lyapunov functions to determine various stabilities of the solution in Lyapunov sense are presented in Theorem 2.1, Theorem 2.2, Theorem 2.3, Theorem 2.4, Theorem 2.5, and Theorem 2.6. The following theorems are the characterizations of boundedness of solutions by using Lyapunov functions.

Theorem 2.7 Suppose there exists a Lyapunov function $V(t, X)$, defined on $I \times R^n$ which satisfies the following conditions:

(i) $a \mid X \mid \leq V(t, X)$ where $a(r)$ is continuous, monotone increasing function and $a(0) = 0$,
(ii) $\dot{V}(t, X,) \leq 0$,
then the solutions of Eq. (4.10) are bounded.

Theorem 2.8 Suppose that there exists a Lyapunov function $V(t, X)$ defined on $0 \leq t \leq R$; $|X| \geq R$ (where R may be large) which satisfies (i) $a \mid X \mid \leq V(t, X) \leq b \mid X|$ where $a(r)$ and $b(r)$ are continuous monotone increasing functions, and (ii) $\dot{V}(t, X,) \leq 0$ then the solutions of Eq. (4.2) are uniformly bounded.

Theorem 2.9 Under the assumptions of Theorem 2.2, if $\dot{V}(t, X,) \leq -cV(t, X)$, where $c(r)$ is positive and continuous, then the solutions of Eq. (4.10) are uniform ultimately bounded.

Theorem 2.10 Suppose that (4.2) has an isolated fixed point at $X = 0$ (w.l.o.g. one can move a fixed point X^e to 0 by letting $y = X - X^e$). If there exists a differentiable function $V(x)$, which is positive definite and for which $\frac{dV}{dt} = \nabla V \cdot f$ is negative definite on some domain, then 0 solution is asymptotically stable. If $\frac{dV}{dt}$ is negative semidefinite (i.e., $\frac{dV}{dt} = 0$ is allowed), then 0 solution is Lyapunov stable.

Example 2.1 Consider the two-dimensional system $\dot{x}_1 = x_2 + \alpha\left(x_1^2 + x_2^2\right)x_1$ and $\dot{y} = -x_1 + \alpha\left(x_1^2 + x_2^2\right)x_2$. Is the equilibrium $(x, y) = (0, 0)$ of this system stable or unstable?

Let $V = \frac{\left(x^2+y^2\right)}{2}$ and compute $\dot{V} = x\dot{x} + y\dot{y} = x(y + \alpha(x^2 + y^2)x) + y(-x + \alpha(x^2 + y^2)y) = \alpha(x^2 + y^2)^2$. If $\alpha < 0$, then the system is stable since, $\dot{V} < 0$ for all $(x, y) \neq 0$. If $\alpha > 0$, then the system is unstable since $\dot{V} > 0$ for all $(x, y) \neq 0$.

Let ϕ_t be the flow map of Eq. (4.4) and let $\phi(X) = \{\phi_t(X)/t \geq 0\}$ denote the set of all points in the solution or orbit $\phi_t(X)$ based at X.

Definition 4 Two orbits $\phi(X)$ and $\phi\left(\widehat{X}\right)$ are ε-close if there is a reparameterization of time $\widehat{t}(t)$ (a smooth, monotonic function) such that $\mid \phi_t(X) - \phi_{\widehat{t}}\left(\widehat{X}\right) \mid < \epsilon$ for all $t \geq 0$.

It is an established fact that the circulation speeds of neighboring periodic orbits are not necessarily same. The same can be observed in the polar form of Example 2.1 $\dot{r} = 0, \dot{\theta} = 1 + r^2$, (Obtained by substituting $x = r\,\mathrm{Cos}\,\theta$ and $y = r\,\mathrm{Sin}\,\theta$ where the period $T(r) = \frac{2}{(1+r^2)}$ depends on amplitude.

Definition 5 A solution $\phi_t(X)$ is orbitally stable if for every $\varepsilon > 0$ there is a neighborhood $s \ni X$ such that, for all $\widehat{X} \in V$, the sets $\phi(X)$ and $\phi\left(\widehat{X}\right)$ are ε-close. In addition to these conditions V may be chosen such that for all $\widehat{X} \in V$, there exists a time shift $\tau\left(\widehat{X}\right)$ so that $\left|\phi_t(X) - \phi_{t-\tau\left(\widehat{X}\right)}\left(\widehat{X}\right)\right| \to 0$ as $t \to \infty$, then $\phi_t(X)$ is orbitally asymptotically stable.

It is always a challenge to find appropriate Lyapunov function for applying the second method on Lyapunov. For a stable system, there may exist an infinite number of suitable Lyapunov functions. Many methods for the construction of Lyapunov functions are available in the literature. The popular methods are Krasovskii's Method (Krasovskii 1963), Schultz-Gibson's Variable Method (Gibson and Schultz 1962), Intrinsic Method (Chin 1988) and for stability analysis one can refer stability analysis by Lakshmikantham et al. (1989).

Example 2.2 For the second order equation, we consider the general linear equation of the form

$$\ddot{x} + a\dot{x} + bx = p(t, x, \dot{x}) \tag{4.16}$$

with corresponding system

$$\begin{aligned} \dot{x} &= y \\ \dot{y} &= -ay - bx + p(t, x, y) \end{aligned} \tag{4.17}$$

where a and b are the positive constants. To construct suitable complete Lyapunov function for the above system, we assume a quadratic form of the form

$$2V = Ax^2 + By^2 + 2Cxy \tag{4.18}$$

where A, B, and C are the positive constants to be determined. Differentiating equation (4.18) with respect to t using the equivalent system (4.17) we have

$$\dot{V}\big|_{(2.1.4.3)} = -Cbx^2 - (Ba - C)y^2 - (Bb + Ca - A)xy + (Cx + By)p\,(t, x, y)$$

to make the $\dot{V}$ negative definite, we adapt the method of Cartwright (1956) by equating the coefficients of mixed variables to zero and the coefficients of x^2 and y^2 to any positive constant (say δ), i.e., (i) $Bb + Ca - A = 0$; (ii) $Ba - C = \delta$; and (iii) $Cb = \delta$. Solving these equations for A, B, and C, we have that $A = \frac{\delta}{ab} \times \left\{a^2 + b\,(b+1)\right\}, B = \frac{\delta}{ab}\{b+1\}$, $C = \frac{\delta}{b}$.

The required Lyapunov function is obtained by substituting for the constants A, B, and C in (4.18) which gives $2V = \frac{\delta}{ab}\,(y + ax)^2 + \frac{\delta}{a}\,(b+1)x^2 + \frac{\delta}{a}y^2$. Clearly, the above function is positive definite and its derivative negative definite.

For the nonlinear counterpart of Eq. (4.16) given as

$$\ddot{x} + g(\dot{x}) + h(x) = p\,(t, x, \dot{x}) \tag{4.19}$$

The above is the procedure for the construction of suitable Lyapunov function. Construction can be completed only after we find conditions on the nonlinear terms. For a third order equation say

$$\ldots x + a\ddot{x} + b\dot{x} + cx = p(t, x, \dot{x}, \ddot{x}) \tag{4.20}$$

with a corresponding system given as

$$\begin{aligned} \dot{x} &= y \\ \dot{y} &= z \\ \dot{z} &= -az - by - cx + p\,(t, x, \dot{x}, \ddot{x}) \end{aligned} \tag{4.21}$$

where a, b, and c are all positive constants. The required quadratic form in this case is given as

$$2V = Ax^2 + By^2 + Cz^2 + 2Dxy + 2Exz + 2Fyz \tag{4.22}$$

where the A, B, C, D, E and F are constants to be determined.

Differentiating equation (4.22) with respect to the system (4.21) we have

$$\dot{V} = -Ecx^2 - (Fb - D)y^2 - (Ca - F)z^2 - (Eb + Fb - A)xy$$
$$-(Cc + Ea - D)xz - (Cb + Fa - B)yz + (Ex + Fy + Cz)p\,(t, x, \dot{x}, \ddot{x}) \tag{4.23}$$

By equating the coefficients of the mixed variables to zero and the coefficients of x^2, y^2 and z^2 to any positive constant (say δ), we get the following system of equation (i) $Ex = \delta$, (ii) $Fb - D = \delta$, (iii) $Ca - F = \delta$, (iv) $Eb + Fc - A = 0$, (v) $Cc + Ea - D = 0$, and (vi) $Cb + Fa - B = 0$. By solving the system of equations (i) to (vi) we get $A = \frac{\delta}{(ab-c)c}\{(ab - c) + (a^2 + c^2 + c)\}$, $B = \frac{\delta}{(ab-c)c} \times \{b(a + bc + c) + a(a^2 + c^2 + c)\}$, $C = \frac{\delta}{(ab-c)c}(a + bc + c)$. $D = \frac{\delta}{(ab-c)c} \times \{(a + bc + c) + a(ab - c)\}$, $E = \frac{\delta}{c}$ and $F = \frac{\delta}{(ab-c)c}(a^2 + c^2 + c)$.

From these values it follows that V is positive definite and $\dot{V}$ is negative definite.

A procedure to construct suitable Lyapunov function for the nonlinear equation,

$$\dddot{x} + \varphi(x, \dot{x})\ddot{x} + f(x, \dot{x}) = p\,(t, x, \dot{x}, \ddot{x}) \tag{4.24}$$

is explained above. However, we need to find conditions on the nonlinear terms to complete the construction. Similar procedure can be adopted to construct Lyapunov functions of for the fourth and higher order equation.

4.2.5 Matrix Differential Equations

A matrix function $Z(t) \in R^{n \times n}$ is a fundamental solution of a linear first-order matrix differential equation

$$L\,(X, X', A_1, A_2, \ldots, A_r) = F(t), \quad t \in \Im \tag{4.25}$$

where $A_i \in R^{n \times n}$ known as the input structure matrix, and $F(t) \in R^{n \times n}$, if Z satisfies the above equation with $F = 0$, $\det(Z(t)) \neq 0$ for all $t \in$ ⍰, and every solution to the above equation can be written as sum of $Z\,C + X_p$, where C is an arbitrary $n \times n$ constant matrix and X_p a particular solution. We express the state transition matrix to (4.25) via the fundamental solution of (4.25). First, rewrite (4.25) as an initial value problem,

$$L\left(X, \dot{X}, A_1, A_2, \ldots, A_r\right) = 0, \;\; X(t_0) = X_0, \quad t \in \Im \tag{4.26}$$

The unique solution to homogeneous system (4.26) is

$$X = Z(t)Z^{-1}(t_0)X_0 = \Phi(t, t_0)X_0$$

The matrix function $\Phi(t, t_0)$ can be generalized as $\Phi(t, s) = Z(t)Z^{-1}(s)$, which is known as the state transition matrix (Fundamental matrix solution) associated with (4.25).

Consider the differential equation

$$Ly(t) = y(t) \tag{4.27}$$

where the linear operator $L = \sum_{i=0}^{n} P_i(t)y^{(i)}(t)$, $P_0(t) = 1$, $P_1(t) \ldots P_k(t)$, $y(t)$ are $(k+2)$ functions defined on R. The homogeneous equation corresponding to (4.27) is

$$Ly(t) = 0 \tag{4.28}$$

If $Z_i(t)$, $i = 1, 2, \ldots n$ are solutions of (4.28), then $\det k(t) \neq 0$ for $t \geq t_0$, provided that $\det k(t_0) \neq 0$ where

$$K(t) = \begin{bmatrix} Z_1(t) & Z_2(t) & \ldots & Z_n(t) \\ \dot{Z}_1(t) & \dot{Z}_2(t) & \ldots & \dot{Z}_n(t) \\ \ldots & \ldots & \ldots & \ldots \\ Z_1{}^{(n-1)}(t) & Z_2{}^{(n-1)}(t) & \ldots & Z_n{}^{(n-1)}(t) \end{bmatrix}$$

The matrix $K(t)$ is called Casorati matrix and its columns are solutions of (4.28).

The space S of solutions of (4.28) is a vector space of dimension n. The state transition matrix satisfies the following properties:

(i) $\Phi(t, t) = I, \quad t \in I$
(ii) $\Phi(t_1, t_2)\,\Phi(t_2, t_3) = \Phi(t_1, t_3), \quad t_1, t_2, t_3 \in$?
(iii) $\Phi^{-1}(t_1, t_2) = \Phi(t_2, t_1), \quad t_1, t_2 \in$?

The fundamental solution of

$$\dot{X} = AX, \tag{4.29}$$

where A, $X(t) \in R^{n \times n}$ and A is time invariant is given by $Z(t) = e^{tA}$. The matrix exponential e^{tA} is formally defined by the convergent power series,

$$e^{tA} = I + tA + \left\{\frac{t^2A^2}{2!}\right\} + \left\{\frac{t^3A^3}{3!}\right\} + \ldots + \left\{\frac{t^nA^n}{n!}\right\} + \ldots$$

There are many numerical methods available for computing e^{tA} and can be found in a tutorial review by Moler and Van Loan (2003). The state transition matrix associated with (4.29) is $\Phi(t, s) = Z(t)Z^{-1}(s) = e^{(t-s)A}$. Since e^{tA} and e^{-sA} commute with each other and $(e^{sA})^{-1} = e^{-sA}$.

Consider matrix differential algebraic equation

$$X'(t) = A(t)\,X(t) + F(t) \tag{4.30}$$

where $A(t)$ and $F(t)$ are square matrices of order n whose elements are real or complex functions defined on R (or C), and $X(t) \in R^{n \times n}$ (or $C^{n \times n}$). If A and F are constant matrices, the solution of the above can be determined by associated matrix pencil, as a result of Laplace transform.

4.3 Approximate Analytical Solutions

Differential equations in which the dependent variable is not combined with any of its derivatives or itself. Most of the phenomena are nonlinear in this world and are represented by nonlinear differential equations. By using HPC (high performance computation), one can easily obtain accurate solution of a linear differential equation. However, fining accurate solution for nonlinear differential equations is always difficult. Obtaining an analytic solution is difficult when compared to that of a numerical solution. The numeric computation techniques are used to solve nonlinear equations in a complicated domain. Numerical methods give discrete points of solutions and it is costly and time consuming because all the points on the curve are to be determined. Difficulties might occur if there are any singularities in the nonlinear equations. Therefore, there are advantages and limitations for both analytical and numerical approach of solving nonlinear equations. The following are some popular analytic techniques to solve nonlinear equations. Murty et al. (1987, 1990, 1997), Srinivas (1989) and Putcha and Malladi (2010) constructed approximate analytical solutions of nonlinear differential equations.

Perturbation Techniques The perturbation techniques are popular and have a wide range of applications. Perturbation techniques reveal important properties and inherent phenomena of nonlinear equations. Perturbation techniques play vital role in the development of science and engineering. Singular perturbation techniques are considered as one of the top ten advancements of theoretical and applied mechanics. These are based on the existence of perturbation quantities. These quantities may be small or large parameters or variables. Perturbation techniques use perturbation quantities to transfer a nonlinear problem into many number of linear of linear problems. The existence of perturbation quantity is the most

important part of perturbation techniques. Perturbation quantity brings some serious restrictions for perturbation techniques. Every nonlinear problem may not contain perturbation quantity. Analytic approximations often breakdown as nonlinearity becomes strong. Thus, it may be concluded that perturbation approximations are valid only for nonlinear problems involving weak nonlinearity. The major drawback of perturbation techniques is that they do not provide any liberty to adjust the region of convergence and rate of convergence.

4.3.1 Non perturbation Techniques

Lyapunov's Artificial Small Parameter Method The dependence of perturbation techniques on small or large parameters can be avoided by introducing a so-called artificial small parameter. In 1892 Lyapunov considered the equation, $\frac{dx}{dt} = A(t)x$, where $A(t)$ is a time periodic matrix. Lyapunov introduced an artificial parameter ε to replace this equation with another equation, $\frac{dx}{dt} = \varepsilon A(t)x$ and then calculated power series expansions over ε for the solutions. In many cases Lyapunov proved that series converge for $\varepsilon = 1$.

δ Expansion Method Artificial small parameter method was further extended by another method, δ-Expansion method was proposed by Karmishin et al. In this method, an artificial parameter δ to replace the given nonlinear equation in the powers of δ. In essence, the δ expansion method is equivalent to the Lyapunov's artificial small parameter method.

Adomian's Decomposition Method It is an effective analytic technique to handle problems involving strongly nonlinearities. This method valid for ordinary and partial differential equations, irrespective of the appearance of small/large parameters in these equations. The convergence of Adomian approximation series is faster. Adomian's decomposition method contains polynomials. This method also does not have any provision to adjust convergence region and rate of approximate solutions.

Both perturbation and perturbation methods are unable to provide flexibility to convergence region and rate of approximation. This difficulty can be overcome in homotopy analysis method. This method can provide freedom to adjust the convergence region and rate of approximation series and gives choice to use various base functions to approximate a nonlinear problem.

4.3.2 Homotopy Analysis Method (HAM)

This method is based on homotopy, a fundamental concept of topology and differential geometry. The idea of homotopy is very simple and straight forward. Construction of a continuous function of an initial guess to the exact solution of the

nonlinear equation of consideration is done in HAM. To ensure the convergence of solution series one has to choose an auxiliary linear operator to construct a continuous function by using auxiliary parameter. This method has the freedom to choose initial approximations and auxiliary linear operators. This freedom allows us to transfer a complicated nonlinear problem into an infinite number of simpler, linear sub-problems. The main feature of this analytic approach is that it is free from all physical parameters. It contains the homotopy parameter $q \in [0, 1]$ to construct a zero-order deformation equation and then to get the homotopy series solution irrespective of the presence small or large physical parameters. Difficulty arises because of the fact that homotopy-series is not always convergent at $q = 1$ though $q = 1$ is a valid case for nonlinear problems. To overcome this difficulty, an auxiliary parameter $h \neq 0$ is introduced. This actually simplifies the application of HAM to various nonlinear problems arise in Science and engineering. Advantages of HAM are (i) It is valid even if a given nonlinear problem does not contain any small/large parameters at all. (ii) There is an opportunity to adjust and control the convergence region and rate of approximation series as per the requirement. (iii) This has the choice of various sets of base functions to approximate nonlinear problems. Homotopy analysis and Homotopy perturbation techniques were presented in He (1999, 2003, 2004) and Putcha (2011).

Consider the following nonlinear problem:

$$N(u(x,t)) = 0, \quad t > 0 \tag{4.31}$$

where N is a nonlinear operator and $u(x,t)$ is unknown function of the independent variables x, t. The zero-order deformation equation

$$(1-q)L[\Phi(x,t,q) - u_0(x,t)] = qhH(x,t)N(\Phi(x,t,q)) \tag{4.32}$$

where $q \in [0.1]$ is the Homotopy or embedding parameter, $h \neq 0$ an auxiliary parameter, $H(x,t) \neq 0$ is an auxiliary function, L is an auxiliary linear operator, $u_0(x, t)$ an initial guess of $u(x,t)$ and $\Phi(x,t,q)$ is an unknown function. By substituting $q = 0$ and $q = 1$ in (4.32) it can easily be observed that $\Phi(x, t, q)$ deforms continuously from the initial guess $u_0(x,t)$ to the exact solution $u(x,t)$ as the embedding parameter q increases from 0 to 1. By expanding $\Phi(x,t,q)$ in a Taylor series, we get

$$\varphi(x,t,q) = u_0(x,t) + \sum_{m=1}^{\infty} u_m(x,t)q^m \tag{4.33}$$

where

$$u_m(x,t) = \frac{1}{m!}\frac{\partial^m \Phi(x,t,q)}{\partial q^m} \tag{4.34}$$

The convergence of the series (4.33) is controlled by h. Assume that the auxiliary parameter h the auxiliary function H, the initial approximation $u_0(x,t)$, and the auxiliary linear operator L are so properly chosen that the series (4.33) converges at $q = 1$. Then, exact solution of (4.33) is given by

$$u(x,t) = u_0(x,t) + \sum_{m=1}^{\infty} u_m(x,t)q^m \tag{4.35}$$

Now the functions $u_m(x,t)$ for $m = 1, 2, 3, \ldots$ are determined by differentiating the zero-order deformation equation (4.32) m times with respect to the embedding parameter q, dividing by $m!$ and then setting $q = 0$ we get the mth order deformation equation

$$L[u_m(x,t) - \chi_m u_{m-1}(x,t) = hH(t)R_m(u_{m-1}(x,t)) \tag{4.36}$$

where

$$R_m(u_{m-1}(x,t)) = \frac{1}{(m-1)!}\frac{\partial^{m-1}\Phi(x,t,q)}{\partial q^{m-1}} \tag{4.37}$$

$$u_m = \{u_0(x,t), u_1(x,t), \ldots, u_m(x,t)\} \tag{4.38}$$

$$\chi_m = \begin{cases} 0, & m \leq 1 \\ 1, & \text{otherwise} \end{cases} \tag{4.39}$$

For any given operators L and N we get the mth order deformation equation (4.36) and solving it we get $u_m(x,t)$ for different m. The solution of problem (4.31) is obtained by substituting the obtained $u_m(x,t)$ in (4.35) and choosing a suitable value of h for the convergence of the series. Homotopy analysis method is based on the following assumptions: (i) There exists the solution of the zeroth-order deformation equation in the whole region of the embedding parameter $q \in [0,1]$. (ii) All the higher order deformation equations have solutions. (iii) All Taylor series expanded in the embedding parameter q converge at $q = 1$.

No theories or procedure are available in the literature to choose the initial approximations, auxiliary linear operators, auxiliary functions, and auxiliary parameter. The rule of solution expression, the rule of coefficient ergodicity, and the rule of solution existence play important role in the homotopy analysis method and are popular among the users of HAM.

Role of Auxiliary Parameter *h*

The auxiliary parameter h is also known as the convergence control parameter. One can assume that homotopy-series converges even without the use of the

convergence-parameter h. This assumption is of no utility since one can always choose a proper value of h to obtain convergent homotopy-series solution. By introducing the auxiliary parameter h the zero-order deformation equation is constructed. This gives a general homotopy and HAM gives a family of solution expressions in the auxiliary parameter h. Therefore, convergence region and rate of solution series depend upon the auxiliary parameter h. This parameter h provides us an opportunity to adjust and control convergence region and rate of solution series given by the homotopy analysis method.

Example 3.1 Let us consider a simple example of a nonlinear problem.

Consider a free sphere dropping in the air from a static state. Let $\widetilde{t}$ denote the time, $U(\widetilde{t})$ the velocity of the sphere, m the mass, and g the acceleration of gravity. Assume that the air resistance on the sphere is $aU^2(\widetilde{t})$, where a is a constant.

According to Newton's Second law,

$$m\frac{dU(\widetilde{t})}{dt} = mg - aU^2(\widetilde{t}), \tag{4.40}$$

Subject to the initial condition

$$U(0) = 0 \tag{4.41}$$

The speed of a freely dropping sphere is increased due to gravity until a steady velocity U_∞ is reached. Without even obtaining the solution $U(\widetilde{t})$, we can get the limit velocity U_∞. From the above equation (4.40), let us say that steady velocity is reached. Steady velocity means constant velocity. Therefore, $mg - aU_\infty^2 = 0$ implies $U_\infty = \sqrt{\frac{mg}{a}}$. Using U_∞ and $\left(\frac{U_\infty}{g}\right)$ as characteristic velocity and time, respectively, and writing $\widetilde{t} = \left(\frac{U_\infty}{g}\right) * t$, and $U(\widetilde{t}) = U_\infty * V(t)$, we have the dimensionless equation

$$\dot{x}(t) + x^2(t) = 1, \tag{4.42}$$

Subject to the initial condition

$$x\,(0) = 0 \tag{4.43}$$

where t denotes the dimensionless time and the (dot) denotes the derivative with respect to t. Obviously, as $t \to +\infty$, i.e., $\widetilde{t} \to \infty$ and $U(\widetilde{t}) \to U_\infty$, we have from (4.34) that $\lim_{t \to +\infty} x\,(t) = 1$, even without solving Eqs. (4.42) and (4.43). The exact solution of Eqs. (4.42) and (4.43) is $x\,(t) = \tanh(t)$.

Approximate Solution of the equations (4.42) and (4.43) can be obtained by analytic methods like Perturbation method, Lyapunov's artificial small parameter

method, Adomian's decomposition method, and the δ-expansion method. We illustrate the homotopy analysis method for this problem.

Zero-Order Deformation Equation Let x_0(t) denote an initial guess of $x(t)$, which satisfies the initial condition $x_0(0) = 0$. Let $q \in [0, 1]$ denote the so-called embedding parameter or homotopy parameter. The homotopy analysis method is based on a special continuous mapping $x(t) \rightarrow \Phi(t; q)$ varies from the initial guess to final exact solution $x(t)$.

Let L be a linear operator defined by

$$L[\Phi(t;q)] = \gamma_1(t) * \frac{\partial \Phi(t;q)}{\partial t} + \gamma_2(t) * \Phi(t;q) \tag{4.44}$$

where $\gamma_1(t) \neq 0$ and $\gamma_2(t) \neq 0$ are real functions to be determined later. From Eq. (4.42), a nonlinear operator is defined as

$$N[\Phi(t;q)] = \frac{\partial \Phi(t;q)}{\partial t} + \Phi^2(t;q) - 1 \tag{4.45}$$

Let $h \neq 0$ be the auxiliary parameter and $H(t) \neq 0$ be the auxiliary function.

Using the embedding parameter, $q \in [0, 1]$, we construct the family of equations,

$$(1-q)L[\Phi(t;q) - x_0(t)] = hqH(t)N[\Phi(t;q)] \tag{4.46}$$

Subject to

$$\Phi[0;q] = 0 \tag{4.47}$$

We have freedom to choose the auxiliary parameter h, the auxiliary function $H(t)$, the initial approximation $V_0(t)$ and the auxiliary linear operator L.

When $q = 0$, Eq. (4.37) becomes $L[\Phi(t;0) - x_0(t)] = 0$, Subject to $\Phi[0;0] = 0$.

According to (4.43) and (4.44), $\Phi(t;0) = x_0(t)$.

When $q = 1$, Eq. (4.46) becomes

$$hH(t)N[\Phi(t;1)] = 0, \tag{4.48}$$

subject to

$$\Phi[0;1] = 0 \tag{4.49}$$

Since $h \neq 0, H(t) \neq 0$, Eqs. (4.45), (4.48), and (4.49) are equivalent to the original equations (4.42) and (4.43), provided

$$\Phi(t;1) = x(t) \tag{4.50}$$

According to Eqs. (4.48) and (4.49), $\Phi(t;q)$ varies from $x_0(t)$ to $x(t)$ as q varies from 0 to 1. By suitably choosing the auxiliary parameter h, the auxiliary function $H(t)$, the initial approximation $V_0(t)$, and the auxiliary linear operator L, the solution $\Phi(t;q)$ of the zero-order deformation equations (4.46) and (4.47) exists for $0 \leq q \leq 1$, and its mth-order derivative with respect to the embedding parameter q, $x_0^m(t) = \frac{\partial^m \Phi(t;q)}{\partial q^m}\Big|_{q=0}$, exists where $m = 1, 2, 3\ldots$ and $x_0^m(t)$ is the mth-order deformation derivative. Define $x_m(t) = \frac{x_0^m(t)}{m!} = \frac{1}{m!}\frac{\partial^m \Phi(t;q)}{\partial q^m}\Big|_{q=0}$.

By expanding $\Phi(t;q)$ using Taylor's theorem with respect to the parameter q.

By Taylor's theorem, we expand $\Phi(t;\ q)$ in a power series of the embedding parameter q as

$$\Phi(t;q) = \Phi(t;0) + \sum_{m=1}^{\infty} \frac{1}{m!}\frac{\partial^m \Phi(t;q)}{\partial q^m}\Big|_{q=0} q^m = x_0(t) + \sum_{m=1}^{\infty} x_m(t)\, q^m \tag{4.51}$$

Now by choosing $q = 1$ in Eq. (4.51) we get $\Phi(t;1) = x_0(t) + \sum_{m=1}^{\infty} x_m(t)$.

Therefore $x(t) = x_0(t) + \sum_{m=1}^{\infty} x_m(t)$.

Higher Order Deformation Equations Define a vector, $\overrightarrow{x_n} = \{x_0(t), x_1(t), x_2(t), \ldots, x_n(t)\}$ Now, we go for the mth order deformation equation, The mth order deformation equation may be defined as,

$$L[x_m(t) - \chi_m x_{m-1}(t)] = hH(t)R_m \vec{x}_{m-1}, \quad \text{Subject to} \quad x_m(0) = 0.$$

The solution of $x(t)$ may be expressed in different forms. The base functions may be in the form of Polynomial functions, Rational functions, Exponential functions. The solutions obtained by all the other methods are special cases of the homotopy analysis method.

From the above given example, let us consider expression of solution obtained by polynomial functions.

$$x(t) = \sum_{k=0}^{m} x_k(t) = \sum_{n=0}^{m} \mu_0^{m,n}(h)\left[\alpha_{2n+1} t^{2n+1}\right], \tag{4.52}$$

where $\alpha_{2n\,+\,1}$ the same constant as which appears in the solution is obtained using perturbation method. The equation (4.52) denotes a family of solution expressions in auxiliary parameter h. The function $\mu_0^{m,n}(h)$ has the property $\mu_0^{m,n}(-1) = 1$, When $n \leq m$.

For any finite positive integer n, it holds

$$\lim_{m\to+\infty}\mu_0^{m,n}(h)=\begin{cases}1, & \text{when } |1+h|<1,\\ \infty, & \text{when } |1+h|>1.\end{cases} \tag{4.53}$$

Therefore

$$V(t)=V_{\text{pert}}(t) \tag{4.54}$$

Therefore, the perturbation solution is only a special case of the solution expression when $h=-1$. The coefficients of the solution expression depend upon the auxiliary parameter h. According to (4.53), the necessary condition for the series (4.52) to be convergent is $|1+h|<1$ implies $-2<h<0$. It is interesting that the convergence region of the solution series depends upon the value of h. The closer the value of h is to 0, the larger the convergence region of the series. Finally, we can say that the solution obtained by the homotopy analysis method solution is dependent on the choice of the auxiliary parameter. Therefore, there can be infinite number of solutions based on this method. That is the reason why this method is better compared to the other methods of solving nonlinear differential equations. Refer (Putcha et al. 2012) for detailed discussion about approximate analytical solutions using Adomian decomposition method, homotopy perturbation method, and homotopy analysis method.

Example 3.2 Consider the Verhulst equation $\dot{x}=bx-ax^2$, where a and b are the positive constants. The exact solution of Verhulst equation can be found by direct integration and is given by $x(t)=\frac{b\ \mathrm{e}^{bt}}{(b+ax(t))/x(0)-a\ \mathrm{e}^{bt}}$ for $b\neq 0$. We solve Verhulst equation for $b=1$ and $a=3$ satisfying the initial condition $x(0)=0.1$ by HAM. Now the initial approximation $x_0(t)=1$ and the linear operator $L[\Phi(t;q)]=\frac{\partial\Phi(t;q)}{\partial t}$ with the property $L(c)=0$, where c is an integral constant. Furthermore, from Verhulst equation, a nonlinear operator may be defined as $N[\Phi(t;q)]=\frac{\partial\Phi(t;q)}{\partial t}-b\,\Phi(t;q)+a\Phi^2(t;q)$. Using this definition, we construct the zeroth-order deformation equation and also the mth order deformation equation for $m\geq 1$ is subject to the initial condition as $x_m(0)=0$ and

$$R_m\left(\vec{x}_{m-1}\right)=\dot{x}_{m-1}(t)-bx_{m-1}(t)+a\sum_{i=o}^{m-1}x_i(t)\,x_{m-1-i}(t) \tag{4.55}$$

Now, the solution of the mth order deformation equation becomes

$$x_m(t)=\chi_m\,x_{m-1}(t)+h\int_0^t R_m\left(\vec{x}_{m-1}\right)d\tau+c \tag{4.56}$$

where the constant of integration c is determined by the initial condition. Now successively we obtain

$$x_1(t) = -\frac{7}{100}\,ht \quad \text{and} \quad x_2(t) = -\frac{7}{100}ht - \frac{7}{100}h^2t + \frac{14}{1000}h^2t^2 \tag{4.57}$$

In general, the analytic solution of via the polynomial base functions is given by

$$x(t) = \sum_{m=1}^{\infty} d_m(h)t^m$$

Example 3.3 Consider a homogeneous system of equations

$$\dot{x}_1 = -102x_1 + 88x_2,\ \ \dot{x}_2 = 88x_1 + 102x_2 \tag{4.58}$$

with the initial conditions

$$x_1(0) = 1, \quad x_2(0) = 3 \tag{4.59}$$

Now apply the homotopy analysis method to solve the equations (4.58) by expressing the solutions $x_1(t)$ and $x_2(t)$ by a set of base functions $\{t^n/n = 0, 1, 2, \ldots\}$ as $x_1(t) = \sum_{n=0}^{\infty} a_n t^n$, $x_2(t) = \sum_{n=0}^{\infty} b_n t^n$ where a_n and b_n are coefficients which are to be evaluated. We choose the initial approximations as $x_{1,0}(t) = x_1(0) = 1$, $x_{2,0}(t) = x_2(0) = 3$ and the auxiliary linear operator as $L[\Phi_i(t;q)] = \frac{\partial \Phi_i(t;q)}{\partial t}$, $i = 1, 2$ with the property $L[C_i] = 0$, where $C_i (i = 1, 2)$ are integral constants. Define a system of nonlinear operators as

$$\begin{aligned} N_1[\Phi_i(t;q)] &= \frac{\partial \Phi_i(t;q)}{\partial t} + 102\Phi_1(t;q) - 88\Phi_2(t;q), N_2[\Phi_i(t;q)] \\ &= \frac{\partial \Phi_i(t;q)}{\partial t} - 88\Phi_1(t;q) - 102\Phi_2(t;q) \end{aligned}$$

Now the zeroth order deformation equation as

$$(1-q)L[\Phi_i(t;q) - x_{i,0}(t)] = qh_iN_i[\Phi_i(t;q)], \quad i = 1, 2 \tag{4.60}$$

From the definition of homotopy we get $\Phi_i(t;0) = \Phi_{i,0}(t)$, $\Phi_i(t;1) = x_i(t)$. It can be understood that as q increases from 0 to 1 initial approximation $\Phi_i(t;q)$ approaches the solution $x_i(t)$ for $i = 1, 2$. Now $\Phi_i(t;q) = x_{i,0}(t) + \sum_{m=1}^{\infty} x_{i,m}(t)q^m$ where

$$x_{i,m}(t) = \frac{1}{m!}\left.\frac{\partial \varphi_i(t;q)}{\partial q^m}\right|q = 0 \tag{4.61}$$

Define the vector $\vec{x}_{i,n} = \{x_{i,0}(t), x_{i,1}(t), \ldots, x_{i,n}(t)\}$. The mth deformation equation is given by

$$L[x_{i,m}(t) - \chi_m x_{i,m-1}(t)] = h_i R_{i,m} \vec{x}_{i,m} \tag{4.62}$$

subject to the initial condition $x_{1,\,0} = 0$, $x_{2,\,0} = 0$, where

$$R_{1,m}\vec{x}_{i,m} = \dot{x}_{1,m-1} + 102x_{1,m-1} - 88x_{2,m-1}$$
$$R_{2,m}\vec{x}_{i,m} = \dot{x}_{2,m-1} - 88x_{1,m-1} - 102x_{2,m-1}$$

Now from (Putcha 2011) the solution of the mth order deformation equation for $m \geq 1$ is

$$x_{i,m}(t) = \chi_m x_{i,m-1}(t) + h_i L^{-1}\left[R_{i,m}\left(\vec{x}_{i,m-1}\right)\right] \tag{4.63}$$

Now get the successive approximations as

$$x_{1,1}(t) = -120ht, \;\; x_{2,1}(t) = 280ht, \tag{4.64}$$

$$\begin{aligned} x_{1,2}(t) &= -120ht - 120h^2t - 18400h^2t^2, x_{2,1}(t) \\ &= 2800ht + 280h^2t + 21600h^2t^2 \end{aligned} \tag{4.65}$$

Now by taking $h = -1$ (without plotting the h-curve) the solution of (4.58) is given by

$$x_1(t) = \sum_{m=0}^{\infty} x_{1,m}(t) = -\mathrm{e}^{-200t} + 2\mathrm{e}^{-40t} \quad \text{and}$$
$$x_2(t) = \sum_{m=0}^{\infty} x_{2,m}(t) = \mathrm{e}^{-200t} + 2\mathrm{e}^{-40t}.$$

4.4 Numerical Methods

As we have mentioned in the introduction, very few ODEs admit closed form solutions in terms of popular known functions such as trigonometric, exponential, and polynomial. The only way-out is numerical solution of ordinary differential equations. These numerical methods can be implemented by software packages like MATLAB. When we cannot find a function which will act as a solution at infinite number of points of an interval, we find the value of the solution at finite number of points. To choose those finite number of points we divide the interval into finite number of subintervals. In all the numerical methods accuracy can be increased by decreasing the step size, i.e., we need to compute the value of the solution at more number of points from the initial point to the point where we need to find the value of

the solution. The sequence of iterations defined by various numerical methods solving nonlinear differential equations will converge to their exact solutions only when conditions for convergence of the corresponding numerical methods are satisfied means latently important concepts of nonlinear differential equations such as Lipschitz condition, fixed point theory, contraction mapping, conditions of Banach fixed point theorem are satisfied and initial values are located in some desired interval. The fundamental required to construct solutions of dynamical systems by using Numerical methods are presented in Stoer and Bulirsch (2002) and Stuart and Humphries (1996).

4.4.1 Euler's method

There are two types of Euler's methods (i) Forward Euler method and (ii) Backward Euler method.

Consider the nonlinear ordinary differential equation

$$\dot{x} = f(x,t), \;\; x(t_0) = x_0, \quad x \in R \tag{4.66}$$

Euler's method is easy to apply but require more steps to arrive at required accuracy in an interval $t \in [t_0, t_0 + T]$. Euler's method is the simplest, but least efficient numerical integrator in terms of the number of steps needed to propagate solutions for times $t \in [t_0, t_0 + T]$ with given accuracy. This method actually discretizes the derivative $\dot{x} \approx \frac{(x_{n+1}-x_n)}{\Delta t}$ to yield the difference equation:

$$x_{n+1} = x_n + \Delta t f(x_n, t_n), \tag{4.67}$$

with $x_0 = x(t_0)$ (naturally), and $t_n = t_0 + n\,\Delta t$. This is the forward Euler method (see below for backward Euler method). Here to find the value of $x(t)$ at $t = t_n$ we evaluated the value of $x(t)$ at $t = t_1, t_2, \ldots, t_{n-1}$. To increase the accuracy of the solution we need to divide the interval in to more number of subintervals. The Euler method is also called the tangent line method, since at each iteration we take the step $x_{n+1} - x_n = \Delta t f(x_n, t_n)$ in the direction of the tangent to a "true" solution and at each step we get an error of $O(\Delta t^2)$.

In the Backward Euler method, we approximate the time derivative $\dot{x} = f(x,t)$ by a backward difference quotient: $\frac{x_{n+1}-x_n}{\Delta t} = f(x_{n+1}, t_{n+1})$ and the Backward Euler formula is given by

$$x_{n+1} = x_n + \Delta t f(x_{n+1}, t_{n+1}) \tag{4.68}$$

Therefore, we have to find the point x_{n+1} that we would have arrived at, leaving from x_n in the direction tangent to the vector field at x_{n+1}. In the backward Euler

formula we may have to use, e.g., Newton's method to find x_{n+1} at each step: an iterative loop within an iterative loop.

In the forward Euler method if the step size Δt is too large, for an asymptotically stable scalar equation whose solutions all converge to fixed points or approach particular solutions $\bar{x}(t)$ as $t \to \infty$, can give growing solutions. The forward Euler method is explicit method and conditionally stable but backward Euler is an implicit method and is unconditionally stable. Euler's method computes a truncated Taylor series of the solution.

4.4.2 Runge–Kutta Method

There are many methods available in literature, but Runge–Kutta method is widely used since it is easy to implement and gives good accuracy. RK algorithms have always been considered as the best tool for the numerical integration of ordinary differential equations (ODEs).

The general p-stage Runge–Kutta method for solving an IVP (4.66) is defined by

$$x_{n+1} = x_n + h \sum_{i=1}^{p} b_i k_i \tag{4.69}$$

where

$$k_i = f\left(t_n + c_i h, x_n + h \sum_{i=1}^{p} a_{ij} k_j\right), \quad i = 1, 2, 3, \ldots, p \tag{4.70}$$

and

$$c_i = \sum_{i=1}^{p} a_{ij}, \quad i = 1, 2, 3, \ldots, p. \tag{4.71}$$

The fourth-order Runge–Kutta algorithm for IVP (4.66) is of the form

$$x_{n+1} + 2k_2 = x_n + \frac{1}{6}[k_1 + 2k_3 + k_4] \tag{4.72}$$

where $k_1 = hf(t_n, x_n)$, $k_2 = hf\left(t_n + \frac{h}{2}, x_n + \frac{k_1}{2}\right)$, $k_3 = hf\left(t_n + \frac{h}{2}, x_n + \frac{k_2}{2}\right)$ and $k_4 = hf(t_n + h, x_n + k_3)$.

4.4.3 Runge–Kutta Butcher method

From the literature (Hossain et al. 2017; Park et al. 2004) it is observed that Butcher's fifth-order Runge–Kutta (RK5) and fourth-order Runge–Kutta (RK4) methods are powerful methods to solve the initial value problems. In the preceding equations (4.69), (4.70) and (4.71) c and b are p–dimensional vectors and $A\,(a_{ij})$ is the $p \times p$ matrix. Then the Butcher array takes the form

c_1	a_{11}					
c_2	a_{21}	a_{22}				
c_3	a_{31}	a_{32}	a_{33}			
.	.	.	.			
.	.	.	.			
.	.	.	.	…		
c_p	a_{p1}	a_{p2}	a_{p3}	…	$a_{p\,p-1}$	a_{pp}
	b_1	b_2	b_3	…	b_{p-1}	b_p

The fourth- and fifth-order RK Butcher formulae for the solution of the IVP (4.66) are given by $y_{n+1} = y_n + \frac{1}{90}[7k_1 + 32k_3 + 12k_4 + 32k_5 + 7k_6]$ and $y^*_{n+1} = y_n + \frac{1}{6}[k_1 + 4k_4 + k_6]$, respectively, where $k_1 = hf(x_n, y_n)$, $k_2 = hf\left(x_n + \frac{h}{4}, y_n + \frac{k_1}{4}\right)$, $k_3 = hf\left(x_n + \frac{h}{4}, y_n + \frac{k_1}{8} + \frac{k_2}{8}\right)$, $k_4 = hf\left(x_n + \frac{h}{2}, y_n - \frac{k_2}{2} + k_3\right)$, $k_5 = hf\left(x_n + \frac{3h}{4}, y_n + \frac{3k_1}{16} + \frac{9k_4}{16}\right)$, $k_6 = hf\left(x_n + h, y_n - \frac{3k_1}{7} + \frac{2k_2}{7} + \frac{12k_3}{7} - \frac{12k_4}{7} + \frac{8k_5}{7}\right)$.

Euler method is popular and examples are available in all the standard books. The following examples demonstrate RK Butcher method and its comparison with RK method. RK Butcher method gives better results when compared with that of other popular methods. These can be used as good predictors and can be improved by using corrector methods.

Example 4.1 Consider the initial value problem $\frac{dy}{dx} = 2y + 3e^x$ satisfying $y\,(0) = 0$. To find the value of y when $x = 0.2$. Take $h = 0.1$. By using RK method of order 4 we find $y_1 = y(0.1) = 0.348$ where $K_1 = 0.3$, $K_2 = 0.345$, $K_3 = 0.349$, $K_4 = 0.401$ and $y_2 = y\,(0.2) = 0.809$ where $K_1 = 0.401$, $K_2 = 0.458$, $K_3 = 0.463$, $K_4 = 0.528$. By using fourth- and fifth-order RK Butcher algorithms we get $y\,(0.1) = y_1 = 0.348$ and $y\,(0.1) = y_1 = 0.348$, respectively, where $K_1 = 0.3$, $K_2 = 0.322$, $K_3 = 0.323$, $K_4 = 0.347$, $K_5 = 0.373$, $K_6 = 0.401$. By using fourth- and fifth-order RK Butcher algorithms we get $y\,(0.2) = y_1 = 0.8106$ and $y\,(0.2) = y_1 = 0.8108$, respectively, where $K_1 = 0.401$, $K_2 = 0.429$, $K_3 = 0.430$, $K_4 = 0.0.461$, $K_5 = 0.493$, $K_6 = 0.528$. Exact solution is given by $y\,(0.1) = 0.348$ and $y\,(0.2) = 0.8112$. In this example it is observed that solutions obtained by RK Butcher algorithms are more close to exact solutions.

Example 4.2 Consider the differential equation $\frac{dy}{dx} = \sqrt{x + y}$ satisfying the initial condition $(0.4) = 0.41$. To find the value of $y\,(x)$ when $x = 0.8$, Take $h = 0.2$. By using RK method of order 4 we find y_1 at $x_1 = 0.6$. We compute $K_1 = 0.18$, $K_2 = 0.2$, $K_3 = 0.2$, $K_4 = 0.22$, $K = 0.2$, $y_1 = 0.61$. To find y_2 at $x_1 = 0.8$ we compute $K_1 = 0.22$,

$K_2 = 0.238$, $K_3 = 0.239$, $K_4 = 0.256$, $K = 0.238$, $y_2 = 0.848$. By using fourth- and fifth-order RK Butcher algorithms we get $y(0.6) = y_1 = 0.6102$ and $y(0.6) = y_1 = 0.654$, respectively, where $K_1 = 0.18$, $K_2 = 0.1902$, $K_3 = 0.1903$, $K_4 = 0.2004$, $K_5 = 0.2103$, $K_6 = 0.22$. By using fourth- and fifth-order RK Butcher algorithms we get $y(0.8) = y_1 = 0.8521$ and $y(0.8) = y_1 = 0.949$, respectively, where $K_1 = 0.223$, $K_2 = 0.233$, $K_3 = 0.233$, $K_4 = 0.242$, $K_5 = 0.251$, $K_6 = 0.2604$.

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Chapter 5
Impact of a Psychological Follow-Up of Diabetics in the Management of Diabetes in Morocco

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Abstract Several studies revealed that people with diabetes are at high risk of decreasing the psycho-emotional well-being that is already present in the majority of diabetic patients at the time of diagnosis. The study aim is to study the impact of psychological follow-up by a psychologist on the glycemic control of diabetics. Population of study is composed of 70 diabetics. The sample is selected based on Rosenberg's self-esteem scale. Glycemic control was carried out, by the three most widely used blood tests for diabetes, viz. fasting blood glucose, post-prandial glucose, and glycated hemoglobin, twice (t_0), first visit and (t_f) at the end of the psychological intervention. Depression was determined using the "patient health questionnaire (PHQ-9)." The body mass index (BMI) was calculated based on the WHO standard recommendation (Weight/Height^2). The whole population is overweight (BMI > 25), for women (26.21 ± 5.65) and for men (26.42 ± 3.44), as well as the values of the three blood tests (HbA1c, PPG, and FBG) are above standards. We found that the difference is significant ($P < 0.01$) for the means of HbA1c (%) from t_0 to t_f; fasting glucose from t_0 at t_f, and post-prandial glucose at t_0 and t_f. The difference is significant ($P < 0.05$) for the PHQ-9 averages from t_0 to t_1; and from PHQ0 to t_1 and t_2. For the correlational analysis we found: a highly significant between PHQ value at (t_2) and FBG value at (t_f) ($r = 0.314$, $P < 0.01$), a significant between the PHQ value at (t_2) and the PPG value (t_f) ($r = 0.274$, $P < 0.01$), a

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significant between the PHQ value at (t_2) and the value of HbA1c at (t_f) ($r = 0.449$, $P < 0.01$) and a highly significant between the value of PPG at (t_f) and the value of HbA1c at (t_f) ($r = 0.618$, $P < 0.01$). This study confirmed the positive role of psychological followed a diabetic and therefore its establishment is required in the management of diabetes.

Keywords Diabetes · Psychological intervention · Depression · Glycemic equilibrium

5.1 Introduction

Several studies revealed that people with diabetes mellitus are at high risk of decreased mental wellness (Gask et al. 2011; Stuckey et al. 2014), which is already present in the majority of diabetic patients at the time of diagnosis (Walker et al. 2012). All this may be a results to strained coping with interchanged life pattern such as financial issues, relationships, and work-related stress (Stuckey et al. 2014) directly after diagnosis of diabetes (Walker et al. 2012). A recent investigation on diabetic animals' model revealed that uncontrolled chronic hyperglycemia elevates remarkably reactive oxygen species induced oxidative stress, which stimulate the emergence of mental health disorder, viz. anxiety and depression-related behaviors (Bikri et al. 2021). An international study in 17 countries across four continents, involved above 16,000 persons comprising patients, family members, and healthcare providers, revealed that the proportion of patients with diabetes who were likely to have diabetes-related distress and depressive symptoms was 44.6% and 13.8%, respectively, with a substandard quality of life evaluated at 12.2% (Nicolucci et al. 2013). Diabetes had a defeatist impact on numerous aspects of life, ranging from 20.5% on relationship with family or friends to 62.2% on physical health. About 40% (18.6–64.9%) of these patients reported their medication interfered with their ability to live a normal life (Nicolucci et al. 2013). Moreover, diabetics patients frequently use negative coping strategies and all the time perceive that diabetes would negatively affect their future (Walker et al. 2012; Rane et al. 2011). The chronic psychosocial disorders without treatment in patients with diabetes, can promote others physical symptoms (Bener et al. 2012), cardiovascular complications (Laake et al. 2014), and depressive symptoms (Skinner et al. 2010; Ghiadoni et al. 2000). Some psycho-emotional symptoms such as depression can promote cognitive impairment and aggravate vicious cycles of self-care ability (Sullivan et al. 2013). Several researches have mostly been on the association between diabetes and depressive symptoms (Park et al. 2013; Baumeister et al. 2012), with the focus on major depressive disorder, hence the need for psychological care of diabetic patients. As a result, the purpose of this work is to study the impact of psychological follow-up by a psychologist on the glycemic control of diabetics.

5.2 Materials and Methods

The present work was conducted in the diabetes referral center in the Kenitra province between January 2016 and April 2016.

5.2.1 Population

The study population consisted of 70 diabetics at the beginning the goal was to have a group of 140 patients (70 women and 70 men), 5 women refused to continue the study for personal reasons, and only 5 men respected the appointments of consultations with the psychologist which explains the big difference between the number of women and men (92.9% of women and 7.1% of men). The average age is 50.19 ± 14.56 with an age range of 18–80 years. The population is not randomly selected, but rather based on Rosenberg's self-esteem scale (Rosenberg 1965). And that is how we included only patients with low self-esteem (score below 25), that is, patients with poor self-perception.

5.2.2 Data Collection

Data collection was performed out using a self-questionnaire containing various information, namely: socio-demographic, anthropometric, glycemic control, etc.

For glycemic control, it was based on the three blood tests most used by the attending physician in the follow-up of diabetics, fasting blood glucose (FBG), postprandial glucose (PPG) and glycated hemoglobin (HbA1c). For the assessment of depression in patients we had used "patient health questionnaire (PHQ-9)" (Kroenke et al. 2001) representing the most used questionnaire in screening for depression in front-line services. In addition, it allows the assessment of depressive symptoms in the last 2 weeks, and is also used in monitoring and evaluating the response to treatment, which represents the fundamental aim of this study.

5.2.2.1 Anthropometric Measurements

The size and weight were measured with a height gage and scale, respectively. Body mass index (BMI) was calculated according to the standards described by the WHO, by using the following formula ($weight/height^2$).

5.2.2.2 Psychological Intervention

The three blood tests (FBG, PPG, and HbA1c), were collected twice:

- (t_0): corresponding to the first consultation,
- (t_f): at the end of the psychological intervention, separated from a period of 3 months because the analysis of HbA1c is done once in 3 months.

The evaluation of depression with the PHQ-9 was carried out in three parts (t_0, t_1, and t_2):

- t_0 represents the initial state of the patient,
- t_1 represents the patient's situation after consultation with the psychologist,
- t_2 represents the patient's situation after the final intervention with the psychologist.

These three times are intended to study the evolution of the patient's depressive situation.

The questionnaire contains nine items, items 1–9 are scored on a 0–3 scale and item 10 (operating level) are counted on a 0–4 scale, ranging from "Not at all difficult" to "Extremely difficult." The quotation is as follows: 1–4 (minimal depression), 5–9 (mild depression), 10–14 (moderate depression), 15–19 (moderately severe depression), and 20–27 (severe depression).

Each participant was individually consulted by a psychologist During five sessions, where the psychologist used the person-centered psychotherapy approach of CARL ROGERS.

5.3 Results

As mentioned in Table 5.1, the entire population is overweight (BMI > 25), for women (26.21 ± 5.65) and for men (26.42 ± 3.44), we also note that the values of the three blood tests (HbA1c, PPG, and FBG) are higher than the norms.

The difference is significant Table 5.2. ($P < 0.01$) for mean HbA1c (%) at t_0 and t_f; fasting blood glucose (g/l) at t_0 and t_f; and post-prandial glucose (g/l) at t_0 and t_f. The difference is significant ($P < 0.01$) for the averages of PHQ0 at t_0 and t_1; and from PHQ0 to t_1 and t_2.

Table 5.3 shows correlation between questionnaire depression (PHQ) at (t_2) and glycemic profile at (t_f):

- Pearson correlation is highly significant between PHQ value at (t_2) and FBG value at (t_f) ($r = 0.314$, $P < 0.01$);
- Pearson correlation is significant between the PHQ value at (t_2) and the PPG value (t_f) ($r = 0.274$, $P < 0.01$);
- Pearson correlation is significant between the PHQ value at (t_2) and the value of HbA1c at (t_f) ($r = 0.449$, $P < 0.01$);

Table 5.1 Characteristics of population

Items	Women M ± SD	Men M ± SD
Age (year)	50.05 ± 14.54	52.00 ± 16.43
Weight (kg)	68.43 ± 13.03	80.40 ± 10.71
Size (cm)	162.25 ± 9.62	174.00 ± 2.24
Body mass index	26.21 ± 5.65	26.42 ± 3.44
Waist size	99.86 ± 22.57	111.20 ± 4.02
Hip circumference	104.26 ± 21.21	112.40 ± 11.78
Value of self-esteem	15.35 ± 2.58	17.00 ± 2.24
Employment	0.03 ± 0.17	0.00 ± 0.00
Duration of illness	8.88 ± 4.95	8.80 ± 7.43
HbA1c	10.66 ± 2.14	8.40 ± 0.18
FBG (g/l)	2.53 ± 0.85	1.57 ± 0.29
PPG (g/l)	3.24 ± 1.08	2.24 ± 0.56

Data are expressed to mean ± standard deviation (M ± SD)

Table 5.2 Longitudinal study of HbA1c, fasting, and post-prandial glucose levels before and after psychic treatment

Values versus time		M ± SD	Paired differences (M ± SD)	Paired samples test
Pair 1	HbA1c (%) at (t_0)	(10.10 ± 1.7)	(2.7; 1.8)	($t = 13$, $P < 0.01$;DS)
	HbA1c (%) at (t_f)	(7.6 ± 1.6)		
Pair 2	FBG (g/l) at (t_0)	(2.45 ± 0.85)	1.00; 0.65)	($t = 12.7$, $P < 0.01$; DS)
	FBG (g/l) at (t_f)	(1.45 ± 0.39)		
Pair 3	PPG (g/l) at (t_0)	(3.16 ± 1.07)	(1.31; 0.79)	($t = 13.9$, $P < 0.01$; DS)
	PPG (g/l) at (t_f)	(1.84 ± 0.53)		
Pair 4	PHQ at (t_0)	(17.1 ± 6.1)	(5.44, 2.83)	($t = 19.07$, $P < 0.01$; DS)
	PHQ at (t_1)	(11.65 ± 4.70)		
Pair 5	PHQ at (t_1)	(11.65 ± 4.70)	(4.67, 2.44)	($t = 16.05$, $P < 0.01$; DS)
	PHQ at (t_2)	(6.98 ± 3.64)		

M Mean, *SD* Standard deviation, *HQP* Value of the questionnaire "patient health questionnaire"

– Pearson correlation is highly significant between the value of PPG at (t_f) and the value of HbA1c at (t_f) ($r = 0.618$, $P < 0.01$).

5.4 Discussion

Several investigations have revealed a significant positive correlation between diabetes and depression, it would be twice present in diabetic patients compared to normal subjects (Anderson et al. 2001) and associate with disease complications and mortality. Compared to patients with non-cardiovascular diseases, the incidence of

Table 5.3 Study of correlations between questionnaire depression (PHQ) at (t_2) and glycemic profile at (t_f)

		PHQ at (t_2)	FBG at (t_f)	PPG at (t_f)	HbA1c at (t_f)
PHQ_2 at (t_2)	Pearson correlation	1	0.314**	0.274**	0.449**
	Sig. (bilateral)		0.008	0.022	0.0
	N	70	70	70	70
FBG at (t_f)	Pearson correlation	0.314**	1	**0.873	0.547**
	Sig. (bilateral)	0.008	0.873**	0.0	0.0
	N	70	70	70	70
PPG at (t_f)	Pearson correlation	0.274*	0.873**	1	0.618**
	Sig. (bilateral)	0.22	0.0		0.0
	N	70	70	70	70
HbA1c at (t_f)	Pearson correlation	0.449**	0.547**	0.618**	1
	Sig. (bilateral)	0.0	0.0	0.0	
	N	70	70	70	70

* Correlation is significant at the 0.05 level (bilateral)
** Correlation is significant at the 0.01 level (bilateral)

depression in patients with cardiovascular diseases is increased to 10–40%, and the incidence of anxiety is increased to 20–70% (Golden et al. 2008). This study confirms this hypothesis; indeed, there is a significant correlation between hyperglycemia and depression. The present study was intended to evaluate the influence of psychological treatment on the metabolic control of diabetes; the results obtained are positively satisfactory.

Indeed, the results of this study revealed that the participants showed an improvement in their glycemic profile (GAJ, GPP, and HbA1c) as well as a psychological improvement during psychological interventions between (t_0) and (t_f), the value of PHQ-9 is from 17.1 in t_0 to 6.98 to t_2 which means that we have gone from a moderately severe depression (value between 15 and 19) to a slight depression (value between 5 and 9), demonstrating the positive effect psychological followed on diabetes care.

In fact, positive psyco-emotional element are major mediators or rindependent isks factors of clinical outcomes in the management of chronic hyperglycemia, and are remarkably associated to self management behaviors (Chan et al. 2009), having a direct impact on subjective health.

Literature (Jaser et al. 2014; Robertson et al. 2013) demonstrates that psychological well-being especially resilience, gratitude, and positive effect is closely related to self-management of blood glucose monitoring, we find the same pace in our study. This self-management is a major factor in the decline of mortality, for all causes in diabetics patients (Robertson et al. 2012; Chan et al. 2009). Nevertheless, little significant research studies have investigated the impacts of positive aspects of psycho-emotional health in normal as well as in diabetics patients outcomes. Other empirical works have shown significant results of the negative and positive effect on glycemic management (Skaff et al. 2009; Ryff et al. 2006).

Even though the relationship between diabetes symptoms, self-care practices and emotional well-being become clearer, a shortage of health programs integrating human psychology and intervention in diabetics patients still persist, despite positive findings on self-management, care behaviors and clinical outcomes (Forjuoh et al. 2014; Piette et al. 2004). Some researchs that have examined the symptoms of depression and methods to limit their development have establish prospective, cross-sectional and nd time-consistent associations with glycated haemoglobin (Aikens 2012; Fisher et al. 2010). However, a causal association between the two requires more prospective studies between diabetes-related distress and glycated haemoglobin (Fisher et al. 2010). From the above discussion, it is possible that glycated hemoglobin may be affected by chronic emotional disorders in a bidirectional model (Xue et al. 2017).

5.5 Conclusion

Our hypothesis was to show the influence of psychological followed on blood-sugar management in diabetic patients. The present research revealed a real positive effect on the glycemic profile of patients, which proves the importance and the need to integrate psychological follow-up in diabetics. Given the limitations of this study, we have not been able to analyze the whole of this very vast subject. However, it would seem interesting, in the future, to explore the profile of the cardiovascular risk factors associated with the disease.

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Chapter 6
Neuroprotective and Anxiolytic Effects of Date Seeds Phenolic Compounds in Nicotinamide-Streptozotocin-Induced Type 2 Diabetic Rats

Bikri Samir, Aboussaleh Youssef, and Wael Mohamed

Abstract Several experimental and clinical data revealed that type 2 diabetes (T2D) is linked with behavioral and biochemical alterations. Date grains, one of the important valuable natural by-products with antioxidant and anti-inflammatory proprieties, have been revealed to have many benefits against diabetes mellitus and its complications. The present work aims to investigate the protective and anxiolytic effects of date seeds extract (DSE) in T2D rat model. Animals were divided into four groups as follows: Group 1 (diabetic control), groups 2 and 3 were diabetic treated with metformin (Met, 300 mg/kg) and DSE (2000 mg/kg), respectively, and the group 4 was normal control. Each group contains 10 rats. T2D in these rats was induced by an intraperitoneal injection of Streptozotocin (65 mg/kg) and Nicotinamide (110 mg/kg) (15 min between the two injections). Treatment lasted for 42 days just after diabetes confirmation. Anxiety-related behavior of rats was evaluated just before sacrifice using four behavioral tests. After rats were sacrificed, the brain was dissected out in order to assess tumor necrosis factor-alpha and lipid peroxidation levels in prefrontal cortex as well as in Hippocampus. Treatments with metformin and/or DSE remarkably decreased the tumor necrosis factor-alpha levels and prevent the lipid peroxidation generation in prefrontal cortex and hippocampus in streptozotocin-nicotinamide diabetic rats. Moreover, the administration of metformin or DSE for 42 days prevented significantly anxiety-related behavior in these rats. In summary, the results of the present study revealed that DSE

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exhibited anxiolytic propriety in T2D rats, which might be due to its powerful anti-inflammatory and antioxidant proprieties.

Keywords Type 2 diabetes · Date seeds · Anxiety · Tumor necrosis factor-alpha · Lipid peroxidation

6.1 Introduction

Diabetes mellitus is a serious public health problem, due to the considerable number of diabetic patient worldwide, which contribute to decrease their daily life quality (American Diabetes Association 2017). Type 2 diabetes mellitus (T2DM) is defined as a complex and chronic endocrine metabolic disease, usually caused by abnormal glucose metabolism, resistance and deficiency insulin, leading to remarkable rise in blood glucose concentrations, which in turn damage several body organs (Zhang et al. 2015; Ascher et al. 2015). Several investigations have clearly established that persistent hyperglycemia in patient with diabetic can lead to many damage of the central and peripheral nervous system (Bloomgarden 2010; Gispen and Biessels 2000).

Recently, it has become clear that T2DM hallmarks are significantly correlated with oxidative stress and inflammation (Reis et al. 2012). While several studies documented that one of the main complication of chronic hyperglycemia is the overproduction of reactive oxygen species in excess, which promotes in turn the brain elevation of inflammation and oxidative stress markers (Reis et al. 2012). Accordingly, these two mechanisms are being envisioned as the crucial players in encephalopathy induced by T2DM. Therefore, the oxidative stress and inflammation related to diabetes mellitus induce neuronal apoptosis, which in turn can ultimately lead to neurodegenerative events (Maiese et al. 2007). Type 2 diabetes (T2D) has clearly revealed to be involved in mental disorders, which is apparent in an elevated of prevalence of psychiatric symptoms such as anxiety-related behavior (Al-Maskari et al. 2010). These symptoms are generally associated to many chronic hyperglycemia factors including oxidative stress, inflammation, drop of monoamine neurotransmitter concentrations in brain regions, dysfunctions of the activity of hypothalamic–pituitary–adrenal axis, and alterations of the synaptic plasticity (Hajebrahimi et al. 2016; de Morais et al. 2014; Beauquis et al. 2010).

Nutritional therapies that limit inflammation and oxidative stress could serve to decrease the risk of diabetes complications (Rains and Jain 2011). However, several works investigation has shown that natural products with anti-inflammatory and antioxidant proprieties protect the neurons against chronic diabetes alterations (Şahin et al. 2019; Kuhad and Chopra 2007). In this sense, it is objective to evaluate the beneficial effects of natural products that contains crucial anti-inflammatory and antioxidant activities on diabetes-induced mental disorder, especially anxiety-like behavior.

Date palm seeds are considered as one of the most valuable natural by-product, which mainly riches in the phenolic compounds (Bikri et al. 2021a). It has been well

evaluated for pharmacological proprieties such as immuno-stimulant (Saryono Dardjito et al. 2019), antioxidant (Bikri et al. 2021a), and anti-inflammatory (Saryono et al. 2020). In addition, date palm seeds have been revealed to have numerous benefits against diabetes mellitus and its complications (El-Fouhil et al. 2010) through inhibiting the alpha-amylase and alpha glucosidase enzymes, repairing pancreatic cells and stimulate endogenous insulin secretion (Saryono 2019; El-Fouhil et al. 2013). There is also increasing evidences indicating that this product enhance significantly the activity of many endogenous antioxidants such catalase and superoxide dismutase (Saryono et al. 2017), in contrast limit lipid peroxidation production in diverse cell (Bikri et al. 2021b). However, there are no published works explored the neuroprotective effect of date seeds extract (DSE) against oxidative alteration and inflammation in central nervous system induced by type 2 diabetes. In this focus, the current study aims to investigate the neuroprotective and anxiolytic effects DSE in nicotinamide-streptozotocin-induced type 2 diabetic rats. We hypothesized that DSE can reduce inflammation and oxidative stress and prevent anxious symptoms in T2D rats.

6.2 Materials and Methods

6.2.1 Extraction of Phenolic Compounds from Date Seeds

Three varieties of locally date known as Boufaggous, Bouzekri, and Bousthammi were used in the present study (These varieties were obtained from "Fint oasis" of Ouarzazate region in south-east of Morocco). Seeds were directly isolated from theirs dates and soaked in distilled water and then dried at 40 °C for 48 h. Date seeds of all varieties used were mixed and ground into powder with coffee grinder. The mixture was extracted three times with water and methanol (9:1) at the ratio of sample/solvent (1:10 w/v) with a magnetic stirring plate (120 rpm for 4 h at 40 °C). The mixture was then centrifuged, filtered, and evaporated at 50 °C to obtain the date seeds aqueous extract. Finally, the extract was lyophilized.

6.2.2 Total Phenolic Contents of Date Seed Extract

To evaluate the total phenolic content, the method of Folin–Ciocalteu was used in this study (Singleton and Rossi 1965). Gallic acid was used as standard, and the result was expressed as mg of Gallic acid/g Dry Weight.

6.2.3 *Effect of Date Seed Phenolic Compounds in NA-STZ Diabetic Rat*

6.2.3.1 Animals

In the current study, 40 Wistar rats weighing (200–220 g) were used. All the rats were housed in standard plexiglass cage under standard laboratory conditions, with free access to water and food.

Experimentation procedures were conducted in accordance with the accepted principles of the Guide for the Care and Use of Laboratory Animals (NRC 1996). This study was also approved by the Ethical Committee for Animal Experimentation of Ibn Tofail University in Kenitra.

6.2.3.2 Acute Toxicity

According to the guideline of the Organization for Economic Cooperation and Development, acute oral toxicity study (AOTS) was carried out in normal Wistar male rats. Two groups of rats ($n = 7$) randomly selected were used for AOTS (test group and control group). The rats were kept without food providing only with water overnight prior to date seeds extract (DSE) administration. The DSE was then administered orally at the dose of 2000 mg/kg of body weight in the test group rats. Then the rats were kept under close observation for the first 2 h (directly after administration) and at regular intervals for 24 h for the next 14 days, in order to detect any symptoms or undesirable effect (e.g. body loss, hyperactivity, irritability, and locomotion disorder) and finally coma and death.

6.2.3.3 Experimental Diabetes Induction and Study Design

All rats except control group were made diabetic by injecting STZ intraperitoneally at a single dose (65 mg/kg) 15 min after receiving nicotinamide intraperitoneally at (110 mg/kg) (Radenković et al. 2016). After 72 h hyperglycemia was checked and confirmed using a glucometer. The rats with fasting blood glucose (FBG) higher to 2 g/L were selected for the present study. Then, the rats were randomized into four groups with 10 rats in each group: normal control group (NC), diabetic control group (NA-STZ), diabetic group treated with metformin (NA-STZ-Met, 300 mg/kg), and diabetic group treated with date seeds extract (NA-STZ-DSE, 2000 mg/kg). The treatment was administered orally for 42 days. During the study, FBG, food intake, and body weight were determined every 2 weeks using a glucometer, electronic balance and metabolic cages, respectively. Before the sacrifice day, anxiety-related behavior of all groups was evaluated using four behavioral tests. Then the rats were sacrificed and the brain was dissected out in order to assess tumor necrosis factor-alpha and lipid peroxidation levels in prefrontal cortex as well as in hippocampus.

6.2.3.4 Anxiety-Related Behavior Tests

Black-White Box Test

We proceeded with BWB test to assess anxiety-related behaviors. This test consists of two chambers (25 × 25 × 25 cm) connected via a tunnel; the first is highly illuminated (white chamber) and the second is dark (black chamber). These parameters were recorded during 6 min; the time spent in the black / white chambers and the number of entries in the white chamber (Bourin and Hascoet 2003).

Open Field Test

We carried the open field test as described by Prut and Belzung (2003) to assess anxiety-related behavior in diabetic rats. Briefly, the apparatus is divided into 25 squares (9 central and 16 peripheral). In individual tests, the animals were placed in the center squares of the apparatus and allowed freely explore the field for 10 min. The following measurements were recorders: time spent in the central squares (TCS) and central squares entries (CSE).

Novelty Suppressed Feeding Test

The NSF test is widely used to study rat models of anxiety (Benmhammed et al. 2019). However, this test is done in an apparatus (100 × 100 cm). All animals were subjected to food restriction for 16 h. Then, all rats were placed individually in the corner of apparatus next to the food (arranged at the center of the apparatus). Then, the time needed to eat the food was recorded.

Elevated Plus Maze Test

The EPM test consists of four arms (two open arms perpendicular to two closed arms) connected by a central zone in the middle (10 × 10 cm). In the beginning, each rat was individually placed in the central zone facing an open arm and allowed to explore freely the plus maze for 5 min. The number of entries in open arms and time spent into the open arms were recorded as an index of anxiety (Walf and Frye 2007).

6.2.3.5 Biochemical Assays

Tissue Preparation and Protein Assay

After sacrifice, prefrontal cortex and hippocampus were dissected out and homogenized in ice-cold lysis buffer. Then, the homogenate was centrifuged at 3500 rpm

for 15 min. After centrifugation, the supernatant obtained was collected for the evaluation of tumor necrosis factor-alpha and lipid peroxidation levels in both regions.

The Bradford method was used to estimate the protein content (Bio-Rad, Hercules, USA). Bovine serum albumin (BSA) was used as a standard.

Lipid Peroxidation Assay

Malondialdehyde (MDA) cencentration was measured in cells, in order to analyses the formation of lipid peroxides in the hippocampus and prefrontal cortex region (Draper and Hadley 1990). TBARS levels were expressed as (nmol/mg protein).

Tumor Necrosis Factor-Alpha Estimation

The TNF-α assay was performed on the prepared homogenates (HP and CPF). Rat TNF-α ELISA kit (Invitrogen KRC3011) was used to estimate The TNF-α content of the samples (according to the manufacturer's instructions). The level of TNF-α was presented as (picogram/mg of protein).

6.2.4 Data Analysis

Statistical analyses were carried out using Graphpad prism 8 software. All data were presented as the mean ± standard deviation. Data were analyzed using one way ANOVA test followed by Tukey post Hoc test for significance of difference and comparison between groups ($p < 0.05$).

6.3 Results

6.3.1 Total Phenolic Content (TPC) and Acute Oral Toxicity of Date Seeds Extract (DSE)

In our study, spectrophotometric estimation of TPC of DSE was evaluated at 14.27 ± 0.27 mg GAE/g DW.

The oral acute toxicity study showed that rats treated with DSE (2000 mg/kg) did not reveal any variation in their behavioral pattern, water and food intakes, and body weight compared to the control group(not submitted data). It was concluded that DSE was safe at this dose.

6.3.2 Changes in Fasting Blood Glucose, Body Weight, and Food Intake in Normal and NA-STZ Diabetic Rat

Figure 6.1 report the effect of daily administration of DSE and/or Metformin during 42 days, on FBG, body weight, and food intake in diabetic Rats. At the end of the experiment, NA-STZ group treated with Metformin and NA-STZ group treated with DSE showed a significant improvement of fasting blood glucose ($p < 0.001$) compared to NA-STZ group. In addition, body weight in treated NA-STZ groups increased significantly ($p < 0.001$) compared to the untreated NA-STZ group. Compared to no-treated NA-STZ group, food consumption in NA-STZ treated groups has significantly decreased ($p < 0.001$).

6.3.3 Lipid Peroxidation Level in Hippocampus and Prefrontal Cortex in Normal and NA-STZ Diabetic Rat

In order to assess the neuroprotective effect of the DSE/Metformin on stress markers in brain structures (hippocampus and prefrontal cortex), the lipid peroxidation (evaluated by TBARS assay through MDA quantification) was analyzed and results are summarized in Fig. 6.2. As presented in this figure, the lipid peroxidation levels in the rat prefrontal cortex and hippocampus in non-treated NA-STZ group and NA-STZ group treated with metformin were significantly higher than those found in NC group ($p < 0.001$; $p < 0.01$), respectively. Treatment with DSE for 42 days significantly attenuated significantly the lipid peroxidation levels in both cerebral regions ($p < 0.001$), furthermore, no significant differences are observed compared with NC group ($p > 0.05$).

6.3.4 Level of Tumor Necrosis Factor-α in the Prefrontal Cortex and Hippocampus in Normal and Diabetic Rat

In order to assess the anti-inflammatory effect of the DSE/Metformin in NA-STZ diabetic rats in the prefrontal cortex and hippocampus regions, the tumor necrosis factor-α level was evaluated and results are presented in Fig. 6.3. The TNF-α production in the prefrontal cortex and hippocampus was significantly increased in treated and no-treated NA-STZ groups compared to normal control group ($p < 0.05$). While a significant improvement of TNF-α levels in both regions was observed in treated groups (DSE/Met) compared to no-treated NA-STZ group ($p < 0.001$).

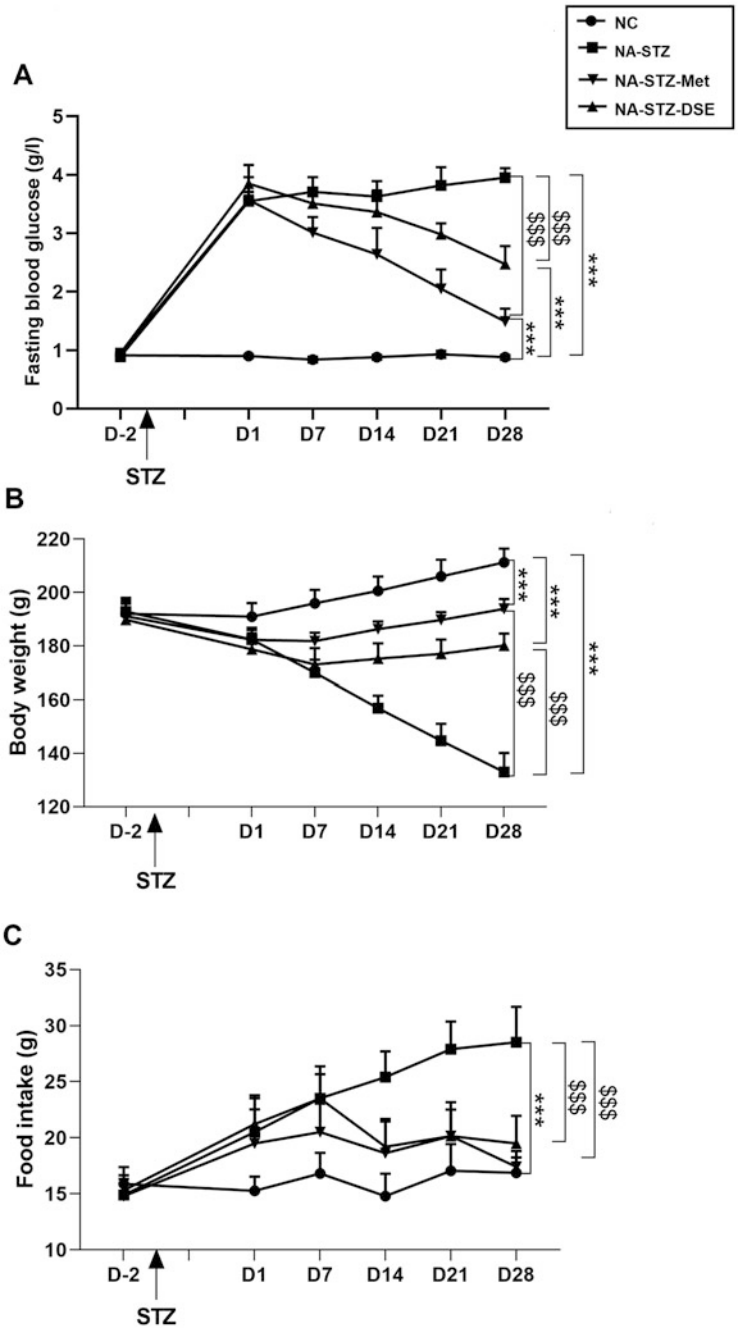

Fig. 6.1 Changes in fasting blood glucose (**a**), food intake (**b**), and body weight (**c**) in normal and NA-STZ rats. Results are presented as mean ± SD. $^{***}p < 0.001$ (normal control versus diabetic groups), $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

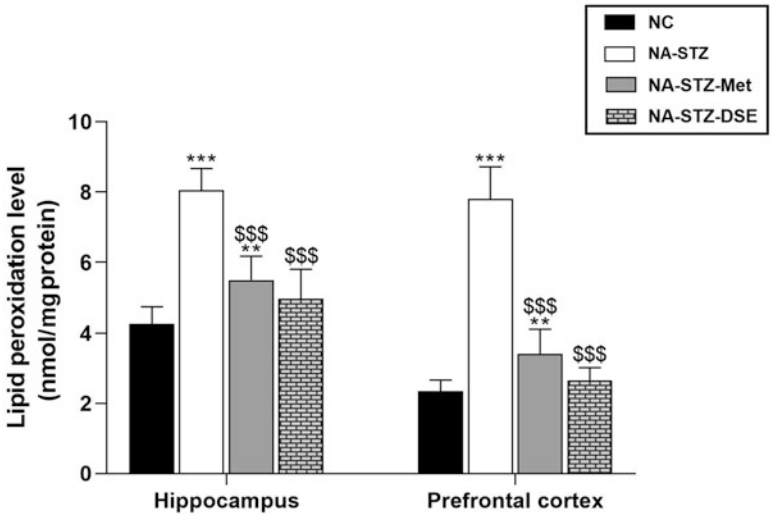

Fig. 6.2 Detection of lipid peroxidation in the prefrontal cortex and hippocampus of normal and diabetic rats. Results are presented as mean ± SD. $^{**}p < 0.001$, $^{***}p < 0.01$ (normal control versus diabetic groups). $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

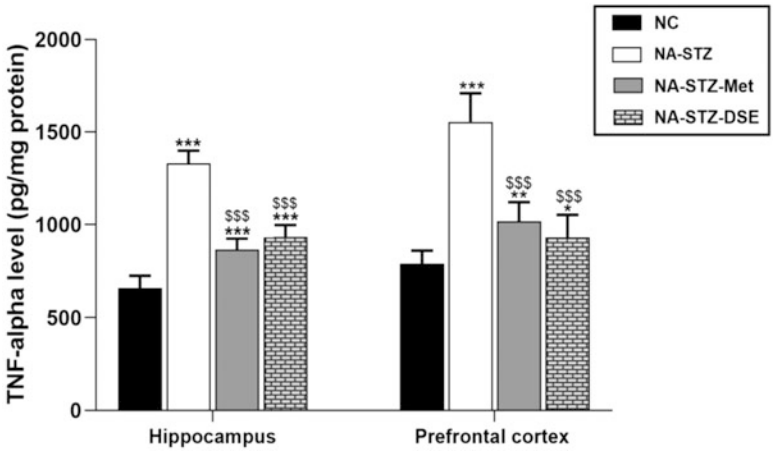

Fig. 6.3 Level of TNF-α in the prefrontal cortex and hippocampus of normal and diabetic rats. Results are presented as mean ± SD. $^{**}p < 0.001$, $^{***}p < 0.01$ (normal control versus diabetic groups). $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

6.3.5 *Measures of Anxiety in Normal and NA-STZ Diabetic Rat*

As shown in Fig. 6.4, EPM test result showed that treated and non-treated NA-STZ rat groups had a significant decrease in the NEOA ($p < 0.01$) and in TOA ($p < 0.05$) compared to NC group. However, sub-chronic DSE treatment significantly increased the NEOA ($p < 0.01$) and the TOA ($p < 0.001$) in the NA-STZ group compared to no-treated NA-STZ group; treatment with metformin increased significantly the TOA in NA-STZ diabetic rat ($p < 0.001$) compared to no-treated NA-STZ diabetic rats.

Regarding the anxiety symptoms evaluated in the open field test Fig. 6.5, the no-treated NA-STZ group revealed a significant decreased in the number of CSE ($p < 0.001$) and TCS ($p < 0.001$) compared to NC group. However, DSE

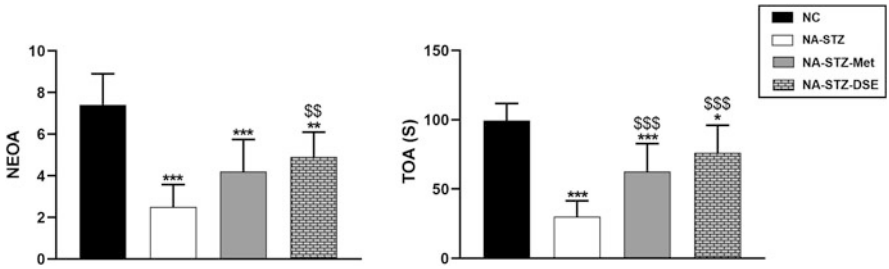

Fig. 6.4 Effects of date seed phenolic compounds and metformin in NA-STZ diabetic rats on the number of entries (NEOA) and the time spent (TOA) in the open arms evaluated in the elevated plus maze. Results are presented as mean ± SD. *$p < 0.05$, **$p < 0.001$, ***$p < 0.01$ (normal control versus diabetic groups). $^{\$\$}p < 0.01$ $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

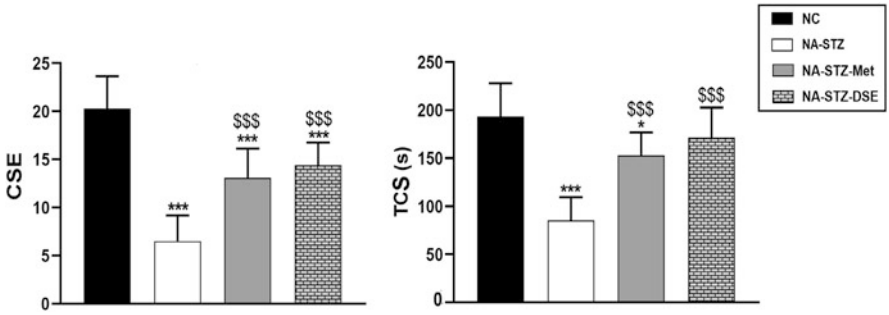

Fig. 6.5 Effects of date seed phenolic compounds and metformin in NA-STZ diabetic rats on the time spent in the central squares (TCS) and central squares entries (CSE) evaluated in the open field test. Results are presented as mean ± SD. *$p < 0.05$, ***$p < 0.01$ (normal control versus diabetic groups). $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

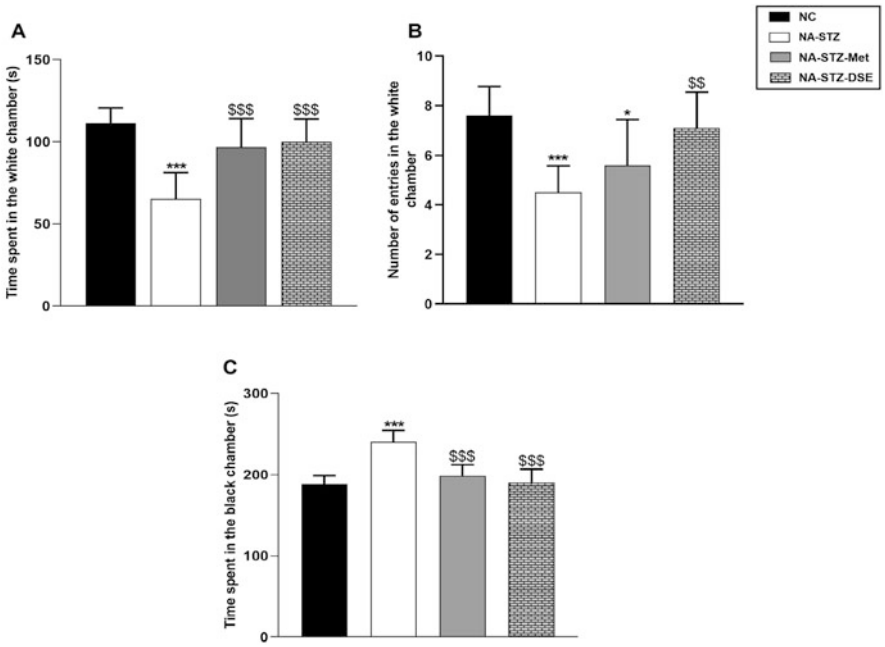

Fig. 6.6 Effects of date seed phenolic compounds and metformin in NA-STZ diabetic rats on the time spent in the black chamber (**c**), the time spent (**a**) and the number of entries in the white chamber (**b**) evaluated in the black-white box test. Results are presented as mean ± SD. $*p < 0.05$, $***p < 0.01$ (normal control versus diabetic groups). $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

supplementation and metformin treatment in NA-STZ rats increase significantly the number of entries and the time spent in the central squares ($p < 0.001$) compared to no-treated NA-STZ group.

Finally, in the black-white box test Fig. 6.6, NA-STZ group exhibited a significant decrease in the number of entries in the white chamber and in the time spent in these arms ($p < 0.001$) compared to NC group. In contrast, there was no significant difference between diabetic rats treated and normal rats control ($p > 0.05$) in the number of entries and the time spent in the white chamber. Similarly, a significant elevation in the time spent in black chamber was observed in the NA-STZ group compared to NC group ($p < 0.001$). In addition, a significant change in this parameter was observed between the treated NA-STZ groups (DSE/Met) and no-treated NA-STZ group ($p < 0.001$).

In the NSF test, no-treated NA-STZ group and NA-STZ group treated with metformin demonstrated a significant increase in their latency feeding time ($p < 0.001$; $p < 0.05$), respectively, compared to NC group Fig. 6.7. While, there was no significant difference between diabetic rats treated with DSE and normal rats control ($p > 0.05$). However, sub-chronic DSE and metformin treatment

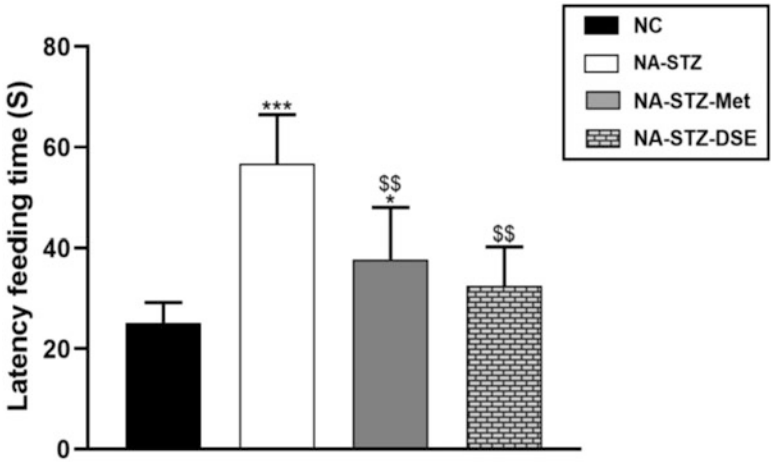

Fig. 6.7 Effects of date seed phenolic compounds and metformin in NA-STZ diabetic rats on the latency feeding time evaluated in the novelty suppressed feeding test. Results are presented as mean ± SD. $^{*}p < 0.05$, $^{***}p < 0.01$ (normal control versus diabetic groups). $^{\$\$}p < 0.01$, $^{\$}p < 0.001$ (NA-STZ versus NA-STZ treated groups)

significantly improve the latency feeding time ($p < 0.01$) in the NA-STZ-induced diabetic rats compared to no-treated NA-STZ group.

6.4 Discussion

The animal model of T2D induced by NA-STZ is widely model used for understanding complications induced by diabetes (Masiello et al. 1998), and for screening of anti-hyperglycemic compounds. The major goal of the current study was to evaluate the neuroprotective and anxiolytic effects of date seeds phenolic compounds in NA-STZ-induced type 2 diabetic rats.

Recently, the interest about natural products contains phenolic compounds has been remarkably increased, mainly due to their valuable biological properties. It has been revealed that date seeds have a multitude of biological functions, its therapeutic activities were explored (Djaoudene et al. 2019). This by-product considered as a good source of natural antioxidants (Al-Farsi et al. 2007). In this study, the spectrophotometer analysis revealed an significant amount of TPC in the extract. This result is in accordance with several studies, which have shown that date seeds represent a potential source of phenolic compounds (Al-Farsi and Lee 2008).

In this study, we induced T2D by injection of NA-STZ (a single intraperitoneal injection) and we observed a remarkable elevation in FBG concentrations and food intake accompanied with a significant drop in body weight of rats after 72 h. Accordingly, several studies have shown that T2D induced by NA-STZ injection was associated with several symptoms such as their reported in our study (Marmouzi

et al. 2017). After 42 days treatment, all these symptoms occurred in this model were significantly attenuated by DSE treatment. These beneficial effects of DSE could be attributable either to stimulate endogenous insulin secretion, repairing pancreatic cells and/or inhibiting digestive enzymes (Bikri et al. 2021a; Djaoudene et al. 2019; El-Fouhil et al. 2013; Walf and Frye 2007). Moreover, many works have proven the valuable effects of phenolic compounds against diabetes by controlling the enzymes implicate in glucose metabolism and stimulation of insulin action (Bahadoran et al. 2013). Likewise, metformin treatment improved significantly blood glucose level enhanced by NA-STZ induced diabetes. This beneficial effect might be due to stimulate glucose uptake and suppression of gluconeogenesis (Natali and Ferrannini 2006).

Date seeds in vitro antioxidant and anti-inflammatory proprieties is well evaluated in literature (John and Shahidi 2019; Al-Farsi et al. 2007). In the current study, the anti-inflammatory and antioxidant proprieties of DSE were evaluated in NA-STZ induced diabetic rats. It has been well demonstrated that persisting hyperglycemia remarkably enhances inflammatory and oxidative stress markers in the central nervous system (CNS), which caused from impairment of antioxidant defenses and/or increasing of endogenous reactive oxygen species (ROS) generation (Reis et al. 2012). Indeed, the chronic accumulation of ROS has been suggested as a significant contributor to the development of diabetes complications including encephalopathy (El-Fouhil et al. 2010). In the present study, Na-STZ-induced T2D revealed a significant increase in lipid peroxidation levels in PFC and HP brain regions. Moreover, previous reports have shown that chronic hyperglycemia associated with type 2 diabetes increased lipid peroxidation products in various brain regions such as cerebral cortex and hippocampus (Obafemi et al. 2020). In the current report, this effect was attenuated significantly by DSE and metformin administration for 6 weeks in Na-STZ diabetic rats. We hypothesize that the beneficial effect of this by-product is attributed to its main phenolic contents, which protect the rat against diabetes-induced oxidative stress complications. In this line, it has been well established that phenolic compounds possesses antioxidant proprieties in CSN, revealed by their ability of scavenge free radicals and upregulate oxidative stress markers (Infante-Garcia and Garcia-Alloza 2019; Orsu et al. 2013). A recent investigation revealed that metformin as antidiabetic treatment ameliorates significantly the oxidative stress markers in brain of rats with T2D (Obafemi et al. 2020).

Moreover, increased pro-inflammatory cytokines markers such as interleukin-6 and TNF-α were observed in CNS of patients with T2D (Evans et al. 2002). It has been established that this elevation resulting probably from oxidative stress induced by hyperglycemia (increased levels of ROS) (Evans et al. 2002). While, increased pro-inflammatory cytokines can strongly damage the activity and development of the CNS, which lead to many undesirable complications (Dinel et al. 2011). In the current study, it was discovered that Na-STZ-induced type 2 diabetes significantly increased TNF-αin HP as well in PFC of diabetic rats. Nevertheless, a significant reduction of TNF-α level was showed in these brain regions of diabetic rat treated with metformin or DSE compared to no-treated diabetic rats. The beneficial anti-

inflammatory effect of metformin in the brain of type 2 diabetic rats has been reported (Hattori et al. 2006). It has been known that metformin treatement decrease the expression of the transcription factor (NF-kB) implicated in inflammation (Bourin and Hascoet 2003). While, it has been well proved that date seeds can act as an anti-inflammatory agent by reducing pro-inflammatory mediators (IL-1, IL-6, IL-2, TGF-β, and TNF-α), TGF-β and lipid peroxide cyclooxygenase enzyme expressions (Djaoudene et al. 2019). Also, It has been known that date seeds suppress NF-kB translocation. A recent report demonstrated that dates seeds (rich on phenolic and flavonoids compound) as anti-inflammatory supplementation ameliorates significantly the immunity and prevent against several inflammatory diseases (Saryono et al. 2020).

The present work highlights also the importance of DSE supplementation in the attenuation of anxiety-related behavior in diabetic rats. When assessing the anxiety-like behavior, the tests, viz. EPM, OF, BWB, and NSF used in this study showed coherent results. All these behavioral tests used in this study are widely accepted tests routinely to evaluate anxiety-like behavior in rodent (Walf and Frye 2007). While, it is well established that T2D is associated with behavioral changes (Keating et al. 2019). In this line, chronic hyperglycemia increases significantly oxidative stress, which promotes the appearance of pathophysiological symptoms of anxiety (Palta et al. 2014). In the current report, the four behavioral tests findings showed increased anxiety-like behavior in control diabetic group compared to normal control group. However, daily treatment with DSE or metformin during 6 weeks was able to prevent significantly diabetic rats against behavioral change induced by hyperglycemia. Thus, the probable explanation suggests that accumulation of ROS and elevation of pro-inflammatory cytokines level caused by a diminution of brain glucose metabolism can lead in apoptosis at PFC as well as in HP, leading probably to the appearance of anxiety-like behavior. Several experimental studies have shown that anxiety-related behavior in hyperglycemic rats could be due to the dysregulation of monoamine neurotransmitter concentrations in brain regions (Ramanathan et al. 1997). Accordingly, an earlier report revealed that phenolic compounds control the release of monoamine neurotransmitters (Tian et al. 2017), which confirm the exhibited anxiolytic-like effect of DSE in type 2 diabetic rats.

In conclusion, the present study adds new evidences respecting the anxiolytic effect of date seeds phenolic compounds in type 2 diabetes in rat, corrobing the antioxidant and anti-inflammatory activity exhibited by date seeds extract. This by-product could represent a new therapeutic approach to prevent persisting hyperglycemia induced anxiety-like behavior.

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Chapter 7
Role of Nutrition in Pathogenesis of Neurological Disorders

Anitha Arumugam and Dhanalakshmi Thiyagarajan

Abstract Neurological disorders are one of the world's most important health concerns. Alterations in normal lifestyle are linked to dramatically increasing chronic disease risk, creating a major social health and financial burden worldwide. Furthermore, a diet which lacks nutrients can lead to a central and peripheral nervous system disturbances. Pathogenesis of many neurological disorders includes various nutritional factors. The ideal functioning of the nervous system is principally based on the B-group vitamins, vitamin E, copper, and folic acid. Patients with key nutrient deficiency leads to neurological diseases include epilepsy, Alzheimer's disease, and other dementias, amyotrophic lateral sclerosis, cerebrovascular diseases including stroke, migraine, and other headache disorders, Parkinson's disease, neuro-infections, brain tumors, and traumatic disorders of the nervous system due to head trauma, etc., increases the risk by several factors associated with food intake, energy consumption disturbances, bad eating, changes in gastrointestinal conditions, and prescribed drug / alcohol side effects. Non-destructive techniques, including diet and exercise, can have significant consequences for improving resilience and maintaining central nervous system (CNS) cognitive skills. A proper nutritional assessment of such patients is essential in the surveillance of their illness and also for the early prevention of possible side effects and treatments.

Keywords Neurologic complications · Nutritional deficiency · Alcoholism · Neuro-disorder management

7.1 Introduction

The pathology of several diseases, which led to the development of more effective treatments, has increased significantly worldwide. In order to eliminate the disease entirely from the population, we could develop a medicine for any disease. This generation begins to understand, however, that medicine will not be what we can

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trust. Although it is able to relieve symptoms or even cure many illnesses, medication also often poses debilitating side effects and extreme economic pressures for its consumers (Whiteford et al. 2015). Nutrition and lifestyle are one aspect of healthcare that slowly generates more focus. Many scientists have studied the link between diet and both chronic and acute diseases. Type 2 diabetes and cardiovascular diseases are among the main chronic diseases studied. Diet has also been a significant factor in its occurrence and prevalence for these chronic diseases. It should be of particular interest to investigate the nutritional effect on neurological disorders following an understanding of the strong association between dietary habits and chronic diseases like those.

7.2 What Are Neurological Disorders?

Any condition induced by a brain injury, or central or peripheral nervous system, leading to physical and/or psychotic disorders (WHO) would be referred to as "neurological illness." Neurological disorders may affect a whole or a single neuron of the neurological pathway. Even a small disturbance to a neuron's structural pathway can result in dysfunction.

The nervous system is susceptible to various disorders. It can be damaged by the following:

- Trauma.
- Infections.
- Tumors.
- Degeneration.
- Autoimmune disorders.
- Structural defects.
- Blood flow disruption.

The following may be implicated in nervous system disorders:

- **Vascular disorders**, for instance, stroke, transient ischemic attack (TIA), subarachnoid, subdural and extradural hemorrhage.
- **Infections**, for instance, encephalitis, polio, meningitis, and epidural abscess.
- **Degeneration**, for instance, Parkinson disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, Alzheimer disease, and Huntington chorea.
- **Functional disorders**, for instance, dizziness, epilepsy, headache, and neuralgia.
- **Structural disorders**, for instance, cervical spondylosis, brain and spinal cord injury/tumors, spinal cord injury, Bell's palsy, carpal tunnel syndrome, Guillain–Barre syndrome, and peripheral neuropathy.

7.2.1 What Causes a Neurological Disorder?

The brain and spinal cord are shielded by thick, submerged membranes and chemically separated by blood–brain barrier within skull bones as well as spinal vertebras, but are extremely vulnerable if they suffer from any conflict. The specific causes of neurological problems vary but include the following.

- Genetic disorders.
- Congenital abnormalities or disorders.
- Infections and physical injuries.
- Lifestyle or environmental health difficulties collected with malnutrition.
- Brain, spinal, and nerve injury.
- Nutrition-related causes.
- Gluten sensitivity (with or without intestinal damage).
- Environmental influences (Zis and Hadjivassiliou 2019).

7.2.2 Classification of Neurological Disorders

The World Health Organization reports the effect of multiple neurological disorders on hundreds of million people worldwide. Figure 7.1 shows the general most common classification of neurological disorders.

Examples of neurological disorders include the following:

- Epilepsy.
- Alzheimer's disease and other dementia.

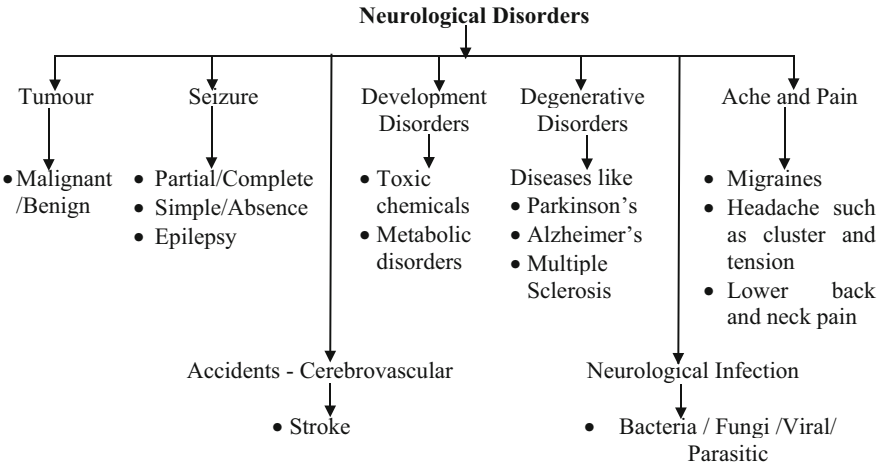

Fig. 7.1 Classification of neurological disorders infections (Khan et al. 2018)

- Migraines and other headache disorders.
- Strokes which include cerebrovascular disease.
- Parkinson's disease.
- Multiple sclerosis.
- Cerebral palsy and more.
- Neuro-infections (bacterial and viral).
- Brain tumors.
- Brain trauma—traumatic disorders of the nervous system.
- Neurological disorders as a result of malnutrition.
- Many viral (i.e., enteroviruses, human immunodeficiency virus), bacterial (i.e., *Neisseria meningitidis* and *Mycobacterium tuberculosis*), fungal (i.e., *Aspergillus* sp., and *Cryptococcus* sp.,), and parasitic (i.e., malaria and chagas) infections (Khan et al. 2018).

7.2.3 Neurological Symptoms

Symptoms of neurology are illnesses due to or maybe in the nervous system. There are two physiological sections of the nervous system. As a central processing network, the central nervous system that comprises the cortex and the backbone. The peripheral nervous system transmits sensory input to your brain via your muscles, tissues, and nerves. Neurological effects arise when such associations are interrupted.

7.2.3.1 What Are the Signs?

The signs of neurological disorders can vary significantly, based on the type of disorders and the area which is affected. Symptom might be emotional or physical symptoms. The local illness, whenever the discomfort well be tied directly to either a trauma or systemic disease affecting your whole body, may cause these symptoms. The sensation of pain in different parts of the body is felt with referred pain and a more complicated condition around where the wound or illness has taken place. The most complicated diagnosis and treatment is referred as pain.

Emotional symptoms which includes

- Mood swings or sudden outbursts,
- Depression or delusions.

Physical symptoms which includes

- Burning and numbness,
- Pins-and-needles (prickling) sensations,
- Partial or complete paralysis,
- Muscle weakness,

- Partial or complete loss of sensation,
- Seizures, confusion,
- Difficulty in reading and writing,
- Poor cognitive abilities/coordination,
- Unexplained pain,
- Decreased alertness,
- Altered levels of consciousness and sensitivity.

7.3 Nutrition and Health

The key health issues in low-income countries are still insufficient food rates (cause problems including childhood hunger and developmental defects) and insufficient food availability (cause of a lack of essential micronutrients, such as vitamins, minerals, or trace minerals). The risk of illness or eventual mortality is increased by malnutrition with all its types. Chronic food shortages impact about 792 million individuals globally. Malnutrition affects a number of tissues, including that of the central nervous system (CNS), explicitly or implicitly. Throughout forming and working the nervous system, nutrition has an important role to play (Gungor 2017). The central nervous system controls food consumption, glucose, and electrolyte homoeostasis as well as begins hunger and satiety sensations (Ezzati et al. 2003). The pathogenesis of many neurological disorders includes numerous nutritional factors.

7.3.1 Etiology

The major nutrition necessary for living organisms can be clustered into macronutrients (energizing nutrients—proteins, carbohydrates, and fats) and micronutrients (vitamins and minerals), particularly for living creatures. The macronutrients are building blocks for the lifeform and the micronutrients are superior building elements, particularly for well-functioning enzymes.

7.3.2 Risk Factors

A number of factors can affect body's vitamin stores. In general, risk of vitamin deficiency is increased during the condition in Fig. 7.2. The shortage of vitamins raises the risk of many issues with well-being.

A reliable supply of sufficient nutrients is mandatory for the proper functioning of the central and peripheral nerve network. The nervous system's optimum function relies primarily on B-group vitamins (vitamin B12, thiamine, niacin, and

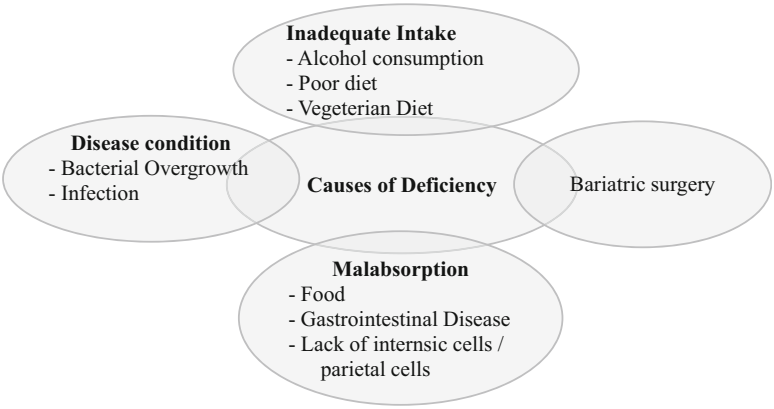

Fig. 7.2 Factors causing nutritional deficiencies

pyridoxine), vitamin E, copper, and folic acid. Multiple dietary shortcomings do not always coexist. Table 7.1 describes the neurological manifestations associated with key nutrient deficiencies.

Vitamin B1 (Thiamine) It is a water-soluble vitamin that is used in most tissues of animals and plants. Beri-beri is a condition caused because of insufficient source of vitamin B1 and polyneuropathy is the principal symptom (Neumann et al. 1979). Cardiovascular impairments, trembling, gait, and visual disturbs can be experienced in extreme cases. The acute form of syndrome is found in the encephalopathy of Wernicke and in the syndrome of Korsakoff. Properly diagnosis and immediate replacement of thiamine, can be quickly reversed the condition. It may take 3–-6 months for neurological recovery, with motor manifestations stronger than sensory symptoms (Koike et al. 2001).

Vitamin B3 (Niacin) Deficiency of niacin leads to "pellagra" (Kertesz 2001). Dermatitis, diarrhoea and dementia with dermatitis symptoms, erythema, pigment complaints, diarrhoea and neuropsychiatric conditions such as anxiety and restlessness are the typical clinical signs of pellagra. Early neurological signs include apathy, carelessness, irritability, and depression (Prousky 2003; Kumar 2007). For treatment, the oral replacement of nicotinic acid is recommended but the dosage due to the flushing may be reduced.

Vitamin B6 (Pyridoxine) The vitamin B6 deficiency includes seizure, migraine, chronic pain, and depression in neuropsychiatric diseases (Malouf and Grimley Evans 2004; Thaver et al. 2006). The deficiency of vitamin B6 can particularly occur during the intake of certain vitamin-adversely affecting drugs (e.g., isoniazid and penicillamine) (Heller and Friedman 1983). Vitamin B6 toxicity produces sensory ataxia, areflexia and skin sensation impairments (So and Roger 2008). Vitamin B6 supplementation is suggested for patients treated with isoniazid, (Corken and Porter 2011).

Table. 7.1 Neurologic disorders associated with key nutrients deficiency (Hammond et al. 2013; Kumar 2007, 2010)

Nutrient	Sources	Deficiencies—major causes	Neurologic significance related with deficiency
Vitamin B1—thiamine	Product of fortified or whole grains, organ meats	Recurrent vomiting, gastric surgery, alcoholism, dieting, increased demand of nutritional status	Beri-beri (dry, wet, infantile), Wernicke's encephalopathy
Vitamin B3—niacin	Meat, fish, poultry, enriched bread, fortified cereals	Alcoholism, malabsorption, Hartnup syndrome	Encephalopathy (neuropathy at peripheral)
Vitamin B6—pyridoxine	Soybeans, nuts, eggs, meat, fish, dairy products	Alcoholism, B6 antagonists (INH, hydralazine, penicillamine), gastrointestinal disease	Infantile seizures, peripheral/sensory Neuropathy with toxicity
Vitamin B12—cobalamin	Meats, egg, milk and milk products, legumes, and fortified cereals	Pernicious anemia, gastric surgery, gastrointestinal disease - therapy for acid reduction, parasitic infestation	Myeloneuropathy, peripheral and optic neuropathy, neuropsychiatric manifestations
Vitamin E	Sunflower and olive oils, leafy vegetables, fruits, meats, nuts, cereals	Chronic cholestasis (in children), pancreatic insufficiency, GI disease, AVED, homozygous hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease	Spinocerebellar syndrome with peripheral neuropathy, ophthalmoplegia, pigmentary retinopathy
Folate	Dark green leafy vegetables, fruits and fruit juices, nuts, beans, peas, seafood, eggs, dairy products, meat, poultry, and grains	Diet, genetic makeup, diseases that affect GI absorption	Neural tube defects of the fetus, cognitive dysfunction in children and elderly
Copper	Meat of organ, seafood, nuts, mushroom, cocoa, chocolate, beans, whole grain products	Gastric surgery, zinc toxicity, GI disease, total parenteral nutrition, and enteral feeding	Myelopathy or myeloneuropathy

Vitamin B12 (Cobalamin) In animal and dairy products, vitamin B12 (cobalamin) is present and synthesized by different microorganisms. When building red blood cells, it plays a significant function. The shortage of vitamin B12 also contributes to a megaloblastic anemia, which is intermittent when administered orally. The worst cause is within the central and peripheral nervous systems (irreversible damage) (Saperstein et al. 2003). The hematological, physiological, and psychological symptoms are referred by vitamin B12 (Cobalamin) deficiency. The typical neurological effects of B12 deficit include subacute cumulative degeneration, neuropsychiatric symptoms, peripheral neuropathy, and optic neuropathy (Saperstein and Barohn 2002). Early diagnosis is crucial as significant residual disability can

occur in patients with advanced disease. Therapy eliminates the further neurological damage, and often patients are left with the neurologic deficits found prior to treatment.

Vitamin E The bioactive source of vitamin E in humans is alpha-tocopherol. For patients with malabsorption or transport deficiencies most vitamin E deficiencies are present. Vitamin E deficiency can develop in patients with cystic fibrosis with malabsorption. Hereditary condition that results in a vitamin E deficiency is a rare autosomal disease (i.e. abetalipoproteinemia) that leads to fat malabsorption (Chardon 2009). Patients with this disorder develop pigmented retinopathy, vibration loss and proprioception, deep tendon reflex loss, ataxia, and brain degeneration and a general muscle weakness if left untreated (Muller 2010). Other neurological indications may include dysarthria, nystagmus, ophthalmoparesis, retinopathy, titubation of the head, reduced sensation, and proximal weakening. Vitamin E treatment deficit can reverse or stop neurological symptoms from worsening. A significant amount of vitamin E may be required to normalize serum vitamin E levels in patients with abetalipoprotienemia. Malabsorption syndromes can require water-mixed or intramuscular vitamin E preparation.

Folate Folate (or folic acid) plays the key role in rapid cell dividing, deficiency leads to megaloblastic anemia and is reversible when folate is administered. In recent years, the incidence of fetal malformations in the form of neural tube defects has mostly increased during pregnancy (NTDs = myelo-meningocele) (Lumley et al. 2001). Folate fortification defends against neural tube defects for women when pregnant. Neurological symptoms are uncommon and mild in adults suffering from folate deficiency. Myeloneuropathy or neuropathy with folate deficiency cannot be distinguished from cobalamin deficiency (Parry 1994; Lever et al. 1986).

Copper Copper deficiency has long been recognized as a cause of hematologic abnormalities, myelopathy or a myeloneuropathy and peripheral neuropathy (Kumar 2006; Gregg et al. 2002). Rich foods of copper include beef, nuts, wheat, and seeds. Previous gastric operation is the most common cause of copper deficiency. Exogenous zinc intakes are also postulated as a cause of copper deficiency and neurological manifestations, both from unnecessary zinc supplement intakes (Rowin and Lewis 2005) and through the use of older zinc containing denture creams (Hedera et al. 2009; Nations et al. 2008). It is important to stop exogenous zinc in patients with copper deficiency due to the excessive intake of zinc. The favored form of copper replacement is elemental copper substitution orally. Although copper insufficiency is a well-known cause of haematological abnormalities, it is commonly misunderstood. While copper substitution prevents neurological abnormality, residual symptoms in patients are often left behind (Kumar 2006).

7.4 Neurologic Diseases Seen in the Setting of Alcoholism

During the development and progression of neurological disorders, alcohol and other drugs have a significant role. Being toxic agents, these chemicals have an effect on the structure and function of both the central and peripheral nervous systems specifically on the nerve cells and the muscles. The following anomalies were ascertained in chronic alcohol drinking populations: cerebral atrophy or decreased brain cortex, reduced blood flow to that part of the brain that performs vital functions and disturbance of the performance of neurotransmitters and signaling molecules. Such modifications may leads to decrease the function of higher cortical and other anomalies, often symptoms of neurological problems is linked to alcohol consumption. Some of the neurological consequences attributable with alcoholism has been described in Table 7.2.

7.4.1 Wernicke's Encephalopathy

The primary consequence of Wernicke's encephalopathy in people with serious drug dependence has been a deficiency in vitamin B1. It is attributed to inadequate diet, malabsorption in the intestines, and the depletion of thiamine in the liver. The beginning may occur during a time of abstinence which, together cerebellar symptoms, hypertonia, paralytic and/or ocular symptoms, is typically marked with mental distress, which gradually deteriorated. When the prediction is postponed, it could be a progression of a Wernicke–Korsakoff syndrome, a dementia, if the vitamin B1 is administered (Vasan and Kumar 2020).

Table 7.2 Neurological consequences associated with alcoholism

1.	**Nutritional deficiencies**
	Wernicke's encephalopathy
	Korsakoff syndrome
	Pellagra
2.	**Direct effect of alcohol**
	Fetal alcohol syndrome
3.	**Alcohol withdrawal**
	Withdrawal seizures
	Delirium tremens
4.	**Disease of uncertain pathogenesis**
	Alcoholic neuropathy
	Alcoholic myopathy
	Alcoholic cerebellar degeneration
	Marchiafava-Bignami disease
	Alcohol and epilepsy
	Amblyopia

7.4.2 Fetal Alcohol Syndrome

Alcohol has played a major role in alcoholic fetal syndrome for many years. Several babies born to women who drink excessively during pregnancy suffers from this disease. Fetal alcohol syndrome signs include facial defects, cognitive and behavioral dysfunction, and impaired development in the clinical conditions (Chaudhuri 2000).

7.4.3 Delirium Tremens

If someone unexpectedly starts drinking after several years of alcohol abuse, they are likely to experience withdrawal syndrome of alcohol or Delirium Tremens (DT). The body developed physical alcohol dependency to control brain activity, causing life-threatening side effects to occur when the drug is unexpectedly removed. Major inclusion are: serious confusion or delirium, physical trembling, excessive aggression and agitation, intense enthusiasm, fear/paranoia, pre requisite blasts, stupor and/or unresponsiveness and convulsions or seizures.

7.4.4 Alcoholic Neuropathy

Alcohol removes food away from your diet, raises demand for B-group vitamins, induces lower lipid soluble vitamins absorption through dysfunction of the pancreatic and liver and may also be a secondary neurotoxin (D'Amour and Butterworth 1994). The B-group vitamin (thiamine) deficiency was more widely used as a basis for neuropathy associated with alcoholism. Alcoholic neuropathy is a slowly progressive, distally dominant, painful, symmetrical, sensorimotor, axonal neuropathy with preferences for small fiber involvement and autonomic dysfunction (Koike et al. 2003). Segmental demyelinization and remyelination due to the extension of successive ranvier nodes are more common in alcoholic neuropathy.

7.4.5 Alcoholic Cerebellar Degeneration

The early intervention of the anterior and superior portions of the brain's vermis and the weaker participation of cerebellar's hemispheres is the characteristic of alcoholic cerebellar degeneration (Yokota et al. 2007). A truncal ataxia, discomfort in tandem walking is the neurologic manifestations of alcoholic brain degeneration. Many brain symptoms are unusual including nystagmus, dysarthria, tremor intention, and hypotonia. Polyneuropathy with accompanying effects is normal. Vermal atrophy

may be linked to thiamine deficiency in alcoholic brain degeneration (Maschke et al. 2005).

7.4.6 *Marchiafava-Bignami Disease*

Marchiafava-Bignami's initial description was that of the selective demyelination of the corpus callous in persons who is consuming excessive red wine. A frontal lobe dysfunction distinguished by personality shifting and psychomotor slowing is the most typical medical presentation. Dysarthria, quadriparesis, incontinence, seized disorders, inter-hemisphere disconnections, and occasionally coma are other indications. Acute demyelination and necrosis are applicable to the main portion of the body of the corpus callosum (Raina et al. 2008; Heinrich et al. 2004).

7.4.7 *Alcohol and Epilepsy*

Alcohol has multiple epilepsy effects, including frequent heavy drinkers and dependents acquiring the disorder to growing rates of seizures in people who are never impaired. Alcohol convulsions may interfere with alcohol tolerance in individuals experiencing withdrawals and seizures such that the effect is increased. The risk for chronic harmful alcohol-related epilepsy between abstainers and light drinkers is low risk is highest at intake levels that exceed 20 g (2 beverages) of pure alcohol per day in women and 40 g (2 beverages) per day in males (Rehm et al. 2004).

7.5 Neuro-Disorder Management

In health and disease, influence of diets has often been appreciated. Hippocrates wrote just under 400 B.C. "Let food be the medicine." In the twenty-first century, media claims about "superfood" bombard us with magnificent diets which promise to cure or prevent diseases, enhance health, and restore functionality. A great deal was based on neurological disorders (comportment, cognition, and emotions) (Brandt 2019). Research has been described on the role of active substances and nutrients in brain activity and disorder and diet in the management and cure of neurological and psychological disabilities (Zamroziewicz and Barbey 2016; Oleson et al. 2017; Sandhu et al. 2017).

Non-invasive strategies, such as diet and exercise, may have significant effects for the improved resilience and preservation of cognitive abilities of central nervous systems (CNS). Diet and exercise as two very important parts of lifestyle and daily routine, will influence the brain's capacity to combat diseases and to respond to challenges (Gomez-Pinilla 2008). Good dieting, including omega-3-high fatty acids

and curcumin, will enhance molecular systems for the neuronal function and plasticity of brain and spinal cord, respectively, found in the foods salmon and plant turmeric. Exercise, similar to healthy foods intake, improves brain healing effects which helps to reverse the age-related mental deterioration and provides advantages underlying rehabilitation approaches after brain injury and SCIs, especially with healthy diet.

7.5.1 Dietary Intervention for Improved Cognitive Abilities

7.5.1.1 Omega-3 Fatty Acids

In certain fish (particularly wild-caught salmon), the polyunsaturated fatty acids (PUFAs; ω-3 and ω-6) have been recorded in great abundance and acted as important component in normal neuronal function and cell membranes. Docosahexaenoic acid (DHA) is a key component of the omega-3 fatty acid family, which indicates that its action is essential to brain function at signaling points in the synapse. DHA may help to maintain synaptic membrane fluidity, improve BDNF level, minimize oxidative stress, and control cell signals (Jones et al. 1997), and to regulate cell signaling (Salem Jr et al. 2001). Omega-3 fatty acids are stabilizing the ratio in major molecular systems to promote energy homeostasis and minimize oxidative stress which in turn reflects it capability to reverse the effects of traumatic brain injury. DHA nutritional supplementation can be crucial for the success of rehabilitative strategies following CNS injury. In general, omega-3 fatty acids offer great neuroprotective potential to help counteract the effects of neurologic injuries (Gomez-Pinilla and Kostenkova 2008). Improved intake of berry fruit, higher diet of omega-3 fatty acids, has a beneficial effect on the decline in cognitive deterioration of aged rodents. Deficiencies of ω-3 PUFAs is correlated with Alzheimer's disease, further from mood disorder to schizophrenia (Fuentes-Albero et al. 2019).

There are at least a form of high fat diet with strong neurotherapeutic and likely neuroprotective effects when it comes to fats. As described by McDonald and Cervenka (2018), the ketogenic diet, incorporating large quantities of fat with extremely low carbohydrate levels, leads to ketone bodies generation by the liver (acetoacetate and β-hydroxybutyrate) which are then used as a source of energy for neurons. It improves the balance of neurotransmitters (excitational and inhibitory), improves genetic expression, and reduces stress and inflammation oxidization and other implications on the function of the brain. The ketogenic diet for epilepsy treatment was introduced 100 years ago and is now a pillar of the treatment of refractive seizures. Ketogenic food can cure a huge spectrum of several other neurological disorders, including stroke, glioblastoma, lateral amyotrophic sclerosis, and Alzheimer's disease.

7.5.1.2 Dietary Polyphenols

Polyphenols are a large array of chemicals found in plants with several classes of phenols. Polyphenols have strong antioxidant properties and curcuminoids and flavonoids are some of the principal groups described for their CNS effects. Because of neuronal signaling stimulation and an improved production of antioxidants as well as an anti-inflammatory, curcumin and flavonoid may have a positive impact on the treatment of brain diseases and brain injury (Spencer 2009).

- **Curcumin**—a polyphenol is derived from the turmeric plant rhizome that helps the brain to protect the cells/tissues from neurological disorders by multiple mechanisms. Curcumin can enhance cognitive function in patients with Alzheimer's disease (AD) as an antioxidant, anti-inflammatory, and antiamyloid agent. Other research indicates curcumin's potential to overcome the deleterious effects of spinal cord injury (SCI), as shown by increasing neuronal survival and attenuating astrocyte diminishment (Lin et al. 2011).
- **Green Tea**—It is a rich composition of flavonoids that reduce cognitive loss of aging and reverse some of the degenerative effects, in particular catechin epigallocatechin-gallate, epigallocatechin, epicatechine, and epicatechin 3 gallate (Assunção et al. 2011). It can protect blood–brain barrier permeability accompanying cerebral ischemia, an action which appears to be associated with reduced caveolin-1 expression (Zhang et al. 2010).
- **Resveratrol**—It is a nonflavonoid polyphenol with two isomeric forms: cis-resveratrol, which is biologically inactive, and trans-resveratrol with biologically active (trans-3,4, 5-trihydroxystilbene). Resveratrol treatment reduces oxidative stress, in the spinal cord after an ischemia reperfusion injury. Increased apoptosis, anti-aging capacity, and tumor growth reduction (Kalantari and Das 2010) as well as defense against Alzheimer's disease (AD) also have many beneficial effects on body physiology such as protect the heart, brain, and kidneys (Daffner 2010).

7.5.1.3 Foods to Be Avoid

While certain nutrients contribute to neuronal health, diets that are rich insaturated fats and refined sugar resulted in poorer neuronal performance in the brain because of decrease levels of BDNF (Brain-Derived Neurotrophic Factor) (Molteni et al. 2002), exacerbated the effects of brain injury (Wu et al. 2003). The results of this high caloric diet seem to be linked to high oxidative damage and decreased synaptic plasticity which can be reversed by treatment with antioxidants (Wu et al. 2004). Often viewed as a risk factor for Alzheimer's disease (AD), high calories have been shown to encourage AD type β-amyloidosis in mouse, while a dietary limitation based on reduced carbohydrates prevents this one from developing (Pasinetti et al. 2007).

7.6 Conclusion

The optimum performance of the central and peripheral nervous system depends largely on lifestyle choices such as consistent nutrient uptake and practice. Vitamins of the B-group (vitamin B12, thiamine, niacin, and pyridoxine), vitamin E, copper, and folic acid are the main nutritional factors for the effective functioning of a nervous system. Through food deficiency, neurological symptoms arise. Deficiency diseases such as Epilepsy, Alzheimer's disease, and other dementia, Migraines and other headache disorders, Strokes which include cerebrovascular disease, Parkinson's disease, Multiple Sclerosis are endemic in underdeveloped countries. The increasing inflation of bariatric and chronic alcohol surgery have been accompanied by nutrient deficiency complications. Neurological consequences attributable with alcoholism is Wernicke's encephalopathy, Korsakoff syndrome, fetal alcohol syndrome, alcoholic neuropathy/myopathy, Marchiafava-Bignami Disease, alcoholic cerebellar degeneration, and delirium tremens. This is a crucial concept because of the preventable and potentially treatable nature of these disorders. Healthy food choices may promote synaptic transmission, enhance cognitive ability, and provide a supportive brain set through the use of molecules that affect metabolism and synaptic plasticity for optimal health.

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Part II
Specific Food and Nutritional Qualities on Neurological Disorders

Chapter 8
Best Foods for Repair of Brain Damage

Geethalakshmi Sundararaman and Ashok Ganapathy

Abstract Brain is the vital organ of human body which is kept safely placed inside the skull surrounded by cerebrospinal fluid. But injuries happening in brain sometimes go undetected. OCD is one common brain damage that occurs in the current day scenario. Treatment and cure protocols are available for this but they have their own disadvantages. Medicines used for treatment will only suppress the symptoms which also produces unwanted side effects. Psychological methods cannot be applied to all categories of patients and takes a longer time of recovery. Hence, a natural curing method which does not require any additional protocol is needed. Medical field is focusing its direction in dietary supplements for curing several complications. This chapter also focuses on the nutritional supplements that can be provided to the brain damage patients. It also describes the action of the components on the brain and their positive impact on brain damage. Also, it explains the role of exercise during recovery.

Keywords Brain injury · OCD · Nutrition · BDNF · Exercise

8.1 Introduction

Brain is the most vital organ in the human system and is the central organ of nervous system. It regulates the abundant quantity of information that the body needs for functioning properly. This includes realizing pain levels, regulating blood pressure, scheming nervous response, creating and secreting hormones, helping in digestion, along with organizing countless other signals the body transmits to the brain to enable our body to function without any deficiency. Thus, supplying brain with vital nutrients is essential for effective functioning of the body (Dimond 2013).

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8.1.1 Brain Damage and Its Types

An injury that causes damage to the brain cells is called **Brain Injury**. It is caused by any type of injury in the head but all head injuries need not be brain injury. It is of two types:

- **Traumatic Brain Injury (TBI)**: It is caused by an external force like a blow to the head. It causes the brain to move inside the skull and/or damages the skull which in turn damages the brain (Ghajar 2000).
- **Acquired Brain Injury (ABI)**: It occurs at the cellular level. It is linked with pressure developed on the brain which could come from a tumor, neurological illness, or other brain related complications (Greenwald et al. 2003).

These injuries are not degenerative and usually occur after birth. But some brain injuries occur during the birth which may be due to genetic defect or birth trauma. They are called as congenital brain damage.

Localized brain damage or focal brain damage is the injury that is restricted to a small area of the brain. Diffused brain damage causes damage to several parts of the brain on the whole. The rigorousness of brain damage varies with the type of brain injury.

- Mild injury—Causes headache, memory problems, confusion, and nausea and last only for few minutes to few hours.
- Moderate injury—Symptoms will be prominent and last longer, may be for few weeks to few months. In both the cases, recovery is possible.
- Severe injury—Results in cognitive, behavioral, and physical disabilities. Recovery is almost impossible (Woodward et al. 1984).

8.1.2 Causes of Brain Damage

Brain damage occurs due to many types of injuries or illnesses. It can also happen when the enough oxygen is not supplied to the brain for a long time. Male individuals in the age group of 15–24, young children of age below 10 years, and elderly people who are above 65 years are more prone to this damage compared to female due to their high-risk behaviors.

Traumatic brain injury may be caused by accidents, blows on the head, injuries caused during sports, falling down from heights or by physical aggression. Acquired brain injury may be caused by poisoning or exposure to toxic substances, infection, strangulation, choking, drowning, stroke, heart attack, tumors, aneurysms, neurological illnesses or by drugs (Lishman 1968).

8.1.3 *Symptoms of Brain Damage*

Symptoms of brain damage are categorized cognitive, perceptual, physical, and behavioral/emotional symptoms.

Cognitive symptoms of brain damage consist of difficulty in processing information, expressing thoughts, understanding others, short attention span, inability to understand concepts, impaired decision-making ability, and finally memory loss.

Perceptual symptoms of brain damage include change in sensing, spatial disorientation, balance issues, and increased sense toward pain.

Persistent headaches, extreme physical and mental fatigue, tremors and seizures, sleep disorders, indistinct speech, loss of conscious, and paralysis are the symptoms of physical damage.

Aggressiveness/sluggishness, decrease in stress tolerance, emotions, and reactions and increase in irritability include the behavioral/emotional symptoms of brain damage (Schulman 1965).

8.2 Obsessive Compulsive Disorder (OCD)

Obsessions are unwanted disturbing thoughts, images or instinct that occurs repeatedly inside the brain that induce stress and cannot be controlled. Persons affected by obsessions will not want these thoughts to happen and finds them disturbing. These obsessions usually go with uncomfortable feelings such as fear, doubt, and aversion. These feelings interfere with a person's day-to-day activities and are time consuming. Ultimately, it affects a person's values and morality.

The individual affected by obsessions may try to get rid of/reduce these feelings by engaging in certain procedures/habits which are called as **compulsions**. But compulsions like avoiding or escaping from the situation only provide a temporary relief. All recurring behaviors are not compulsions. This concept has to be seen in the context of brain functioning. For example, learning new skills, daily routines, and other day-to-day practices are repetitive activities but involve active and functional brain. Such disorder arising in the brain is called **obsessive compulsive disorder (OCD)**. All people experience such conditions in their lifetime and that does not mean they are affected by OCD (Leckman et al. 1997; Obsessive Compulsive Cognitions Working Group 1997). The onset of the disorder can be confirmed only when these obsession and compulsion cycles repeat and at one stage, they become extreme. At this point, diagnosis and proper treatment is essential; else, the individual will experience a severe brain damage which may be fatal (Fig. 8.1).

Several studies have analyzed the process involved in OCD and found that it involves decrease/loss of communication between the front part and interior of the brain. The neurotransmitter **Serotonin** is (Fig. 8.2) is responsible for this communication between body and brain (Baumgarten and Grozdanovic 1998). The normal level of this neurotransmitter is 101–283 ng/ml in the blood. During OCD

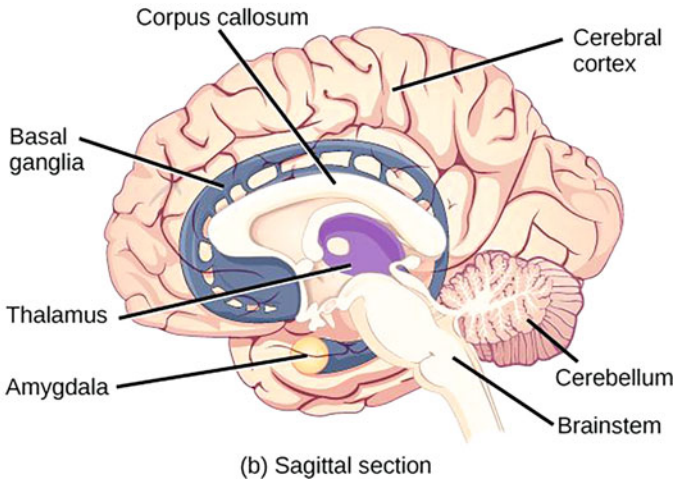

Fig. 8.1 Anatomy of human brain

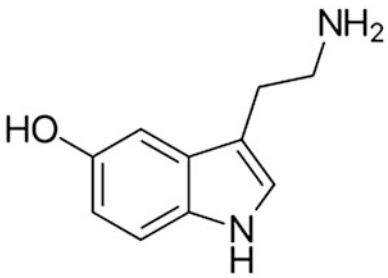

Fig. 8.2 Structure of serotonin

conditions, the level of serotonin is found to decrease. Hence, symptoms such as depression, anxiety, nausea occurs. If left untreated in the initial stages, these symptoms lead to the onset of OCD. If left untreated, OCD leads to brain damage, which ultimately end up in paralysis, stroke, coma, and brain death (Van Dijk 2008).

8.3 Treating OCD and Brain Damage

8.3.1 Antidepressant Drugs

The initial stages of the brain damage where the serotonin levels are less can be treated with antidepressant drugs. They are medications that help to relieve anxiety disorders and depressions. These drugs work by balancing the neurotransmitters and

their transmission to brain (Zafonte et al. 2002). There are several types of these drugs:

- Serotonin and noradrenaline reuptake inhibitors (SNRIs).
- Selective Serotonin reuptake inhibitors (SSRIs).
- Tricyclic antidepressants (TCAs).
- Monoamine oxidase inhibitors (MAOIs).
- Noradrenaline and specific serotoninergic antidepressants (NASSAs).

But these drugs cause various side effects on prolonged usage. Constipation, dry mouth, weight gain, drowsiness and sedation, blurred vision, hypertension, edema, tremors, and hypoglycemia are some of the side effects of these antidepressant drugs (Elmorsy et al. 2017).

8.3.2 Rehabilitation Therapies

Rehabilitation therapies are therapies given to brain damage patients under controlled environment to help the body heal, relearn skills and new ways to do activities without any difficulty. There are three types of rehabilitation therapies: occupational, physical, and speech.

Occupational therapies help patients who require assistance to execute their day to day activities like eating, brushing, sleeping, etc. Physical therapies are given to patients who experience pain in functioning of their body parts. Such therapies help people to relieve pain, improve the movement of body parts, and recover from injuries and strengthen the cardiovascular operations. Speech therapy is given to patients who have difficulty in speech and communication especially in Parkinson's disease, Huntington's disease, etc. (Soo and Tate 2007; Williams et al. 2003).

8.3.3 Psychological Support

Some basic management skills such as controlling stress, anger, and unwanted thoughts can be done using psychological treatment along with some medications.

Though there are enough number of treatments, drugs, and support mechanisms for handling brain damage, these methods have their own disadvantages such as:

- Wrong diagnosis;
- Non-cooperation from the patients;
- Time duration;
- Theorizing on brain damage;
- Optimizing the treatment methods depending on the patients' age, gender, damage vigor, potency of the patient, etc.;

- Side effects of the drugs;
- Allotment of specific time duration for the treatment;
- Cost;
- Requires experts.

Thus, alternative methods of treating brain damage are required. The novel method must be natural, without causing/causing minimal side effects, applicable to patients of all categories, must not require specific time duration, expertise, and must be easily available and cost effective. One such method is devising treatment using natural food supplements (Jenike 2001).

8.4 Nutrition for Brain Damage

As conventional treatment methods have their own disadvantage and are not suitable for all people and situations, natural and convenient methods of treating brain injuries are devised. During normal working condition, the human brain needs lot of energy and this is drastically increased when it sustains injury and damage. Hence, proper diet must be designed which is rich in nutrients and energy boosters which will rejuvenate the brain and make it function effectively. Thus, certain essential elements such as protein, magnesium, zinc, antioxidants, and minerals must be present in the diet on a daily basis to boost up the brain function (Gomez-Pinilla and Kostenkova 2008). There are also certain elements that have to be avoided during brain damage because poor diet affects the function, behavior, and mood of the brain. Essential elements in the food help in enhancing proper biochemical reactions in the nerves and brain and also maintain the level of neurotransmitters. Thus, healthy diet is very essential for effective and speedy recovery from brain damage. The diet must include vegetables, fruits, and grains, low fat foods such as fish, beans, and lean meat. The quantity of salt, sugar, and alcohol must be reduced and quantity of water intake must be increased. Recent research indicates choline, creatine, omega-3 fatty acids, and zinc are useful for recovery (Gomez-Pinilla 2011).

8.4.1 Essential Vitamins

Different foods have different vitamins in them and each has their own role to play regarding the brain health. Table 8.1 gives the consolidated purpose of each type of vitamins (Aquilani et al. 2011; Spector and Johanson 2007).

Table 8.1 Vitamins and their role in brain health

S. No.	Vitamin	Source	Role in brain health	Deficiency
1.	B1 (thiamine)	Grains, legumes, pork, nuts, and seeds	Metabolism of glucose which promotes muscle growth and as energy source	Beri-Beri
2.	B12 (cobalamin)	Eggs, meat, and milk	Maintains the myelin sheath	Impaired brain function and nerve damage
3.	B9 (folic acid)	Yeast, beans, wheat, nuts, and broccoli	Effective function of neuro-transmitters and brain	Nervous disorders and anemia
4.	B3 (niacin)	Wheat bran, meat, fish, peanuts, and milk	Effective function of neuro-transmitters and brain	Pellagra, psychosis, and loss of memory
5.	A (retinol)	Spinach, eggs, carrot, fish, and meat	For functioning of eyes and protection against infection	Vision impairment
6.	E (tocopherol)	Greens, cereals, and plant oils	Oxygen supply to brain	Peripheral neuropathy
7.	B6 (pyridoxine)	Fish, pork, chicken, wheat, fruits, and vegetables	Supports nervous system functioning	Mental depression, confusion, convul-sions, and anemia

Table 8.2 Minerals and their role in brain health

S. No.	Minerals	Source	Role in brain health
1.	Iron	Fish, poultry, and meat	Formation of hemoglobin to carry oxygen throughout the body
2.	Manganese	Grains, nut, fruits, and vegetables	Helps in brain functioning
3.	Selenium	Liver, eggs, and sea foods	Synthesis of hormones and protection from cell damage
4.	Zinc	Liver, eggs, red meat, dairy products, and vegetables	Protection from cell damage
5.	Magnesium	Grains, buts, green leafy vege-tables, and seeds	Transmission of nerve impulse
6.	Copper	Seeds, nuts, sea food, cereals, and dark chocolates	Maintains immune response and brain function

8.4.2 Essential Minerals

Minerals, like vitamins, plat an important role in maintaining the brain health. Table 8.2 lists the essential minerals that must be supplied to brain (Hasan et al. 2011).

Considering these parameters, the best food that must be taken by patients affected by brain damage is consolidated as follows.

8.5 Best Food for Brain Injury

In order to recover from brain damage naturally with minimal side effects and complications, dietary supplements are formulated. Some of the required diet components are discussed in the following.

8.5.1 Omega-3 Fatty Acids

Omega 3 fatty acids are very essential for nerve and brain functioning, signal transmission, neurotransmitters functioning, and all operations related to brain and nervous system. Human brain consists of 60% fat and most of these fat molecules belong to Omega-3 FA category: α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Bourre 2004). There are many studies done recently on polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) and there is increasing evidence that these fatty acids play an important role in maintain the brain health. They help in rejuvenating the damaged brain and nerve cells. It also helps in maintaining the neuroplasticity (Avallone et al. 2019). Omega-3 and Omega-6 FA which comprises linoleic acid (LA) and arachidonic acid (ARA) comes under PUFA and Omega-9 FA under MUFA. Of these FAs, Omega-3 determines several cerebral functions and DHA plays an important role in facilitating the functioning of the brain. Figure 8.3 shows the structure of PUFA. These PUFAs are present adequately in fish such as sardines, salmon, and trout. They contain 0.6–1.24 g/portion of DHA. These fish varieties must be baked or broiled to get the maximum effect of PUFA. PUFA is also present in walnuts, pumpkin seeds, flax seeds, soybeans, and dark leafy vegetables like spinach (Dyall 2015; Healy-Stoffel and Levant 2018).

DHA is presents in esterified form in food. When consumed, in the intestine, lipases convert esterified DHA into unesterified form and transfer it to small intestine. In the small intestine, it under goes metabolism and is converted to free DHA. These free DHA molecules pass through the blood–brain barrier (BBB) with the help of fatty acid-binding proteins (FABP) and endothelial lipases and get distributed within the central nervous system (Medina and Tabernero 2002; Song et al. 2019).

8.5.2 Dark Chocolate

Dark chocolates contain high level of magnesium and antioxidants. These two nutrients are essential for recovery of the brain from TBI. Especially the variety of dark chocolate which contains more than 60% cocoa is the most preferred type of chocolate to be given to the brain damage patients (Toker et al. 2018).

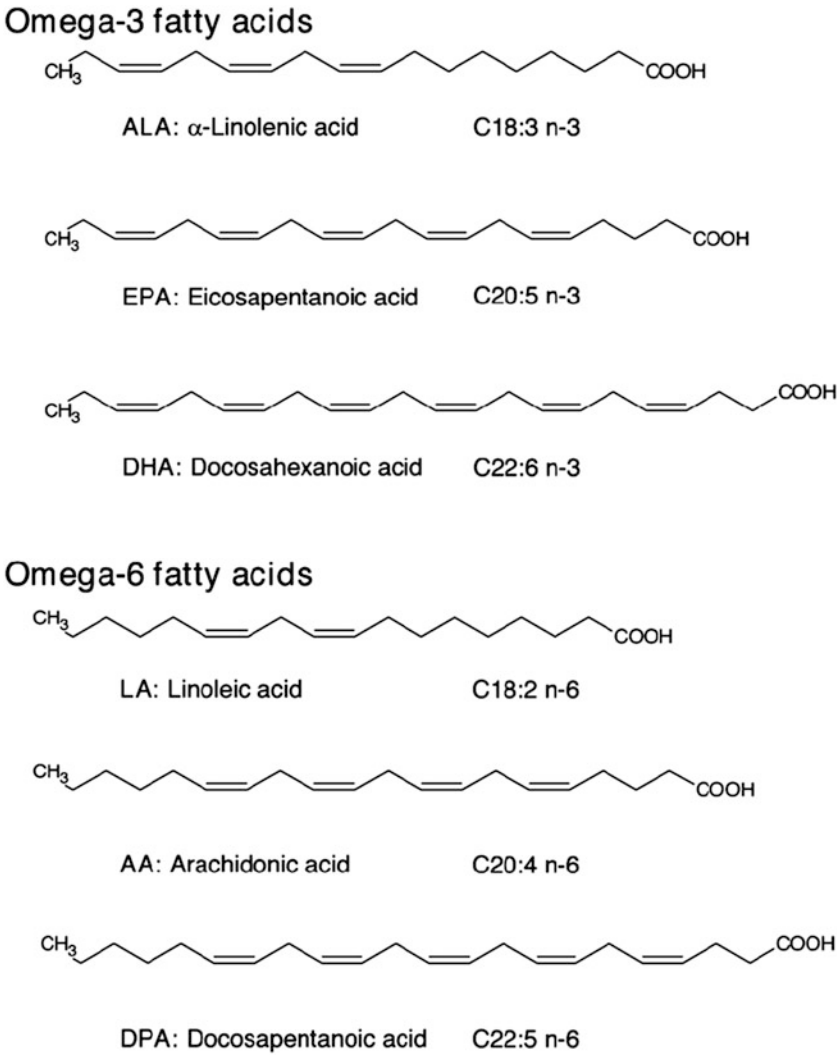

Fig. 8.3 Structure of PUFA

Magnesium acts as a neuroprotective agent and is found to reduce the infarct zone and neurodeficiency. It actually reduces the mortality rate of the brain cells and also exhibits antioxidant effect on damaged tissues. It acts as a protective agent of blood–brain barrier (BBB); if administered as magnesium sulfate, its effect show many fold increase on the brain and nerve cells. The antioxidative protection mechanism of magnesium can be understood in two steps: one is inhibiting the lipid peroxidation which is catalyzed by Fe ions and the other is restoring the glutathione level in the cells thereby increasing the level of GSH in the blood. There are evidences which indicate the direct correlation between the concentration of Mg^{2+} and GSH. GSH

along with α-tocopherol, β-carotene, and ascorbic acid scavenges the free radicals generated due to the damage of brain cells, thereby stimulation adequate oxygen supply, which helps in rejuvenating the damaged cells. Mg^{2+} also plays an important role in activating neurotransmitter function (Zheltova et al. 2016; Shadman et al. 2019).

8.5.3 Berries

Berries are rich in antioxidants, which are very helpful in protecting the brain from damage and reducing inflammation. Strawberries and blueberries are essential for improving memory, learning, and other cognitive functions. They promote brain derived neurotrophic factor (BDNF) which plays an essential role in neuronal survival and growth, modulates neurotransmitters, maintains neuronal plasticity, and helps in learning and improving memory power (Choi 1993; Arteaga et al. 2017).

8.5.4 Meat

Another nutrient that gets depleted due to brain damage is zinc. Zinc (Zn) helps to modulate responses of neurotransmitters to their receptors (Pillsbury et al. 2011). It also has neuroprotective properties. Zn occurs in two forms inside the brain cells: (1) Tightly bound to proteins and (2) As a free ion in the cytoplasm or extracellulary in presynaptic vesicles. Under normal conditions, Zn released from the synaptic vesicles modulates both ionotropic and metabotropic post-synaptic receptors. Numerous specific transport mechanisms are required to transport Zn across the cell membrane (Cuajungco and Lees 1997). Deficiency of Zn affects the secretion and activity of serum thymulin, a thymic hormone, which is essential for maturation and differentiation of T helper (Th) cells (Mezzaroba et al. 2019).

Red meat, legumes, soybeans, squash, and flax seeds are rich in Zinc. However, large consumption of red meat can cause other health issues such as heart disease, diabetes, and cancer.

8.5.5 Turmeric Root or Powder

Turmeric is one of the well-known Indian spice which is a rich source of curcumin. Curcumin has high benefits for TBI patients, being an antioxidant and stimulating the production of BDNF. BDNF induces neurogenesis, a process in which new nerve cells are formed and damaged cells are rejuvenated (Bathina and Das 2015; Bath et al. 2012). The mechanism of BDNF in inducing neurogenesis is as follows.

BDNF affects the synaptic and neuronal plasticity via a mechanism in which CREB protein (cyclic AMP response element binding protein) and GAP-43 (growth associated protein 43, also known as Synapsin-I) has vital roles. Synapsin-I belongs to the family of proteins called nerve terminal specific phosphoproteins which inhibits the release of neurotransmitters, elongation of axons and maintaining the synaptic associations. Synapsin-I synthesis and its phosphorylation is controlled by BDNF and hence there will be an increase in the synthesis and release of neurotransmitters (Rossi et al. 2006; Bath et al. 2012).

Similarly, GAP-43 located in the terminal region of axons stimulates the growth of axons and release of neurotransmitters which is helpful in memory and learning. One of the transcription factors in brain, called cAMP response element binding protein (CREB), in association with BDNF regulates the gene expression involved in neuronal resistance. Thus, BDNF has a vital role in neurogenesis (Habtemariam 2018).

The curcumin present in turmeric is essential for synthesis of BDNF, thereby indirectly helps in revitalization of brain cells. Being a spice, turmeric can be added to any type of food. Even if boiled, its properties do not change. Also, turmeric powder increases the immunity of the entire system (Sangiovanni et al. 2017).

8.5.6 Eggs and Avocados

One of the important sources of choline (2-hydroxyethyl-trimethyl-ammonium) is eggs. Choline in brain helps to improve the cognitive functions of the brain. It also has many important physiological functions in brain like:

1. Choline is responsible for synthesis of acetyl choline, an essential neurotransmitter in brain.
2. It regulates cholinergic neurotransmission in specific brain regions that are involved in the cognitive behavior.
3. It acts as a precursor for the synthesis of several phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), and sphingomyelin (SM). These phospholipids mediate cell signaling, myelin sheath formation, cell division, lipid transport, membrane biogenesis and help in development and functioning of the brain.
4. Choline is an effective methyl group donor. With the help of S-adenosine methyl transferase (SAM), choline transfers methyl group which plays a vital role in nerve rejuvenation, plasticity and development of cognitive skills (Bekdash 2018; English et al. 2009).

Another important component essential for normal brain functioning is oleic acid (OA). It is a monounsaturated fatty acid present in oils, fats, and avocados. Oleic acid is the major component of phospholipids and is present abundantly in myelin. OA is also needed for axonal and dendritic growth, in synapse formation, neuronal

aggregation and also act as a neurotrophic factor. OA reduced nerve cell death by decreasing the toxic effects of lipid peroxidation cycles.

Combining choline and oleic acid helps to boost the neurotransmission and helps in reformation of brain and nerve cells (Canty and Zeisel 1994; Tayebati and Amenta 2013).

8.5.7 Foods to Avoid During Brain Injury

Though many nutrients help in restoring from brain damage, there are some food which should be avoided during brain damage conditions because these foods interfere with the supplements thereby affecting the role of essential components like BDNF, choline hence decreasing the signaling and plasticity of the brain. Also, to break down certain nutrients, the body utilizes vitamins and minerals, like the case of alcohol and caffeine. Hence nutrient deficiency occurs, which leads to decrease in ATP level. As a result, the brain cells starve for energy which alleviates the damage (Selhub 2015). Hence, certain food has to be avoided like:

1. Saturated fats and processed sugar,
2. Alcohol, caffeine,
3. Other drugs,
4. Butter, cream, milk, cheese,
5. Processed meat.

8.6 Role of Exercise During Recovery

Physical exercise, much like the diet is beneficial to the neurons facilitating increase in BDNF levels and decreasing the stress. Specifically, exercise induces axon or dendrite growth and development, maintaining the synaptic structure and for the formation of new neurons (neurogenesis) (Matsuda et al. 2010). There are research studies which indicate continuous exercise helps the brain to be stronger in cognitive point of view. Also, it helps in reducing infarction and induced prophylactic effect on brain damage (Leddy et al. 2016).

In conditions like Parkinson's disease (PD), exercise seems to increase the motor ability of the patients but the time duration, period, and time of exercise is still controversial. One of the most effective forms of exercise for brain damage is cardiovascular exercise. Swimming and treadmill have a visible effect during the recovery process. Along with these activities, running and walking is also found to have effect on nerve regeneration. It also increases neuroplasticity and increases the cellular expression of neurotransmitters. Drastic increase in the coordination of

sensory motor cortex, increases hippocampal volume and spatial memory were observed in animals.

The primary growth factors that mediate the effects of physical exercise on brain are BDNF, VEGF (vascular endothelial derived growth factor), and IGF-1 (insulin-like growth factor-1). These three factors function together to regulate the plasticity, function, and health in the brain, thereby producing functional effects. IGF-1 and BDNF combine together to regulate the cognitive skills and stress relief, while VEGF and IGF-1 combine to stimulate neurogenesis and angiogenesis. During angiogenesis, IGF-1 helps in the increase of VEGF protein level, which in turn is involved in the increase of mitotic activity specific to vascular endothelial cells. This helps in proliferation of blood vessels, capillary tube formation, adhesion, and survival (Cotman et al. 2007).

8.7 Combined Effects of Diet and Exercise

Neuronal plasticity and effective functioning of the brain is enhanced by the combined effects of diet and exercise. Among many nutrients that can improve the brain function, omega-3 fatty acids, saturated fats and polyphenols work well when combined with physical exercise (Gomez-Pinilla 2011).

The effects of DHA are enhanced by exercise; they combine to influence the hippocampal plasticity and stimulate the cognitive function. It is found that DHA is retained on the plasma membrane of the brain cells which in turn enhances the signal transmission. This is due to the fact that the receptors on the plasma membrane for DHA are activated by BDNF, whose secretion is increased by physical strain thereby preserving the DHA on the cell surface. Similarly, flavanoid-rich diet in combination with exercise has been shown to enhance the gene expression that is directly related to plasticity simultaneously, decreasing the negative gene expression causing inflammation and cell death. Also, the energy homeostasis in hypothalamus and hippocampus was boosted up with the combined effects (Gómez-Pinilla et al. 2002; Grande et al. 2010).

It was also found that combination of curcumin and DHA has an enormous effect on the mechanism of neuronal repair in comparison with their individual effects. Energy generating metabolic pathways are directly associated with pathways that govern neuronal plasticity. Thus, the rate of energy generation can influence the learning and behavioral capacity of the brain. Hence, exercise has a direct effect on molecular systems such as IGF-1, AMPK, ubiquitous mitochondrial creatine kinase (uMtCK), UPC-2 (uncoupling protein-2) which are the critical mediators of energy metabolism. Thus, dietary therapy which boosts the energy of the patient, in combination with exercise can help in faster recovery of brain damage (Gomez-Pinilla 2011).

8.8 Conclusion

Brain damage and neurological disorders are not caused by single factors but are the combinations of malfunctioning of various targets. Thus, pharmacological studies are quite complicated and do not provide reliable results. Hence, a multi-targeted treatment methodology is mandatory in this regard. Dietary supplements and exercise influence molecular systems which afford resistance to cell damage, enhance synaptic transmission and increase cognitive skills. In particular, DHA and curcumin are shown to improve the membrane physiology and signal transduction. Certain other supplements like omega-3 fatty acids have the capacity to store energy and in combination with exercise can stimulate restoration of brain function (Yu et al. 2018). An extensive research is needed in this aspect which highlights the application of these concepts to a majority of the population and also that will be able to explain in detail the action of all the components of diet in restoration of brain and nerve functioning after damage. In conclusion, it can be understood that recovery from brain damage can be faster using natural food supplements compared with synthetic drugs and pharmaceutical products.

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Chapter 9
Role of Micronutrients in Neurological Development

Neenu Ravikumar, Madhubalaji Chegukrishnamurthi, and Swarnalatha Gadde Venkata

Abstract Food is an essential component for reinforcing the physical and mental health of an individual. Balanced nutrients are essential for normal body functions. Micronutrients such as vitamins (Vitamin-A, B_{12}, B_6, folate), minerals (iron, magnesium), and omega fatty acids have a crucial role in cognitive and neuronal function, as well as amelioration of neurological disorders. The production and storage capability of micronutrients inside the body decreases with age, and it needs to be supplemented externally through the diet. In contrast, the absence of micronutrients in the body leads to various neurological disorders. Pharmacological interventions for treating neurological disorders are restricted and are correlated with a notable risk of adverse events. Diet predominantly with micronutrient supplementation is recommended as a safe and effective way for ameliorating neurological disorders. Studies with supplementation of micronutrients have evolved from single-use vitamin/mineral to broad-spectrum micronutrients (BSM) in the ministration of neurological disorders. Suboptimal nutrition is the key to mental illness, and multi-micronutrient supplementation in addition to food intake could improve symptoms associated with neurological disorders. This chapter explains the importance of micronutrients in neurological development, the combination of micronutrient effects, recent studies on neurological disorders, improvements observed with single micronutrient supplementation, multi-nutrient supplementation, and also neurotoxic effects of some heavy metals.

Keywords Micronutrients · Neurological disorders · Single-use micronutrients · Broad-spectrum-micronutrients · Heavy metals

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Abbreviations

5-HTP	5-Hydroxytryptophan
AD	Alzheimer's disease
ADHD	Attention-deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
ASD	Autism spectrum disorder
BDNF	Brain-derived neurotrophic and immunologic factors
BSM	Broad-spectrum micronutrients
CHAP	Chicago Health and Aging Project
CNS	Central nervous systems
CSF	Cerebrospinal fluid
DALYs	Disability-adjusted life years
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
GABA	Gamma-aminobutyric acid
GBD	Global Burden of Disease
GWS	Gulf War syndrome
HD	Huntington's disease
IDA	Iron deficiency anemia
LCPUFA	Long chain poly unsaturated fatty acids
NMDA	*N*-methyl-D-aspartate
NT3	Neurotrophin 3
NTD	Neural tube defects
OCD	Obsessive-compulsive disorder
PD	Parkinson's disease
PUFA	Polyunsaturated fatty acids
RA	Retinoid acid
ROS	Reactive oxygen species
SJW	St. John's wort
TK	Transketolase
WD	Wilson's disease
WHO	World Health Organization

9.1 Introduction

A balanced diet is necessary for the mental and physical well-being of an individual. Nutrients (especially micronutrients) have an influential role in brain development and functions, including intellectuals and cognition (Bourre 2006). World Health Organization (WHO) reported that globally around two billion people were affected with micronutrient deficiencies. Global Burden of Disease (GBD) study includes many nutritional conditions such as protein-energy malnutrition, vitamin-A

deficiency, iodine deficiency, and iron deficiency anemia. GBD indicated that malnutrition is estimated to be the main reason for 15% of the disability-adjusted life years (DALYs) lost worldwide (Ezzati et al. 2002). In this context, micronutrient deficiency-induced neurological disorders are one of the significant public health concerns. Micronutrients are essential dietary ingredients requisite in microgram or milligram quantities, involving in various biochemical pathways and metabolic processes. Micronutrients comprise of water-soluble vitamins (B complex vitamins and vitamin C), fat-soluble vitamins (Vitamin-A, Vitamin-D, Vitamin-E, and Vitamin-K), essential minerals (including iron, iodine, calcium, and magnesium), and trace elements (copper, manganese, selenium, and zinc, etc.). The essential micronutrient deficiency arises due to inadequate food diversities, which is the main scenario observed in low-income countries. These deficiencies pave the way for numerous health problems. Clinical signs of micronutrient deficiency become discernible once its deficit becomes critical, less obvious "invisible" effects afflict the health and development of a much larger share of the population. That is why micronutrient deficiencies are often termed as "hidden hunger." "Let food be thy medicine, and medicine be thy food" quoted by Hippocrates emphasis on food to nurture an individual's physical and mental health. An inadequate diet, especially micronutrient imbalance in diet, negatively impacts the body's mental health (Kaplan et al. 2007). The problems related to insufficient food diversities cause a deficiency in vital micronutrients that disrupt everyday physical and psychological well-being. In addition, micronutrient deficiencies are not always associated with the quantity of food and consumption patterns. It can be related to physiologic effects, which disrupt optimal health function and life-threatening conditions (Tulchinsky 2010).

Neurodevelopment is a highly complex process. The first 2 years of an individual's life are most crucial for brain development, i.e., "first 1000 days" (the period between the conception and first 2 years of life). Nutrients play a significant role in many critical neurodevelopmental processes across brain regions, even supporting the high brain metabolism rate during early life. Impairment in early neurological development may lead to many health consequences (Mattei and Pietrobelli 2019).

Impairment in activities related to learning, behavior, socializing, and communication are few conditions characterized for diagnosing neurodevelopmental disorders in children (Taylor et al. 2018). Overall health and quality of life are significantly influenced by nutritional status in children with neurological disorders. The efficiency of numerous dietary and nutritional supplementations on the medication of neurological disorders was studied and indicated an improvement in symptoms of neurological disorders (Pancheva-Dimitrova et al. 2018). Each nutrient plays a specific role in normal neurological functioning and development and its deficiencies pave the way to neurological disorders. The functions of the major micronutrients, which have a key role in the central nervous system, are shown in Fig. 9.1. Nutrients are used for alleviating psychosis, mood, irritability, and other psychiatric symptoms. The ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) are essential for the membranes of neuronal cells and their normal function. Studies have shown an association of ω-3 PUFAs deficiencies in mood disorders (such as

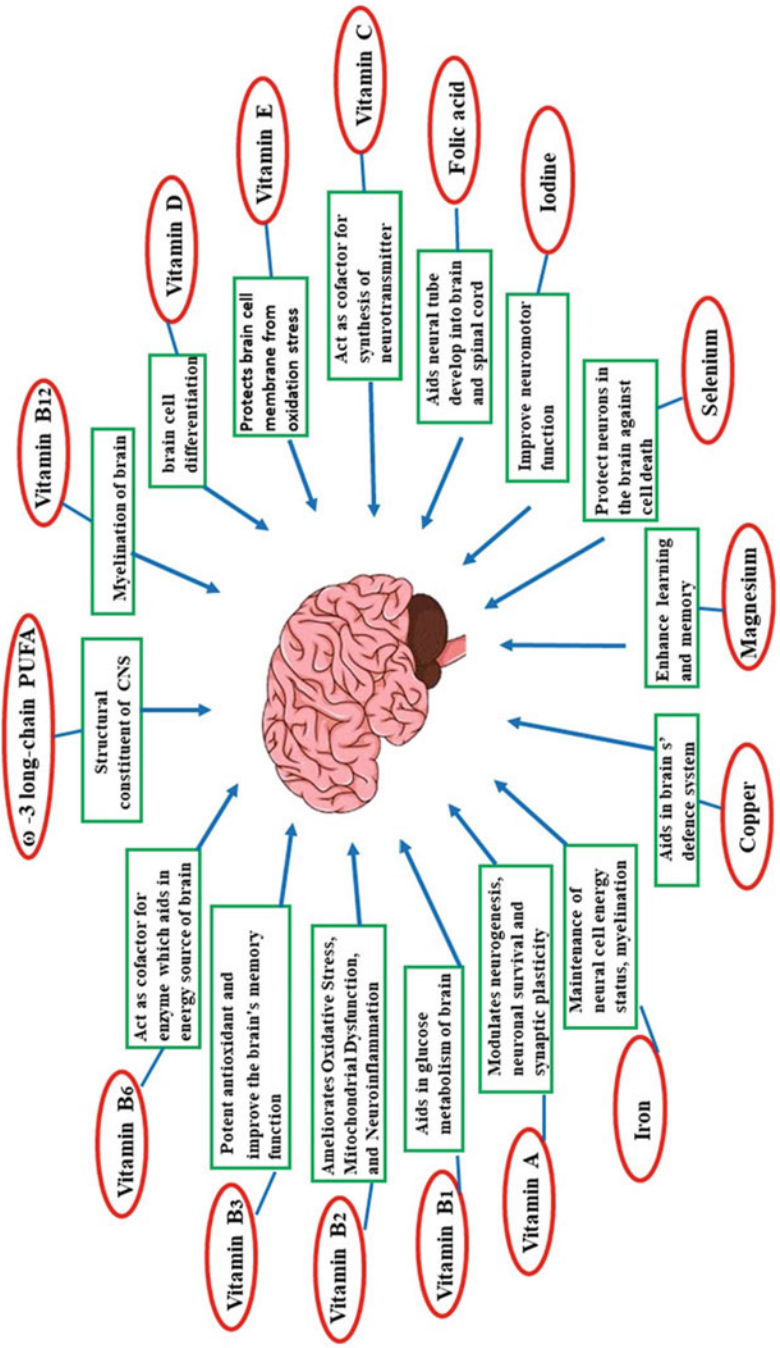

Fig. 9.1 Major micronutrients and their functions in the central nervous system

schizophrenia) and Alzheimer's disease (AD) (Fuentes-Albero et al. 2019). Lozoff and Brittenham (1987) observed a noteworthy outcome of iron deficiency anemia on affective behavior, showing the development of long-term behavioral and developmental disorders in anemic infants. Iron status affects attention or arousal, which, in turn, changes performance. Bayley Mental Developmental Index was reported lower in Iron deficient children (Kretchmer et al. 1996). Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurological disorder connected to the catecholaminergic and serotonergic systems. The studies revealed the effect of vitamin D on pathways associated with the synthesis of serotonin, dopamine, and neurotrophic factors. ADHD patients reported to have lower serum vitamin D levels, and it was observed that supplementation with vitamin D for children with ADHD, caused a rising serum dopamine levels (Seyedi et al. 2019).

Neurotransmitters can contribute to depression if they fail to function properly. Micronutrients are required for the production and proper functioning of neurotransmitters, indicating a positive correlation between micronutrients and neurochemical systems related to an anxiety response. Micronutrients act as anti-depressants on neural systems related to anxiety and depression (Rucklidge 2009). Folate plays a vital role in serotonin neurotransmission. Decreased folate levels are related to raising depression and reduced response to anti-depressants. Folate deficiency and malabsorption are common in our society since folate in the diet is heat-labile and easily oxidized (Kong et al. 2006). A decrease in vitamin-E level was observed in cerebrospinal fluid (CSF) of AD patients.

The caudate nucleus and the putamen are integral parts of the brain. The caudate nucleus acts like an automatic transmission for the intellectual part of the brain, while putamen act as an automatic transmission for the portion of the brain that controls body activities. The effective coordination of thought and movement in everyday activities is regulated by the caudate nucleus, but this is not happening in the case of the individual with Obsessive-compulsive disorder (OCD). The automatic transmission of the caudate nucleus gets affected in OCD, which can be improved by enhancing serotonin neurotransmission through psychotropic medications. Several factors affect serotonin synthesis, which includes nutrition, anxiety, and neurotoxins. Serotonin production can also be affected by the accessibility of L-tryptophan and essential cofactors, including niacin, vitamin B_9, vitamin B_6, and zinc. Their deficiencies can adversely affect the optimal balance of serotonin levels. The optimum concentrations of magnesium and zinc are necessary for sustaining ideal serotonin levels. Zinc act as a coenzyme for decarboxylase activity and 5-Hydroxytryptophan (5-HTP) to serotonin conversion. Magnesium is critical for converting L-tryptophan to serotonin (Schwartz and Beyette 1996). In recent studies, serotonin production enhancement through natural remedies such as 5-HTP as well as correcting deficiencies regarding vitamin B_3, vitamin B_6, vitamin B_9, magnesium, zinc, and inositol, have been intensively used for improving OCD (Kong et al. 2006). This chapter mainly focuses on the relation between nutrition (micronutrients benefits) and neurological disorders. In addition, current nutritional formulas used for improving neurological disorders and neurotoxic effects of some heavy metals are also discussed.

9.2 Role of Major Micronutrients in Neurological Disorders

Micronutrients play a crucial role in normal body function and brain development. They act as cofactors in the enzymatic process responsible for neurotransmitters synthesizing and metabolism. Micronutrients involved in neurological development, their dietary sources, function, and recommended dietary allowance levels are presented in Table 9.1. Micronutrient deficiencies have important and complex effects on the central and peripheral nervous system functioning (Maxwell et al. 2013). Numerous micronutrient deficiencies including vitamin B_1, niacin, vitamin B_6, vitamin B_{12}, copper, vitamin E, and folate led to peripheral neuropathies, and polyneuropathy in the legs (Hammond et al. 2013). The lack of various micronutrients will have a long-term impact on human cognitive development (Anjos et al. 2013). Taylor et al. (2018) observed application of nutritional supplementation (such as omega-3 and micronutrients) on neurological disorders. This section focus on major micronutrients that are essential for neurological development and their role in neurological disorders.

9.2.1 Vitamin-A (Retinoid Acid)

Retinoid acid (RA) is a biologically active metabolite of vitamin-A. It is an active signaling molecule in the brains of young and adult animals, which modulates neurogenesis, and control variety of gene products regulating neurogenesis and neuronal survival (Olson and Mello 2010). Retinoid acid also affects different pathways of molecular signaling in the developing brain by regulating several genes expression and stimulating cell differentiation (Anjos et al. 2013). Vitamin-A improves neurogenesis and differentiation of astrocytes by stimulating the production of stem cells responsive to the epidermal growth factor (Medina 2007). The embryonic central nervous systems (CNS) require vitamin-A and its byproducts, the retinoid, particularly RA, for its normal development. Maden et al. (1998) observed a defect in CNS of quail embryos in the absence of vitamin-A, which indicates the importance of vitamin-A in CNS development. Supplementation of vitamin-A through diet improves learning and memory. In a study, vitamin-A deficient rodents on supplementation with vitamin-A ameliorated cognitive declines related with normal aging (Olson and Mello 2010).

9.2.2 Vitamin B_1 (Thiamine)

Vitamin B_1 is water-soluble and is involved in the maintenance of normal functioning of nerve membrane, myelin formation, and synthesis of neurotransmitters (e.g., serotonin, acetylcholine, and amino acids). At the cellular level in the brain, thiamine

Table 9.1 Micronutrients associated neurological disorders and their sources, recommended daily allowances

Micronutrient	Dietary source	RDA	Associated neurologic disorder
Vitamin B_1 (thiamine)	Liver, nuts, oranges, fish, pork, eggs, asparagus, sunflower seeds, green peas, flax seeds, beet greens, spinach, cabbage, eggplant, mushrooms, barley, dried peas, lentils, oats, sesame seeds, kidney beans, peanuts, sweet potato, tofu, tuna, pineapple, oranges, broccoli, green beans, dried beans, and lean meats	1.1 mg	Wernicke–Korsakoff syndrome
Vitamin B_3 (niacin)	Chicken, Turkey, mushroom, salmon, lamb, asparagus, tomatoes, sardines, peanuts, shrimps, brown rice, sweet potato, sunflower seeds, barley, green peas, potatoes, corn, carrots, mushrooms, and spinach	15 mg	Alzheimer's and Parkinson's diseases
Vitamin B_6 (pyridoxine)	Tuna, spinach, cabbage, garlic, cauliflower, Turkey, chicken, salmon, sweet potato, potatoes, banana, broccoli, carrots, and tomatoes	1.6 mg	Polyneuropathy
Vitamin B_{12} (cobalamin)	Sardines, salmon, tuna, lamb, scallops, shrimps, yogurt, cow's milk, eggs, chicken, cheese, mushrooms and microalgae such as *spirulina*	2.4 μg	Legs with progressive myelopathy with sensory disturbance
Vitamin B_9 (folate)	Spinach, turnip greens, broccoli, beets, black beans, kidney beans, papaya, green peas, green beans, cabbage, strawberries, tomatoes,dried peas, avocado, peanuts, sunflower seeds, quinoa, oranges, pineapple, raspberries, carrots, mushrooms, kiwifruit, mushrooms, basil, eggplant, lemons, limes, orange juice, cereals and nuts, seafood, eggs, dairy products, meat, poultry, and grains	180 μg	Neural tube defect
Iron (Fe)	Beans, lentils, meat, fish, poultry, cereals Tofu, legumes, cashews, dark green leafy vegetables, spinach, whole grains, pulses, fruits, and vegetables	15 μg	Delayed motor development in children
Iodine (I)	Fish, seaweed, shrimp, other seafood, dairy products such as milk, yogurt, and cheese and grains	150 mg	Iodine deficiency disorder(cretinism)
Zinc (Zn)	Whole grains, oysters, red meat, poultry and milk products, baked beans, chickpeas, and nuts	12 mg	Depression
Selenium (Se)	Wheat, meat, fish, spinach, and potato	55 mg	Adverse mood states

is converted into thiamine pyrophosphate, which plays a crucial role in many biochemical pathways, mainly in glucose and energy metabolism. The Wernicke–Korsakoff syndrome (WKS) is the most adverse neurological disorder caused by a vitamin B_1 deficiency. Thiamine deficiency could cause a decrease in the transketolase (TK) activities in Alzheimer's disease (AD) patient's brains since studies in rats with thiamine-deficient reveal early prevalent reductions in TK activity all over the brain. Blass et al. (1988) showed a major enhancement in cognition in AD patients who took oral thiamine 3 g every day for 3 months. Thiamine plays a helpful role by stimulating dopamine release and ameliorating the symptoms related to Parkinson's Disease (Lương and Nguyễn 2013).

9.2.3 Vitamin B_2 (Riboflavin)

Riboflavin ameliorates oxidative stress, neurogenic inflammation, mitochondrial dysfunction, and homocysteine neurotoxicity. Riboflavin decreases glutamate release, thereby reducing its levels in the synapses, eventually reducing glutamate ex-cytotoxicity potential (Marashly and Bohlega 2017). The deficiency of vitamin B_2 leads to depression. Mutations in the PARK2 gene enhance the vulnerability to glutamate neurotoxicity, influencing the early onset neurodegeneration of Parkinson's Disease. Studies of encephalomyelitis in C57BL/6 mice exhibited that supplementation of riboflavin reduced (26.4%) the neuronal disability which was higher than placebo supplementation reduced (15.4%) neuronal disability. Riboflavin supplementation to multiple sclerosis containing experimental autoimmune encephalomyelitis model's showed lower IL-6 brain-derived neurotrophic and immunologic factors (BDNF) expression which was related to the observed positive effects of riboflavin on neuro motor disorders (Naghashpour et al. 2016).

9.2.4 Vitamin B_3 (Niacin)

Niacin includes two types of vitamers. They are nicotinic acid and nicotinamide. Nicotinamide impacts neurogenesis by stimulating the differentiation of embryonic stem cells into post-mitotic neurons. Nicotinamide also aids in neuronal survival during oxidative stress conditions (Gasperi et al. 2019). According to the population-based Chicago Health and Aging Project (CHAP) study, dietary niacin can protect against AD and cognitive decline associated with age. Nicotinamide and/or nicotinamide mononucleotide reduce the gene expression connected to AD (presenilin 1 and amyloid precursor protein) and production of reactive oxygen species (ROS) and also improve neuron survival, thereby inhibiting amyloid toxicity. In vitro (cultures of organotypic hippocampal slice) and in vivo (model rats of AD) studies have recognized the protective role of vitamin B_3 against Aβ-induced neurotoxicity. Niacin is essential for converting tryptophan to serotonin, so they are used in treating

depression. Clinical trials with niacin have revealed several benefits for neuroinflammation, including a decrease of GPR109A (a human protein that encodes for the niacin receptor HCAR2 gene), which is normally enhanced in Parkinson Disease patients (Seamon et al. 2020).

9.2.5 *Vitamin B_6 (Pyridoxine)*

Vitamin B_6 plays a significant role in producing neurotransmitters like serotonin from 5-HTP, dopamine from L-DOPA, and gamma-aminobutyric acid (GABA) from glutamate. Pyridoxine can control glutamate levels, glutamatergic system, and GABA, which have an essential neuroprotective role. Vitamin B_6 plays a significant role during gestation, postnatal brain development, and also for the regulation of GABA levels. Vitamin B_6 is intracellularly phosphorylated to form the active interconvertible 5′-phosphate esters pyridoxine 5′-phosphate, pyridoxal 5′-phosphate (most important coenzyme variant) also acts as a cofactor in sphingolipid formation and is thereby important for synthesis of myelin. The neuroprotective role of vitamin B_6 is shown by its critical role in dopamine biosynthesis and its independent antioxidant ability (Murakami et al. 2010). Behavioral disturbance in Parkinson's Disease patients was observed to be improved when supplemented with vitamin B_6 (De Lau et al. 2006).

9.2.6 *Vitamin B_{12} (Cobalamin)*

Vitamin B_{12} acts as cofactors in neurotransmitters synthesis, namely norepinephrine and serotonin. Vitamin B_{12} available sources are mostly animal-derived, vegetarians are more prone to vitamin B_{12} deficiency (Madhubalaji et al. 2019), and vitamin B_{12} aids in myelin formation (Dror and Allen 2008), and its deficiency lead to neurological dysfunction. Studies by Esnafoğlu and Yaman (2017) suggest that one-carbon metabolism that involves vitamin B_{12} and homocysteine plays a vital part in the onset of OCD (Valizadeh and Valizadeh 2011). The risk of dementia associated with high homocysteine levels or cognitive deterioration might be altered by supplementation with vitamin B_{12} (Haan et al. 2007). A minor subset of dementia that is reversible with vitamin B_{12} was observed, and it must be emphasized that this treatment is reasonable and safe (Visioli and Burgos-Ramos 2016). The literature showed that dysregulation in the serotoninergic system in patients with OCD.

9.2.7 Vitamin D

Vitamin D stimulates glial cell line-derived neurotrophic factor, neurotrophin 3 (NT3), and nerve growth factor. Vitamin D helps neuroprotection in AD patients *via* controlling nerve growth factors and neurotransmitters (Di Somma et al. 2017). Numerous studies have been done which exhibit the association of vitamin D with numerous neuropsychiatric diseases that include schizophrenia, major depressive disorder, autism, and OCD. In dopamine, epinephrine, and norepinephrine synthesis tyrosine hydroxylase is the rate-limiting enzyme (Cui et al. 2015), while in serotonin synthesis, tryptophan hydroxylase is the rate-limiting enzyme (Kaneko et al. 2015). Vitamin D_3 active form (1,25-dihydroxy-vitamin D_3) controls the levels of these two enzymes (Valizadeh and Valizadeh 2011), thereby regulating the synthesis pathway of catecholamines and serotonin. Vitamin D deficiency can aid in OCD etiology. OCD patients have been observed with an increased concentration of nitric oxide. Vitamin D aids in reducing the nitric oxide levels by inhibiting an essential enzyme, which induces nitric oxide synthase. Thus, vitamin D has a significant role as a neuroprotectant, and its deficiency results in the deterioration of neuroprotection in OCD patients (Garcion et al. 1998).

9.2.8 Vitamin E

Prolonged vitamin E deficiency leads to demyelination of axon and gliosis in the gracilis in the cuneate nuclei. Studies in rodents have shown that vitamin E deficiency has been related with congenital defects, and neural tube defects (NTD) (Santander et al. 2017). Ishihara et al. (2013) observed that α-tocopherol supplementation in transgenic 6 months old AD mice expressing the mutant human genes presenilin1, APP, and tau, which improves cognitive function and also decreases the reactive radicals levels in the brains. In vivo studies signify that vitamin E controls the irregular inflammatory response associated with the Alzheimer disease.

9.2.9 Vitamin C

Vitamin C plays a crucial role in the development of brain and myelin production and acts as an enzyme cofactor in producing neurotransmitters. Studies have revealed that high vitamin C dose lowers amyloid plaques afflicted in the cortex and hippocampal part of the brain, thereby protecting against Alzheimer's Disease. Neurological disorders are mainly characterized by raised oxidative stress, that can be lowered by powerful antioxidant vitamin C supplementation (Visioli and Burgos-Ramos 2016).

9.2.10 Folic Acid

Folic acid is an essential micronutrient and is necessary for growth and activities of brain in the prenatal and early postnatal periods. Neural tube defects in children is one of the major consequence due to folate deficiency in pregnancy (Chmielewska et al. 2019). The folate's role in early pregnancy to prevent neural tube defects is well-known. It is also necessary for brain development due to its contribution to methylation processes, nucleotide production, DNA integrity, and transcription (Anjos et al. 2013). Chmielewska et al. (2019) observed a positive correlation between maternal folic acid status with the cognitive development of the child. Folate affects alterations in neurobehavioral, neuro-structural defects, emotional skills, including autism spectrum disorders (ASDs). A case study in the US regarding the Childhood Autism Risks from Genetics and Environment suggests that an average daily intake of folic acid $\geq$600 μg during the first month of the pregnant was related to lowered ASD risk (Gao et al. 2016).

9.2.11 Copper

Copper is an essential micronutrient due to its association in brain energy metabolic process, antioxidant activity, dopamine metabolism, and iron accumulation in the fetal and neonatal brain (Anjos et al. 2013). Copper deficiency results in degeneration of the spinal cord posterior columns, which leads to ataxia. Elevated ceruloplasmin levels are observed in OCD patients. Ceruloplasmin largely determines copper concentration. A rise in ceruloplasmin level is directly associated with an increase in serum copper since about 95% of the blood copper is attached to ceruloplasmin. In schizophrenia, an increased level of ceruloplasmin increases copper levels, resulting in dopaminergic dysregulation in OCD (Virit et al. 2008).

9.2.12 Iodine

At the first-trimester end and the early part of the II trimester of gestation, iodine deficiency is related to compromised intellectual ability and will cause irreversible defects in brain development. Iodine deficiency can affect cognitive performance and development. Research studies showed that iodine deficiency has an adverse effect on the intellectual performance of children. Randomized intervention studies with iodine in school children have confirmed enhanced cognitive performance, but these enhancements were possibly restricted to those children exhibiting previous iodine deficiency (Anjos et al. 2013).

9.2.13 Zinc

Zinc plays a vital role in the growth of neuronal cells. Zinc is present in neurons, specifically in glutamatergic neurons. Zinc is crucial for the zinc finger structure present in proteins such as neuronal receptors (e.g., NMDA receptors). The release of zinc from zinc-containing neurons and cortical synapses underscores the importance of zinc for normal cognitive function (Hubbs-Tait et al. 2005). Zinc is important for neurogenesis, synaptogenesis, and neuronal migration. Its deficiency could interfere neurotransmission and subsequent behavior (Anjos et al. 2013). Zinc plays an essential role in amyloid plaques development which is a major characteristic of Alzheimer's disease. Zinc act as an adjuvant for OCD, and its supplementation improves outcomes by reducing obsession and compulsion. Enhancement of zinc with fluoxetine can initiate the therapeutic effects in lesser time with more efficiency than fluoxetine alone (Sayyah et al. 2012). Zinc level is lower in the OCD patients indicating an elemental homeostasis imbalance as well as oxidative stress-induced neuron damage (Shohag et al. 2012).

9.2.14 Magnesium

Magnesium is essential for neuromuscular conduction and nerve transmission. Magnesium is protective against extreme excitation that results in the death of neuronal cells and has been linked in several neurological disorders. Magnesium depletion has been observed in the hippocampus of AD patients (Andrasi et al. 2000). Balmuş et al. (2017) observed patients with minor cognitive impairment and AD have low magnesium concentration in serum compared to controls.

9.2.15 Selenium

Studies revealed the reduced levels of selenium in AD patients (Pillai et al. 2014). Dietary selenium is converted to selenide (Se^{2-}), which acts as the donor for integrating Se into selenoproteins (Turanov et al. 2013). Selenoproteins have many functions throughout the body, such as modulators of immune function, xenobiotics, antioxidants, and detoxification agents for heavy metals (Holben and Smith 1999). Oral supplementation of selenium and zinc in protein-deficient rats has improved the neurobehavioral deficits as well as antioxidant enzyme activity (Adebayo et al. 2014).

9.2.16 Iron

Iron availability is also crucial for CNS development. Iron is present in the brain, and it is necessary for neurotransmitter production and myelination. Iron deficiency during an early stage of life can affect brain development detrimentally (Chmielewska et al. 2019). Alterations in the myelination of neurons and dopamine metabolism can be induced by low prenatal levels of iron, which can continue if there is an iron deficiency during the neonatal period (Anjos et al. 2013). In populations containing a high prevalence of IDA (>10%), 6–12-month-old children were supplemented with iron for 4–12 months resulted in IDA amelioration toward the neurological development (Chmielewska et al. 2019).

9.2.17 ω-3 LCPUFA

PUFA plays a vital role in brain structure and function. Docosahexaenoic acid (DHA) accumulates in retinal photoreceptors and all of the brain regions. They regulate the cell membrane's fluidity as well as the ion channels activity, enabling transmission of synapse and supporting substrate binding to membrane receptors. ω-3 LCPUFA improves cognition by elevating the speed of information acquisition and by speed up visual acuity and the development of retina. The sufficient provision of DHA during early life is essential for optimal visual and neurologic development. DHA in neurons plays a crucial role as a target for therapeutic intervention in AD (Jicha and Markesbery 2010).

In the evolution of neurological disorder treatments, various combinations of micronutrients were used. Many combinations have shown potential results in brain and neurological development. Some of the combinations are discussed in the following.

9.3 Combination of Micronutrients/Micronutrient Mixtures Used to Combat Neurological Disorders

Research on the development of neurological disorders has evolved by using various combinations of micronutrients. Micronutrients (vitamin and mineral) deficiencies and mood problems can be improved with supplements, which can be achieved through both single nutrient and complex formulations (Rucklidge 2009). A single micronutrient may not be able to minimize the symptoms of neurological disorders to such extent as combinations. The combined effects of magnesium (Mg) and vitamin B_6 are related with the production of several significant neurotransmitters, including dopamine and serotonin (Taylor et al. 2018). Iron and zinc are correlated to children's cognition, and both play an essential role in neuronal development

(Hubbs-Tait et al. 2005). Many studies have shown that vitamin B and vitamin E dietary supplementation positively affects the pathological hallmarks observed in moderate AD patients, including a delay in cognitive deterioration (Visioli and Burgos-Ramos 2016). Seleno-l-methionine and vitamin E together can protect against oxidative stress and toxicity from β-amyloid (Pillai et al. 2014). Vitamin E alone and combination of vitamin E and vitamin C were given to AD patients so that CSF levels of these vitamins were elevated as well as lipoprotein oxidizability in the brain was also decreased (Kontush et al. 2001). Esnafoğlu and Yaman (2017) have studied the relation between OCD patients and serum micronutrient levels such as vitamin B_{12}, vitamin D, folic acid, and homocysteine in 52 patients and 30 healthy controls and results showed a negative correlation between the adversity of OCD and vitamin D levels. Yazici et al. (2018) showed no significant difference in vitamin D, alkaline phosphatase, calcium, and phosphate levels between OCD patients and healthy controls. Shohag et al. (2012) evaluated the levels of serum zinc, iron, and magnesium in 48 OCD patients and compared with 48 healthy controls. The results showed a substantial decrease in the concentration of serum zinc, iron, and magnesium while an increase in the concentration of serum calcium and manganese levels in OCD patients. Improving serotonin synthesis through natural therapies such as 5-HTP as well as amending deficient micronutrients (vitamin B_3, B_6, B_9, zinc, magnesium, and inositol) have been studied intensively for improving OCD (Kong et al. 2006).

Many micronutrient formulations and broad-spectrum supplementation are available in the market, which is beneficial for mental health as well as other health benefits. Micronutrient formulae have influenced psychiatric indications such as anti-social and violent behavior (Simpson et al. 2011). Research has widened their field from the practice of single-use vitamin/mineral supplementation to broad-spectrum micronutrients (BSM) in neurodevelopmental disorders treatment which is graphically presented in Fig. 9.2. Initial research recognized micronutrient deficiencies such as iron, zinc, and magnesium among ADHD patients, whereas, in the case of neurological disorders, mainly B complex vitamins, vitamin D, magnesium, and amino acids deficiencies were observed. However, the use of single-supplement in individuals with neurological disorder has essentially yielded inconsistency (Taylor et al. 2018). Further research was continued with supplementing various formulas in the neurological disorders amelioration. Compositions of currently available micronutrient formulation for improvement in cognition are presented in Table 9.2. Few major formulations are discussed in the following sections.

9.3.1 EMPowerplus

The formula with 36 ingredients in an ABAB design resulted in on–off control of mood and anxiety symptoms (Rucklidge 2009); the formula was originally called EMPower. Later the formulations were modified to decrease the number of capsules to be consumed per day and also enhanced the bioavailability of the product. The

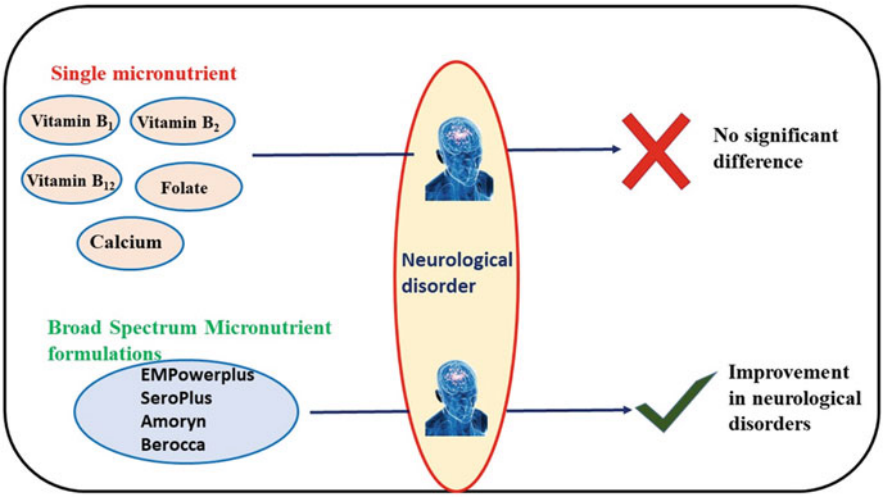

Fig. 9.2 Broad spectrum of micronutrient formulations and single micronutrients supplementation effect in the development of neurological disorders

subsequent product also has the same 36 ingredients but with the new name EMPowerplus. EMPowerplus (EMP+) that consists of 16 minerals, 14 vitamins, 3 antioxidants, and 3 amino acids. Rucklidge (2009) observed that the EMPowerplus formula had improved the symptoms of neurological disorders. This micronutrient formula has proven to be effective in decreasing or eliminating the symptoms of depression, and their related disorders, and few forms of OCD. Studies also indicating that EMPowerplus Methylated Advanced™ can enhance brain-cell health and cognitive function.

9.3.2 SeroPlus

It is a nutritional supplement to aid patients suffering from OCD and depression. SeroPlus offers serotonin building blocks with beneficial doses of 5-HTP (direct antecedent to serotonin), Taurine, and Inositol in addition to vital cofactors, i.e., magnesium, vitamin B_6, vitamin C, and Metafolin® (activated folate). Inositol raises the sensitization of serotonin receptors while taurine sustains healthy sympathetic nervous system that controls serotonin activity. SeroPlus formula also comprises niacin and zinc picolinate, which improve the 5-HTP bioavailability by decreasing the quantity of 5-HTP utilized for activation and absorption of above mentioned nutrients. Synergistically, components in SeroPlus work efficiently together to enhance serotonin production and reestablish normal serum levels of common deficiencies (Greenblatt 2017).

Table 9.2 Available micronutrient formulations in the market for improvement in cognition

S. No.	Formula	Ingredients
1.	EMPowerplus	Biotin—144 μg Calcium (as chelate)—176 mg Chromium (as chelate)—83.2 μg Copper (as chelate)—0.96 mg Iodine (from pacific kelp)—27.2 μg Iron (as chelate)—1.8 mg Magnesium (as chelate)—80 mg Manganese (as chelate)—1.28 mg Methyl folate—192 μg Molybdenum (as chelate)—19.2 μg Niacin (as niacinamide)—12 mg Pantothenic acid (as calcium pantothenate)—2.8 mg Phosphorus (as chelate)—112 mg Potassium (as chelate)—32 mg Riboflavin—1.8 mg Selenium (as chelate)—27.2 μg Thiamin (as thiamin mononitrate)—2.4 mg Vitamin B_{12} (as methylcobalamin)—120 μg Vitamin B_6 (as pyridoxine hydrochloride)—4.8 mg Vitamin C (as ascorbic acid)—80 mg Vitamin D (as cholecalciferol)—192 IU Vitamin E (as d-alpha tocopheryl succinate)—48 IU Vitamin-A (as retinyl palmitate)—768 IU Zinc (as chelate)—6.4 mg *Proprietary blend [Choline bitartrate, DL, phenylalanine, vanadium chelate, citrus bioflavonoids, inositol, L-glutamine, L-methionine, boron chelate, grape seed extract, ginkgo biloba leaf, germanium sesquioxide, nickel chelate]—355 mg* *Other ingredients: Gelatin, magnesium stearate, glycine, citric acid, microcrystalline cellulose, silicon dioxide, mineral wax*
2.	SeroPlus	Vitamin B (as pyridoxal 5′ phosphate) (activated B6) 6.7 mg Vitamin C (as ascorbic acid) 100 mg Niacin (as niacinamide) 20 mg Folate (as Metafolin®, L-5-MTHF) 833 μg DFE (L-5-MTHF 500 μg) Magnesium (as di-magnesium malate) 100 mg Zinc (as zinc picolinate) 10 mg 5-hydroxytryptophan 100 mg Inositol (as myo-inositol) 500 mg Taurine (free-form) 200 mg Other ingredients: Vegetarian capsule (cellulose, water)
3.	Amoryn formula	Folate—300 μg Selenium—70 μg Vitamin B_{12}—30 μg Vitamin B_6—20 mg Vitamin C—10 mg Vitamin D_3 (cholecalciferol)—400 IU Zinc—15 mg Hyperforin from Hypericum perforatum (St. John's wort) extract—18 mg 5-hydroxytryptophan (5-HTP) from Griffonia simplicifolia extract—

(continued)

Table 9.2 (continued)

S. No.	Formula	Ingredients
		25 mg Rhodiola Rosea extract (root)—90 mg
4.	Berocca	Biotin—150 µg Calcium—100 mg Magnesium—100 mg Vitamin B_1—15 mg Vitamin B_{12}—10 µg Vitamin B_2—15 mg Vitamin B_3—50 mg Vitamin B_5—23 mg Vitamin B_6—10 mg Vitamin B_9—400 µg Vitamin C—500 mg Zinc—10 mg

9.3.3 Amoryn

Amoryn is a commercially available supplement, which helps patients suffering from anxiety, depression, and OCD. St. John's Wort is the key ingredient in Amoryn, which helps people with OCD to better cope with recurring thoughts and compulsive behaviors. Two double-blind, placebo-controlled studies conducted by Szegedi et al. (2005) with St. John's Wort (SJW) supplement showed a 57% reduction in OCD symptoms and a 47% reduction in the side effects of the condition. The neurobiological effects of SJW include inhibiting monoamine reuptake, regulating neuroendocrine, increasing sensitivity, and binding to receptors (such as 5-HT) that may have potential benefits for OCD symptoms. (Karcı and Celik 2020).

9.3.4 Berocca™

Berocca™ supplies vitamin B complex and all essential micronutrients, which play an significant role in the production of healthy RBC, energy production, and utilization. This formula also contains minerals that aid in muscle function and regulate brain activity. Improved ratings of alertness, concentration, mental and physical stamina. Studies also demonstrated that this formula improved the mood and physiological condition of individuals (Kennedy et al. 2011).

Micronutrients have a vital role in the development of neurological disorders. However, some heavy metals have a role in neurodegeneration processes.

9.4 Role of Toxic Metals in Neurodegeneration

Heavy metal contamination is a severe threat to human health and it adversely affect neurodevelopment. Physiological processes in the central nervous system need trace elements at less than 0.01% of body weight. Trace elements that accumulate more than the required level cause neurodegenerative conditions such as Alzheimer's disease, Down syndrome, and Parkinson's disease (PD). Weaker detoxifying mechanisms and poorer immune systems in children make them more susceptible to neurotoxic effects due to exposure to heavy metals when compared to adults. Increasing reports suggest that metal mixtures may adversely impact cognitive and motor development (Gorini et al. 2014). Accumulation of excessive metal in the nervous system may be detrimental by disrupting mitochondrial function, inducing oxidative stress, and impairing the activity of numerous enzymes, etc. Metal-induced neurotoxicity has been related to multiple neurological diseases in humans such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism spectrum disorders (ASDs), Gulf War syndrome (GWS), Huntington's disease (HD), multiple sclerosis, Parkinson's disease (PD), and Wilson's disease (WD) (Chen et al. 2016). This section explains the major heavy metals associated with neurological disorders.

9.4.1 Copper (Cu)

Copper is an indispensable trace element necessary for physiological activities in mammals that act as a cofactor for various enzymes such as cytochrome-c oxidase and SODs. Copper also play a key role in oxygen transportation, electron transport, protein modification, and neurotransmitter synthesis. Copper levels higher than required can lead to the production of reactive oxygen species (ROS), DNA damage, and mitochondrial dysfunction, thereby enhancing the self-aggregation of amyloid precursor protein and β-amyloid peptide. Elevated levels of copper in the CSF have been found in some AD patients. The interaction of Cu with α-synuclein promotes its aggregation, leading to PD (Chen et al. 2016).

9.4.2 Lead (Pb)

Lead is one of the non-essential heavy metal that does not have any biological functions. Pb exposure leads to mitochondrial dysfunction, oxidative stress, and calcium homeostasis disruption (Chen et al. 2016). Acute Pb poisoning can result in death. Children with elevated blood copper levels affect the CNS and have shown deficits in natural concentration, memory, behavior, and cognition, but they were asymptomatic (Needleman 1988). In children, Pb exposure can decrease intellectual ability based on dosage, difficulty in grammatical reasoning, improper verbal

concept formation, not able to follow a command, etc. while in adults, impairment of verbal memory, lower decision-making speed, the deficit in visuomotor coordination, visual memory performance, and increased interpersonal conflict were observed (Chen et al. 2016).

9.4.3 Mercury (Hg)

Mercury is known for neurotoxicity. Mercury can cross the blood–brain barrier, blood–placenta barrier, and the lipid bilayers of cellular membranes. Hence, it reaches CNS through the lungs, where mercury is absorbed in its vapor form (Park and Zheng 2012). Mercury affects many neuronal activities such as neuronal stem cell differentiation, dopamine metabolism, DNA damage, generation of ROS, and mitochondrial dysfunction. Hg exposure can increase β-amyloid in the hippocampus and decrease it in the cerebrospinal fluid, which is hallmark of AD (Chen et al. 2016). Adams et al. (2007) observed that infants with autism have a reduced ability to expel mercury because of decreased reduced-glutathione, higher usage of oral antibiotics, and the development of oxidative stress.

9.4.4 Cadmium (Cd)

Cadmium is a non-essential transition heavy metal. Permeability of the blood–brain barrier can be disrupted by cadmium by entering the peripheral and central neurons from the olfactory bulb (Wang and Du 2013). Cd exposure leads to oxidative stress that inhibits DNA damage repair, apoptosis, and suppresses gene expression (Bishak et al. 2015). Jiang et al. (2007) observed that cadmium accelerates the self-aggregation of Alzheimer's tau peptide R3. Bao et al. (2009) showed that children with higher levels of cadmium in the hair exhibited social difficulties and attention deficits.

Therefore, heavy metals accumulation in the body severely affects the central nervous system through neuro degeneration.

9.5 Conclusion

Diet is an exclusively modifiable lifestyle factor. Adoption of healthy diet habits allows reducing the risk of developing neurological disorders. Micronutrients have beneficial effects on neurochemical systems related to anxiety responses. The behavioral and cognitive symptoms of neurological disorders are related to various nutrients and pathways associated with brain function. A single nutrition approach to the treatment of the neurological disorders may be too simplistic due to the

requirement of an array of nutrients for an effective neurochemical synthesis. Some combination of micronutrients has shown significant improvements in specific neurological disorders, e.g., iron and copper can interact with vitamin C and generate an excessive amount of free radicals. In the case of neurological disorders, the total element distribution pattern in the system will be affected rather than that the effect of increase or decrease in the concentration of a single element alone. In this regard, a broad-based micronutrient formula may be a more appropriate response since they can rectify and stabilize imbalance to this level of complexity, and research on broad micronutrient supplementation for neurological disorders should be explored more in the future. Avoid excessive consumption of iron, copper, manganese, or zinc to avoid the initiation and progression of neurological disorders like AD. Furthermore, Heavy metals cause neurotoxicity and neurodegeneration when ingested at a higher concentration than required levels.

Finally, diet is proposed as the best therapy for neuronal disorders. Optimized nutrition could be potential in controlling neurological disorders. Further clinical studies with early children, pregnant and lactating women, for specific neurological disorders are needed for better understanding and narrowing down the use of micronutrients in maintaining brain health and the prevention of neurological disorders.

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Chapter 10
Algae as a Potential Vegetative Source of PUFA for the Prevention of Neurological Disorders

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Abstract Epidemiological and observational studies indicated neurological and mental disorders are associated with reduced diet intake or lower abundance of polyunsaturated fatty acids (PUFA) in the diet. Progressive neurodegeneration is the major cause of neurological disorders. Unfortunately, there are no proper cure and pharmacological medicine currently to overcome neurological disorders. Omega-3 fatty acids are the structural components of neuronal membranes and play a key role in the central nervous system and brain contains 50–60% of lipids, in which PUFA contributed to a maximum percentage. Fatty fish and plant-based foods are popularized dietary sources of omega-3 fatty acids. In recent times, highlighting research has been conducted in algae and its potential in neuroprotection. Algae are considered as one of the potential sources for various secondary metabolites including PUFA especially omega-3 fatty acids due to its sustainability. Algae reported to have neuroprotective effects such as anticholinesterase inhibitory activity, anti-neuroinflammatory activity, antioxidant, and inhibition of neuronal death. Algae grabbed attention as a vegetative source and researchers have explored various possible ways to produce omega-3 fatty acids. PUFAs such as alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are reported to have a crucial role in the betterment of psychiatric, obsessive-compulsive disorders, and neurodegenerative conditions. This chapter discusses the importance of omega-3 fatty acids in neurological development and the sources including algal sources. The strategies for enhanced omega-3 fatty acid production in algae, and studies conducted with

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algal supplementation on improvement of the neurological disorders and degenerative conditions. Further, neurotoxic compounds from cyanobacteria are also discussed.

Keywords PUFA · Neurological disorder · Algae · ALA · EPA · DHA

Abbreviations

AChE	Acetylcholinesterase
ALA	Alpha-linolenic acid
ARA	Arachidonic acid
BChE	Butyrylcholinesterase
DALY	Disability-adjusted life years
DHA	Docosahexaenoic acid
EFA	Essential fatty acids
EPA	Eicosapentaenoic acid
GBD	Global Burden of Disease
GLA	Gamma-linolenic acid
PUFA	Polyunsaturated fatty acids
TFA	Total fatty acid
WHO	World Health Organization

10.1 Introduction

Global attention has increased towards neurological disorders as it resulted in considerable morbidity and disability. Neurological disorders are one of the supreme threats to a public health concern. Global burden of neurological disorders: estimates and projections showed 6.77% of the total disability-adjusted life years (DALY) attributable to neurological disorders and globally 12.22% of the total deaths attributable to neurological disorders by 2030 according to Global Burden of Disease (GBD) study by WHO (WHO|Neurological Disorders: Public Health Challenges 2020). Neurological disorders are characterized by the progressive degeneration of the neurons in the portions of the brain and spinal cord. Most common neurological disorders are Alzheimer's disease, dementia, epilepsy, headache disorders (migraine), multiple sclerosis, neuro-infections, Parkinson's disease, stroke and traumatic brain injuries, neurological disorders also associated with malnutrition and pain. The major events that cause the progressive neurodegeneration are neuroinflammation, oxidative stress, protein aggregation, mitochondrial dysfunction, and apoptosis of the neuronal cells (Hammond et al. 2019). In this regard, worldwide neurological disorders and its prevention routes are the need-of-hour. Various scientists have performed experiments with different natural and synthetic

compounds and evaluated their effects on neurological disorders. However, most of the synthetic neuroprotective compounds have shown side effects such as drowsiness, dry mouth, tiredness, anxiety, nervousness (Narang et al. 2008; Olasehinde et al. 2017). Hence, most of the current studies are highly focused on natural bioactive compounds, which have a potential role as neuroprotective agents.

10.2 Importance of PUFA

In recent years, extensive research has been conducted in the prevention of neurological disorders and indicated that consumption of omega-3 long-chain polyunsaturated fatty acids (LC-PUFA) can reduce the risk of neurological disorders. In general, the adult brain contains 50–60% of lipids in which 35% are attributable to phospholipids containing LC-PUFA especially arachidonic acid and docosahexaenoic acid at higher concentrations (Assisi et al. 2006). As these LC-PUFA cannot be synthesized by the humans and required to take through external supplementation, so these are referred as essential fatty acids (EFA). This EFA belongs to majorly two families, i.e. omega-3 and omega-6 fatty acids, which can be determined based on the presence of carbon atoms present before the double bond in cis-configuration. Omega-3 fatty acids are alpha-linolenic acid (ALA) (C18:3, n-3), eicosapentaenoic acid (EPA) (C20:5, n-3), docosahexaenoic acid (DHA) (C22:6, n-3). Omega-6 fatty acids are linoleic acid (LA) (C18:2, n-6), gamma-linolenic acid (GLA) (C18:3, n-6), and arachidonic acid (ARA) (C20:4, n-6). The brain can synthesize de novo saturated and monounsaturated fatty acid, but PUFA must be obtained through the blood (Bazinet and Layé 2014). ALA is obtained through diet, which acts as a precursor for ARA and DHA. Brain has necessary enzymes involved in the conversion of ALA to ARA and DHA. However, the rate of conversion is very slow compared to PUFA uptake from the plasma. Overall observations suggest that brain mostly relies on the external supplementation of DHA and ARA obtained from the food. Further, the fatty acid composition determines the biophysical properties of neuronal membranes and influences neurotransmission. Higher omega-3 PUFAs concentrations lead to higher membrane fluidity, which in turn increases serotonin transport.

The brain, neurodevelopment, and cognitive functions depend majorly on the optimal balance of omega-3/omega-6 fatty acid ratio (Assisi et al. 2006). Imbalance of this ratio may lead to Alzheimer's disease (Dyall 2015) and other neurological disorders. Eating habits play a major role in maintaining the omega-3/omega-6 ratio. For example, eating habits in western countries, having less omega-3 fatty acids and also intake of unbalanced omega-6 fatty acids resulted in the omega-3/omega-6 ratio in the range of 15–20, which is one of the threats to the brain health and cognitive development. Most of the diet practices are supplementing higher omega-6 fatty acids, while omega-3 fatty acids are limited. The brain is enriched with DHA, ARA, and EPA long-chain fatty acids, which have a crucial role in the regulation of several processes such as neurotransmission, neuro-inflammation, cell survival, and in the

development of the brain and cognitive health (Bazinet and Layé 2014). PUFA plays a significant role in the treatment of various disorders such as hyperlipidaemia, hypertension, hypertonia, premenstrual tension. The recommended daily intake levels of EPA and DHA are ranging from 0.2 to 0.3 g/day (Patel and Matsakas 2020).

In humans, compared to other parts, central nervous system (CNS) is more sensitive to reactive oxygen species (ROS), due to its high lipid content and high oxygen content (Pangestuti and Kim 2011). Increased oxidative stress of the CNS resulted in lipid peroxidation, protein, and DNA damage (Akyol et al. 2002). Oxidative stress in CNS causes cytotoxicity and apoptosis of neuronal cells which leads to the death of neuronal cells (Pangestuti and Kim 2011). Further, oxidative stress in the CNS has been implicated to the progression of various neuronal diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Behl and Moosmann 2002; Migliore and Coppedè 2009). In order to protect CNS damage with ROS, antioxidants have shown promising effects in neuroprotection therapy (Andersen 2004). Endogenous antioxidants of body are always not sufficient to fight against ROS; so, exogenous antioxidants are required. Brain lipid, which is enriched with PUFA is reported to have significant antioxidant activities.

10.3 Available Sources of PUFA

The available sources of linoleic acid (LA) (C18:2, n-6) are vegetable oils. Alpha-linolenic acid (ALA) (C18:3, n-3) is mostly found in nuts and vegetable oils such as flaxseed, mustard oil, walnut, and soya bean. ALA acts as a precursor for long-chain omega-3 fatty acids (EPA/DHA). EPA is primarily found in herring, fatty fish, salmon, cod liver, menhaden, mackerel, and sardine. DHA is predominantly found in fish, salmon, tuna, canned tuna, trout, mussels, oysters, cod, fish eggs, pickled herring, clams, and snow crab, and breast milk (FoodData Central 2020). EPA cannot be synthesized by humans as a deficit of enzyme desaturase, which inserts a double bond at the omega-3 position (Patel and Matsakas 2020). However, humans have the processing enzymes for the conversion of ALA to EPA and DHA. But the conversion process is prolonged and limited in the human body. In this regard, external dietary supplementation of omega-3 fatty acids is recommended. Besides, most of these EPA and DHA available sources are animal-derived. Also, unpleasant odour of the extracted fish oil and depletion of fish resources lead to look for an alternative vegetative source for the natural production of EPA and DHA to meet the growing global demand (Guihéneuf and Stengel 2013).

10.4 Algae as a Source of PUFA

Algae are an extremely complex and diverse group of photosynthetic eukaryotic and prokaryotic microbes. Algae exist in both marine and freshwater habitats. Algae possess diverse physiological, morphological, genetic traits which enable to yield various bioactive. Algae are majorly classified into three categories based on coloured pigments such as Green (Chlorophyta), Red (Rhodophyta), Brown (Phaeophyta) algae. Based on the size of algae, they are divided as macroalgae and microalgae. In recent decades, a lot of research has been conducted in the field of algal biotechnology and explored the algal potential in various areas. The studies are also geared towards the discovery of algal new compounds and their potential in the treatment of neurological disorders (Olasehinde et al. 2017). Algae is a sustainable vegetative source to produce various secondary metabolites in addition to ALA, EPA, and DHA (Madhubalaji et al. 2020a). The algal biomass and its extracts have shown some pharmacological activities, i.e. anticholinesterase, antioxidant activities towards the neuroprotection (Gany et al. 2015).

Algae are reported to have glycolipids, non-polar glycerolipids, phospholipids, betaine lipids, and sulpho-lipids (Dominguez 2013). Comparatively marine algae have higher long-chain polyunsaturated fatty acids than freshwater, even though their contents are minimum. In most of the algae, PUFA is found in cell membrane components as membrane lipids, i.e. glycolipids and phospholipids (Schüler et al. 2017). Further, LC-PUFA (EPA/DHA) are essential in maintaining the membrane fluidity, which changes according to external environmental parameters (light, salinity, and temperature). PUFA also acts as an antioxidant and protects the algae from oxidative damage, which is caused by reactive oxygen species (ROS). PUFA biosynthesis pathways in microalgae are well defined, for more details, the reader can refer to the article (Khozin-Goldberg et al. 2011). Although omega-3 fatty acid production from autotrophic algae is technically promising; however, a lot of challenges (i.e. low-cost extraction, purification) need to be addressed to make it economically feasible. Most of the algae were rich in saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA) rather than PUFA. However, the microalgal fatty acid contents varied from species to species. Research is being conducted by various researchers across the globe on new algal species and their potential toward the production of omega-3 fatty acids. Biomass productivity is one of the major limitations for higher PUFA production. In order to obtain higher biomass productivity, different configurations of the algal biomass cultivation systems were reported (Madhubalaji et al. 2019a), which resulted in remarkably higher biomass productions. Nutritional values of the algae majorly depend on their essential fatty acid contents. PUFA rich algal oil is most desirable for dietary consumption. Various algae and their omega-3 contents are presented in Table 10.1. PUFA content of algae is grabbing attention due to its vegetative origin, while most of the rich sources are animal-derived. In order to meet the growing global demand, there is a need to explore the possible ways to produce higher fatty acid production.

Table 10.1 Omega-3 fatty acid contents of various algae

S. No	Algae name	PUFA content (%TFA)			References
		ALA	EPA	DHA	
1.	*Nitzschia* cf. *ovalis BIMS-PP0004*	0.37	23–26.67	3.9–4.20	Pratoomyot et al. (2005)
2.	*Thalassiosira* sp. *BIMS-PP0014*	1.1–1.5	11.32–16.65	0.80	Pratoomyot et al. (2005)
3.	*Tetraselmis* sp. *BIMS-PP0017*	16.17–16.9	4.18–4.70	–	Pratoomyot et al. (2005)
4.	*Dictyosphaerium pulchellum BIMS-PP0033*	26.49–30.63	–	–	Pratoomyot et al. (2005)
5.	*Stichococcus* sp. *BIMS-PP0045*	25.71–28.25	–	–	Pratoomyot et al. (2005)
6.	*Chlorella* sp. *BIMS-PP0081*	15.35–20.02	–	–	Pratoomyot et al. (2005)
7.	*Scenedesmus falcatus BIMS-PP0082*	16.78–20.79	–	–	Pratoomyot et al. (2005)
8.	*Anacystis* sp. *BIMS-PP0028*	23.18–27.9	–	–	Pratoomyot et al. (2005)
9.	*Pavlova lutheri*	–	16.2–28.3	3.6–15.5	Mansour et al. (1999)
10.	*Pavlova salina*	–	25.4–28.2	10.2–11.0	Mansour et al. (1999)
11.	*Pavlova* sp.	–	23.5–25.0	8.4–9.2	Dunstan et al. (1992)
12.	*Amphiprora hyalina*	–	30	1.9	Dunstan et al. (1992)
13.	*Phaeodactylum tricornutum (transgenic)*	–	24.8	10.3	Hamilton et al. (2015)
14.	*Thalassiosira stellaris*	–	25.3	4.8	Salvesen et al. (2000)
15.	*Isochrysis galbana*	3.8	0.8	15.8	Patil et al. (2007)
16.	*Pavlova* sp.	1.8	18.0	13.2	Patil et al. (2007)
17.	*Phaeodactylum tricornutum*	0.3	28.4	0.2	Patil et al. (2007)
18.	*Porphyridium cruentum*		6.1	–	Patil et al. (2007)
19.	*Rhodomonas baltica*	12	4.4	–	Patil et al. (2007)
20.	*Oocystis* sp.	8.1	1.1	–	Patil et al. (2007)
21.	*Pseudokirchneriella subcapitata*	11.4	–	0.1	Patil et al. (2007)
22.	*Tetraselmis suecica*	6.4	4.8	0.2	Patil et al. (2007)
23.	*Tribonema* sp.	–	3.2	–	Patil et al. (2007)
24.	*Nannochloropsis oceanica*	–	23.4	–	Patil et al. (2007)
25.	*Phaeodactylum tricornutum*	0.22	9.56	1.05	Wang et al. (2019)
26.	*Isochrysis aff. galbana clone T-Iso*	2.97	0.57	15.2	Wang et al. (2019)
27.	*Rhodomonas baltica*	15.7	6.31	3.83	Wang et al. (2019)
28.	*Nannochloropsis oceanica*	2.3	5.43	5.43	Wang et al. (2019)
29.	*Isochrysis galbana*	–	27.66	14.16	Fidalgo et al. (1998)
30.	*Nannochloropsis* sp.	–	38–39	–	

(continued)

Table 10.1 (continued)

S. No	Algae name	PUFA content (%TFA)			References
		ALA	EPA	DHA	
					Chaturvedi and Fujita (2006)
31.	*Phaeodactylum tricornutum*	–	40–57	–	Fernández et al. (2000)
32.	*Nitzschia laevis*	–	25–33	–	Xiao-Hong et al. (2007)
33.	*Thalassionema nitzschioides*	–	25.2	1	Dunstan et al. (1992)
34.	*Thalassiosira pseudonana*	–	7.7–32.7	1.4–6.2	Dunstan et al. (1992)
35.	*Porphyridium cruentum (P. cruentum)*	–	2.9–37.5	–	Cohen et al. (1987)
36.	*Nannochloropsis oculata*	–	13.0–40.0	0.0–0.6	Zhukova and Titlyanov (2003)
37.	*C. cohnii*	–	–	25–60	Mendes et al. (2007)
38.	*Porphyridium cruentum*	–	25	–	Durmaz et al. (2007)
39.	*Odontella aurita*	–	26	–	Guihéneuf et al. (2010)
40.	*Pavlova lutheri*	–	22–29	–	Guihéneuf et al. (2009)
41.	*Cyclotella cryptica*	–	17–23	–	Pahl et al. (2010)
42.	*Cylindrotheca* sp.	–	24–25	–	Suman et al. (2012)
43.	*Schizochytrium mangrovei*	–	–	31–41	Fan et al. (2001)
44.	*Schizochytrium limacinum*	–	–	25–35	Ethier et al. (2011)
45.	*Schizochytrium* sp. *(HX-308)*	–	–	40–56	Lian et al. (2010)
46.	*Schizochytrium* sp.	–	–	45–52	Ren et al. (2010)
47.	*Thraustochytrium* sp.	–	–	23–24	Burja et al. (2007)
48.	*Thraustochytrium aureum*	–	–	32–37	Taoka et al. (2011)
49.	*Thraustochytrium striatum*	–	–	37	Fan et al. (2001)
50.	*Ulkenia* sp.	–	–	10–23	Quilodrán et al. (2010)
51.	*Aurantiochytrium* sp.	–	–	40	Hong et al. (2011)
52.	*Crypthecodinium cohnii*	–	–	63	Da Silva and Reis (2008)
53.	*Crypthecodinium cohnii*	–	–	53–57	Jiang and Chen (2000)
54.	*Biddulphia aurita*	–	25.6	–	Orcutt and Patterson (1975)
55.	*Coscinodiscus* sp.	–	26	4.6	Orcutt and Patterson (1975)
56.	*Nitzschia closterium*	–	2.6–44.6	01–2.4	Orcutt and Patterson (1975)
57.	*Skeletonema costatum*	–	19.3–26.1	3.9–4.7	Orcutt and Patterson (1975)

10.5 Strategies for Enhancement of Omega-3 Fatty Acids in Algae

10.5.1 Light

Light is the primary growth factor for algae. However, low light conditions are well reported for the higher production of LC-PUFA, which might be for counterbalancing of the lower light availability by increasing thylakoid membranes of algae (Berner et al. 1989; Fisher et al. 1998). Under low light conditions (50–-60 μmol m^{-2} s^{-1}), *Nannochloropsis* sp. has increased its EPA content up to 38% of TFA (Meng et al. 2015; Van Wagenen et al. 2012). While higher light intensities have favoured the higher productions of DHA, which is increased from 12.6 to 19.2% and 8 to 14% of TFA in *P. lutheri* and *I. galbana*, respectively (Guihéneuf et al. 2009; Tzovenis et al. 1997). Higher contents of PUFA would be beneficial to algal cells due to its antioxidant activity, which protects the photosynthetic apparatus from photo-oxidation (Tzovenis et al. 1997). The combined effect of UV radiation (UVA-R, UVB-R, UV-R) on two algae, i.e. *Pavlova lutheri* and *Odontella aurita* was evaluated and indicated that UV radiation sensitive microalgae could produce higher PUFA (Guihéneuf et al. 2010).

10.5.2 Temperature

Temperature is one of the growth promoting and lipid inducing parameters during the algal cultivations. Changes in the temperature cause alterations in the fluidity of the thylakoid membrane and cytoplasmic membrane, which resulted in the regulation of the fatty acid composition according to thermal changes. The fluidity of the membranes is an important factor for the functioning of photosystem and light-harvesting complex proteins, i.e. sensor proteins, translocators, and ion channels. Under lower temperature conditions microalgae synthesize the EPA and DHA to maintain the proper membrane fluidity. When mesophilic species of microalgae grown at lower temperatures (13–17 °C) resulted in 2–3 times increase in the production of EPA and DHA (Van Wagenen et al. 2012). Whereas the combined effect of low light and low temperature resulted in a four-fold increase in the EPA of TFA in phospholipids while cultivating *Nannochloropsis* sp. (Mitra et al. 2015). Low temperatures in *Porphyridium cruentum* resulted in production of polyunsaturated fatty acids contents up to 43% (Durmaz et al. 2007).

10.5.3 Nutrients

For maximum PUFA production in algae, various studies with changes in nutrients have also been conducted. Lipid synthesis pathway and fatty acid profiles were affected majorly due to nutrient availability (nitrogen, phosphate, sulphate and silica) and with the culture age (Gong et al. 2013). Indeed, various stress conditions such as high light, alkaline pH, salt concentrations are also reported to induce the substantial amount of TAGs up to ~80% in some species (Hu et al. 2008). For higher production of LC-PUFA, various concentrations of sodium bicarbonate were provided during the batch cultivation of *Pavlova lutheri* and results showed increased EPA (55%) and DHA (67%) contents (Guihéneuf and Stengel 2013). Nutritional modes such as autotrophic, mixotrophic, and heterotrophic conditions influence the fatty acid profiles in microalgae (Ratha et al. 2013). In this regard, understanding of their mechanism to produce LC-PUFA is vastly required.

Nitrogen is one of the essential nutrients, which supports the growth of algae. Starvation of algae for nitrogen induces its TAGs contents. Nitrogen limitation strategy has been widely used in the algal cultivations to enhance the lipid productions (Chen et al. 2017). Nitrogen and phosphorus limiting conditions elevate the production of EPA and DHA. It may be due to the higher synthesis of membranes in actively growing cells. Under nitrogen limitation conditions higher EPA production in *N. oceanica* (32% of EPA in TFA), *Pavlova lutheri* (29% of EPA in TFA) was reported. Whereas nitrogen limitation resulted in higher DHA production in *P. tricornutum* (30% of TFA) and *I. galbana* (14% of TFA) (Liu et al. 2013; Meng et al. 2015). In a study, under nitrogen limitation four different algae, i.e. *Phaeodactylum tricornutum, Isochrysis aff. galbana clone T-Iso, Rhodomonas baltica,* and *Nannochloropsis oceanica* reported to influence the accumulation of EPA and DHA of total microalgal lipid (Chen et al. 2017). Various nitrogenous sources (nitrate, nitrite, and urea) were also influenced by DHA and EPA productions while cultivating *Isochrysis galbana* (Fidalgo et al. 1998).

Phosphorus is also one of the vital nutrients, which supports division and growth of algae. Some reports have shown the interactions between nitrogen and phosphorus, which induces the biosynthesis of lipids (Chen et al. 2017). In a study, under nitrogen limitation conditions phosphorus supplementation to *Chlorella* has induced the higher lipid productivity up to 58.4 mg L^{-1} day^{-1} (Chu et al. 2013).

Salinity is another factor which influences the composition of the fatty acid in the algae. The reported studies have shown that higher salinity conditions increase the saturation of the fatty acids, while under low salinity conditions unsaturated fatty acids are increased. Modification of membrane permeability is required to overcome an extensive influx of Na^+ and Cl^- ions during salinity exposure condition (Schüler et al. 2017). In a reported study with lower salinity conditions of 10 ppt have increased the EPA and DHA contents to higher levels while cultivating *Nannochloropsis* sp. and *I. galbana* (Pal et al. 2013; Renaud and Parry 1994; Tsai et al. 2016).

Jiang and Chen (2000) investigated various concentrations of glucose (5–40 g/L) on *Crypthecodinium cohnii* and the highest DHA content of 53% of TFA was achieved at a glucose concentration of 5 g/L. Nutrients play a major role in enhanced oil production in algae. In a study, it has been revealed that by controlling glucose, nitrogen, and sodium, an increase in DHA content up to 50% was observed in *Schizochytrium* species. Inorganic CO_2 is another vital requirement nutrient for the phototrophic growth of microalgae. The CO_2 percentage required for the induction of lipid production varied with different algae. Besides, some recent studies have shown that supplementation of CO_2 had increased the production of EPA (Madhubalaji et al. 2020b) and DHA in microalgae. Ethyl methanesulfonate induced mutations in *Nannochloropsis oculata*, which resulted in a markedly 29% increase in eicosapentaenoic acid compared to wild type strain (Chaturvedi and Fujita 2006).

10.6 Strategies

Two-stage cultivation strategy is one of the well-known strategies to produce higher lipid content in microalgae. In this process, the first stage is provided with sufficient nitrogen concentration which allows the biomass growth, in the second stage exposed to nitrogen-deficient conditions or other stress conditions, which induce the synthesis of the lipid in microalgae. Two-stage cultivation strategies allow for higher biomass production as well as high lipid productions. In photobioreactor, two-stage cultivations of *Nannochloropsis* sp. by decreasing the temperature and light intensity in the second stage have favoured the EPA production by 3.4 fold (Mitra et al. 2015). In addition to two-stage cultivation, researchers have explored various other strategies and stresses for the higher productions of PUFA in microalgae are shown in Fig. 10.1. A few of those widely reported strategies are genetic engineering of algae, induction of mutations, and metabolic engineering strategies (Schüler et al. 2017).

10.7 Experiments Conducted on Neurological Disorders

Neurological disorders majorly cause oxidative stress to the brain that can degenerate lipids by exposing to free radicals, i.e. reactive oxygen species (ROS). Studies have been reported that EPA has a significant effect on lowering of inflammation. Besides, omega-3 fatty acids are very useful in treating depression especially autistic spectrum disorders (Bent et al. 2009). Several evidences suggest that diminished omega-3 fatty acid concentrations are associated with mood disorders. There are studies regarding the possible use of omega-3 fatty acids in the treatment of major depression, bipolar disorder, and schizophrenia. Nevertheless, omega-3 fatty acids may be helpful in the treatment of dementia and are a safe treatment for psychiatric disorders in pregnancy and in breast feeding. Many studies have shown the

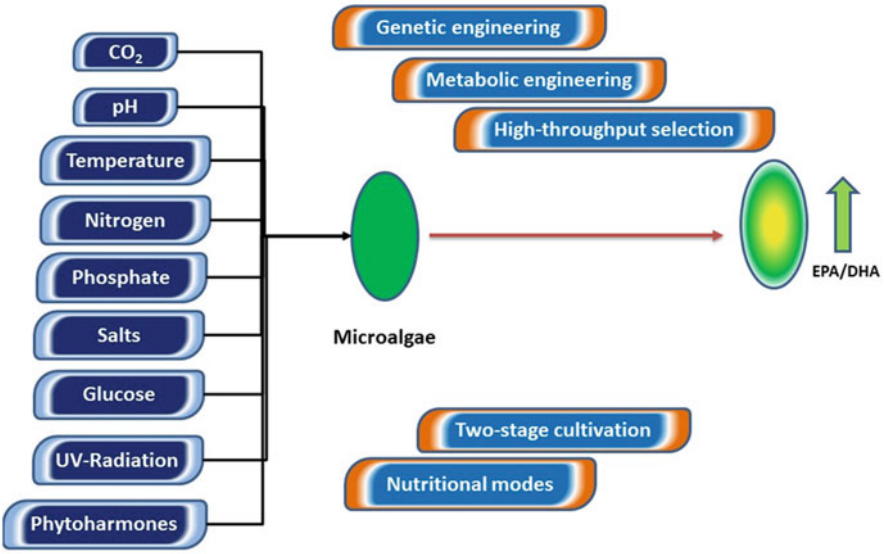

Fig. 10.1 Stresses and strategies for increasing the PUFA production in algae

neuroprotective potential of PUFAs, which can improve neurotransmission in cholinergic neurons (Lauritzen et al. 2000).

10.8 Neuro-Inflammation

Neuro-inflammation is the major cause for the progression of various neurodegenerative diseases such as Parkinson's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. Microalgal biomass supplementation has shown significant improvement in neurodegenerative disorders, which could also be due to the presence of other bioactives of algae besides PUFA. PUFA is also reported to regulate microglia majorly concerning the neuro-inflammation (Laye et al. 2018). Various experiments conducted on neuro-inflammation by supplementing the different algal extracts are presented in Table 10.2.

Several studies have been reported in the neuroprotective potential of algae through in vitro, in vivo (Abad et al. 2008). However, very few studies are only reported for analysing and scientific validation of anti-neuroinflammatory activities of algae. Microglia are vital modulator of the neuro-inflammation process, which communicate with astrocytes by releasing the pro-inflammatory cytokines such as TNF-α and IL-1β as a loop process (Kirkley et al. 2017). A deviation from normal communication and unrestrained neuro-inflammatory loop harms neuronal cells and causes neurodegenerative diseases. From centuries East Asia people use algae as a

Table 10.2 Algal extracts and their anti-neuro-inflammatory (acetylcholinesterase inhibitory activity/inhibition of cholinesterase/inhibition of 5-lipoxygenase) effect along with IC_{50} values

S. No	Algae	Extracts/compounds	IC_{50}/effective concentration used in the study	References
1.	*Caulerpa racemosa*	MeOH extracts	5.5 mg mL^{-1}	Stirk et al. (2007)
2.	*Codium capitatum*	MeOH extracts	7.8 mg mL^{-1}	Stirk et al. (2007)
3.	*Ulva fasciata*	MeOH extracts	4.8 mg mL^{-1}	Stirk et al. (2007)
4.	*Halimeda cuneata*	MeOH extracts	5.7 mg mL^{-1}	Stirk et al. (2007)
5.	*Amphiroa ephedraea*	MeOH extracts	5.1 mg mL^{-1}	Stirk et al. (2007)
6.	*Amphiroa bowerbankii*	MeOH extracts	5.3 mg mL^{-1}	Stirk et al. (2007)
7.	*Dictyota humifusa*	MeOH extracts	4.8 mg mL^{-1}	Stirk et al. (2007)
8.	*Hypnea valentiae*	MeOH extracts	2.6 mg mL^{-1}	Yoon et al. (2008)
9.	*Padina gymnospora*	MeOH extracts	3.5 mg mL^{-1}	Yoon et al. (2008)
10.	*Ulva reticulate*	MeOH extracts	10 mg mL^{-1}	Yoon et al. (2008)
11.	*Gracilaria edulis*	MeOH extracts	3 mg mL^{-1}	Yoon et al. (2008)
12.	*Ecklonia stolonifera*	EtOH extracts	108.11 μg mL^{-1}	Yoon et al. (2009)
13.	*Ecklonia stolonifera*	24-hydroperoxy-24-vinylcholesterol	389.1 μM	Yoon et al. (2009)
14.	*Ecklonia stolonifera*	Eckstolonol	42.66 μM	Yoon et al. (2009)
15.	*Ecklonia stolonifera*	Eckol	20.56 μM	Yoon et al. (2009)
16.	*Ecklonia stolonifera*	Phlorofucofuroeckol A	4.89 μM	Yoon et al. (2009)
17.	*Ecklonia stolonifera*	Dieckol	17.11 μM	Yoon et al. (2009)
18.	*Ecklonia stolonifera*	2-phloroeckol	38.13 μM	Yoon et al. (2009)
19.	*Ecklonia stolonifera*	7-phloroeckol	21.11 μM	Yoon et al. (2009)
20.	*Ishige okamurae*	MeOH extracts	163.07 μM	Suganthy et al. (2010)
21.	*Ishige okamurae*	EtOAc extracts	137.25 μM	

(continued)

Table 10.2 (continued)

S. No	Algae	Extracts/compounds	IC_{50}/effective concentration used in the study	References
				Suganthy et al. (2010)
22.	*Ishige okamurae*	6,6′-bieckol	46.42 μM	Suganthy et al. (2010)
23.	*Ulva conglobata*	Methanol extract	10–50 μg mL^{-1}	Jin et al. (2006)
24.	*Myagropsis myagroides*	Ethanolic extract	5–25 μg mL^{-1}	Kim et al. (2013)
25.	*Myagropsis myagroides*	Ethanolic extract	5–25 μg mL^{-1}	
26.	*Nannochloropsis oceanica*	Ethanol extract	50–100 mg kg^{-1}	Choi et al. (2017)
27.	*Padina australis, Sargassum polycystum* and *Caulerpa racemosa* extracts	–	0.05–0.4 mg mL^{-1}	Gany et al. (2015)
28.	*F. guiryi*	Acetone extract	33.96 μg mL^{-1}	Fernandes et al. (2018)
29.	*F. serratus*	Acetone extract	51.78 μg mL^{-1}	Fernandes et al. (2018)
30.	*F. spiralis*	Acetone extract	57.45 μg mL^{-1}	Fernandes et al. (2018)
31.	*L. ochroleuca*	Acetone extract	72.62 μg mL^{-1}	Fernandes et al. (2018)
32.	*S. latissima*	Acetone extract	>105.19 μg mL^{-1}	Fernandes et al. (2018)
33.	*S. polyschides*	Acetone extract	62.31 μg mL^{-1}	Fernandes et al. (2018)

functional food and as a rich source of bioactive which contain pharmaceutical potential in neuroprotective processes. Further, research clearly showed the anti-neuroinflammatory potential of algae (Pangestuti and Kim 2011). Omega-3 fatty acids act as antioxidants to reduce the ROS. In case of in vitro studies, fatty acids transport occurs in milliseconds, while in case of in vivo studies, the plasma un-esterified fatty acids half-life is ~30 s, and they can be taken up by the liver. Later they are secreted as lipoproteins within 30 min. So, there are some challenges in conducting experiments with omega-3 fatty acids (PUFA). Uptake of PUFAs into the brain may have arisen confusion because studies on brain PUFA levels in which

fatty acids were infused into the plasma and measured in the brain hours later often do not distinguish between the effects of transport, uptake, and metabolism processes (Bazinet and Layé 2014). Poor intake/diet without omega-3 fatty acids resulted in early Alzheimer's disease onset (Igarashi et al. 2012).

In neurodegenerative disorders, Alzheimer's disease (AD) is supreme, which results in memory loss and declines in cognitive abilities. Alzheimer's disease-related neuropathological studies have shown deficiency of the neurotransmitter acetylcholine in the brain. An enzyme acetylcholinesterase (AChE) plays a major role in the breakdown of the acetylcholine, which was mostly observed in AD patients. This reaction can be avoided by inhibiting the acetylcholinesterase enzyme activity. Diets supplemented with PUFA can modify the membrane fluidity and prevent neurons from oxidative damage (Yehuda et al. 2002). Several researchers have been used algal extracts for inhibiting the enzyme activity (Stirk et al. 2007; Suganthy et al. 2010; Yoon et al. 2008, 2009). Some algal extracts have shown the inhibitory potential of choline esterase (ChE) activity, which improves the cholinergic transmission in Alzheimer's disease patients (Pangestuti and Kim 2011). Studies with methanol and hexane extracts of *R. salinam, Nannochloropsis oculata*, *Chlorella minutissima*, and *Tetraselmis chuii* exhibited AChE inhibition activity in vitro (Custódio et al. 2012). Methanol extracts of *Nannochloropsis* sp., *Picochlorum* sp., and *Desmochloris* sp. exhibited the butyrylcholinesterase (BChE) inhibitory activity (Pereira et al. 2015). Even though few reports showed algae rich PUFA supplementation on AChE and BChE activities, another report showed cholinergic activity and enhancement of nerve impulse transmission of cholinergic neurons (Willis et al. 2009). In other studies, DHA supplementation had restored membrane contents and enhanced acetylcholine release in rats hippocampus (Favreliere et al. 2003). In neuronal cultures, PUFA supplementation has also shown neuroprotective potential through inhibiting the abnormal synaptic transmission and neuron cell death (Lauritzen et al. 2000). It has been reported that several algae have been shown to have acetylcholinesterase inhibitor activity and the details are presented in Table 10.2. In algae besides PUFA, other bioactives have shown effective improvement in neurological disorders and their mechanisms were explained (Pangestuti and Kim 2011). A recent study, with Spirulina biomass supplementation showed improvement of vitamin B_{12} status, which has crucial role in the neurological and cognitive developments (Madhubalaji et al. 2019b). One of the major applications of PUFA enriched algal biomass is widely used in aquatic and animal feed (Patil et al. 2007). Further, studies have explored the possible use of algae as aquaculture feed, animal feed for enhanced omega-3 rich value-added products (e.g. eggs, milk, etc.).

10.9 Neurotoxins from Cyanobacteria

Even though algal supplementation has most of the positive effects on the development of the brain, there are some compounds from cyanobacteria that have shown the toxic effects. Based on the environmental conditions such as light, nitrogen, pH, iron, and interactions between other microbes within the system, cyanobacteria produce various toxins. β*N*-methyl amino-L-alanine (BMAA) is one of the known neurodegenerative toxins produced by cyanobacteria. In addition to it, other neurodegenerative toxins such as saxitoxin, anatoxin, nodularin, microcystin, and ciguatoxin (Nicholson and Lewis 2006) are also shown to have a diverse range of effects on human tissues, which includes majorly neurotoxicity followed by hepatotoxicity and gastrointestinal irritation (Mello et al. 2018). *Oscillatoria, Microcystis, Planktothrix, Cylindrospermum, Aphanizomenon,* and *Phormidium* are reported to produce water-soluble neurotoxic agent anatoxin (Aráoz et al. 2010). *Anabaena, Cylindrospermopsis, Planktothrix, Lyngbya,* and *Aphanizomenon* are reported to produce saxitoxins, which induce lipid peroxidation pathways and resulted in neuronal cell death (Mello et al. 2018). Very few algae were explored but most of them are not yet fully explored for its effects on neurodegenerative actions. However toxic compounds are mostly contributed by the cyanobacterial species of algae. So, it is cautionary while consuming cyanobacteria and more studies need to be required for further evaluation of different cyanobacterial biochemical composition and its effect on neurodegenerative disorders.

10.10 Conclusion

Global estimates indicate that neurological disorders are a more common cause of death by 2040 (Ansari et al. 2010). Scientists have expressed their interest in the discovery and evaluation of various safe neuroprotective agents, many studies have been conducted and reported. Clinical studies remained unsuccessful in treating patients with neurological disorders by using various compounds of different origins. Recent studies and global statistics showed that LC-PUFA is conditionally essential for humans. Long-chain EPA/DHA could act as co-preventive and co-therapeutic supplements for human health. Algae are a highly diversified group and a valuable source for various neuroprotective agents. As fish oil is the major source of LC-PUFA, alternative natural, sustainable, and vegetative source for the production of EPA and DHA is algae. The development of commercial-scale production from algae is greatly required to meet the global demands. The global market demand is high for essential oils and much research needs to be conducted for exploration of new algal species, extraction and purification procedures to reduce the price of the algal oils, which have applications in human health.

Marine algae are more prone to produce higher PUFA compared to freshwater algae. Both macro and microalgae produce omega-3 fatty acids. The macroalgae

have other compounds besides omega-3 fatty acids, which play a role in the development of neurological disorders. In algae, cyanobacterial compounds have shown to produce toxins which severely affect the brain and increase the progression of neurodegeneration. However, their mechanisms are poorly understood. So, it is recommended and advised to consume specific algae after evaluating its potential for neurodegenerative disorders.

Most of the studies with algal biomass supplementation have been limited to in vitro, in vivo animal models. Very few clinical studies have been conducted with algae supplementation in the improvement of neurological disorders. Therefore, more studies and validations are required to establish to consume whole biomass for improvement of neurological disorders, while purified omega-3 fatty acids have higher antioxidant potential that could be used for the development of neurological disorders.

Evaluation and validation of microalgal biomass for a synergistic effect of different metabolites, time of intake, doses, extraction and preparation methods for optimum utilization of algal bioactive towards the prevention of neurological disorders needs to be explored more in future.

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Chapter 11
Natural Foods for Suppressing Dementia

N. Nirmala Devi and C. Viswanathan

Abstract Memory loss and problems with thinking, solving, or language are symptoms of "dementia." These variations are usually slight, but for one having this disability will become serious and affect daily life. This is a common clinical condition that shows advancements gradually over years. Many people who are affected by this are disabled not only by cognitive impairment then again also by common connected diseases of advanced years such as stroke, arthritis, and heart disease. The overburden of dementia on patients, careers, and the health system is large, and there are chances of increase as populations grow older. Dementia has gained an increasing public health concern and is likely to continue through this path even though it has smaller amount of risk factors. This article is to highlight many other related diseases that result in dementia and some of the natural remedies that will help in suppressing dementia and also some of the new methods to develop novel therapies.

Keywords Dementia · Symptoms · Types · Diagnosis · Natural remedies

11.1 Introduction

World Health Organization (WHO 2017) in its description says that dementia is a term used for group of diseases affecting memory, cognitive abilities, and behavior that affect the ability to maintain daily living activities. Although age is considered to be the strongest risk factor, it is not a normal part of aging. Two or added brain functions like memory and language complications are found with individuals with dementia. The disease is often long term, but has slow decrease in cognitive abilities, lack of motivation, memory loss, emotional and language complications. Furthermore memory loss is not a common symptom of dementia. It is not a part of aging

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even though the disease is commonly seen among aged people (Bathgate and Scotland 2015). Numerous cognitive abilities can be compared with dementia which includes memory, language, thinking, decision making, visuospatial function, attention as well as orientation. In people with dementia, cognitive impairments often go with changes in personality, emotional regulation, and social behaviors. The cognitive and behavioral changes that occur with dementia impede work, social activities, and bonding and impair a person's ability to perform daily activities like driving, housekeeping, cooking, taking care of finances and personal care (Gilman 2010; McKhann et al. 2011).

Widespread diseases such as Alzheimer's disease (AD), front temporal dementia (FTD), Lewy body dementia (LBD), vascular dementia (VD), syphilitic dementia (SD), mixed dementia (MD), senility dementia (SD), or the combined effect of two or more dementia types, and even stroke are known to cause dementia. Some of the symptoms of the above said diseases can be cured by drugs but not the diseases themselves. These drugs only aggravate the symptoms or foremost slow down the disease rather than curing it or repair brain damage. Indeed, there is no known cure for dementia (Fymat 2018a, b, c, d).

11.2 Types

Common types of dementia are discussed below:

11.2.1 Alzheimer's Disease

It is said to be the most common cause of dementia where an abnormal protein is found surrounding the brain cells and one more protein damaging their internal structure. Within the stipulated time, the chemical connections between cells in brain are lost and cells ultimately begin to die.

Symptoms: Problems like remembering the daily activities are often the first thing to be observed, then certain kind of difficulties like finding the right words, solving problems, making decisions, or recognizing things in three dimensions is also observed in addition.

11.2.2 Vascular Dementia

Here occurs narrowing or blockage of blood vessels because of which oxygen supply to the brain is reduced and some of the brain cells become damaged or die. This can also be triggered by disease known as subcortical vascular dementia which affects the small blood vessels deep in the brain.

Symptoms: Series of small strokes for a longer period of time can lead to vascular dementia, and other symptoms include struggling with problem-solving or planning, thinking speedily, and focusing which may overlap with those of Alzheimer's disease.

11.2.3 Mixed Dementia

Accumulation of abnormal proteins occurs, and the person may have noticeable changes in the brain which is linked to Alzheimer's disease, vascular and Lewy body dementia. Symptoms may vary, depending on changes in the brain and the area that is affected.

11.2.4 Dementia with Lewy Bodies

Chemistry of the brain cells is destroyed by the formation of tiny abnormal structures known as Lewy bodies inside the brain cells. It is found to be one of the reasons leading to the death of brain cells.

Symptoms: Early symptoms can have many variations which include lack of attentiveness that has fluctuations throughout the day, hallucinations, and also trouble in judging distances. These symptoms are found to be closely related to Parkinson's disease that also shows some difficulty with action.

11.2.5 Front Temporal Dementia (Including Pick's Disease)

The front and side parts of the brain are damaged because of clumps of abnormal proteins that are formed inside brain cells, causing them to die. Because of this there are certain changes at first noted in personality and then in behavior.

Symptoms: Person may have difficulties with communication or forget the meaning of words that clearly depend on which part of the brain is being damaged (Alzheimer's Society 2017).

11.3 Signs and Symptoms

The signs and symptoms follow the three phases given below and the diagnosis is entirely different from prior mental functioning with much difference than would have been projected due to aging.

11.3.1 Early Phase

Slow and often ignored with common symptoms which include forgetfulness, space, and time confusion.

11.3.2 Middle Phase

As there is a progression in disease, it shows clear and more restricting symptoms that include need for help, having balance problems, tremors, difficulties in eating and swallowing, speech and language difficulties, behavioral changes like wandering, restlessness, repeated questioning, forgetting recent events, and other difficulties that include lack in communication, attention, problem-solving, and memory misrepresentations that include remembering sequence of events, combination of memories, confusion of people, etc.

11.3.3 Late Phase

Severe memory disturbances which include not recognizing relatives and friends, greater physical difficulties, near total dependence and inactivity, aggressiveness, crying, anger that comes under behavioral changes, unawareness of time and space.

Serious changes in behavioral and mental level are noted like abnormal motor behavior, anxiety, aggression, interestedness, sleep changes, delusions, depression and impulsivity; also excited mood; irritability; and psychosis that shows total dependence and inactivity of the person (Fymat 2017a, b; Dougall et al. 2004; Van der Steen et al. 2014; Fink et al. 2018).

11.4 Stages of Disease

Dementia has four progressive and successive stages.

Mild cognitive impairment (MCI): Signs and symptoms in this stage are not severe enough to disturb routine work.
Early stage dementia (ESD): Symptoms are more noticeable.
Middle stage dementia (MSD): Symptoms generally worsen.
Late stage dementia (LSD): Symptoms change significantly (Fymat 2018a, b, c, d).

11.5 Diagnosis

Individuals with problems in their memory or thinking require proper assessment. Uncovering the reason may allow us to identify the path for the person to get the right treatment. However, diagnosis is usually done based on the information collected regarding the illness, initial tests, and cognitive testing with medical imaging, and probably by the blood tests which help in ruling out other causes or conditions.

11.5.1 Preliminary Testing

- **Niacin, Folate, or Vitamin B12 deficiency**:
  For proper growth, cell production, and nerve function vitamin B12 is found to play an important role. But it did not show any improvement in persons with cognitive problems.
- **Delirium ("acute confusional state (ACS)")**:
  This basically includes attentional deficit behavior and disorganization. It includes signs that involve changes in arousal, cognitive deficits, perceptual deficits, and a change in sleep-wake cycle, and psychotic features such as hallucinations and delusions.
- **Mental illnesses (depression and psychosis) testing**:
  This can be studied by assessing psychiatry relating mental or emotional inconvenience to disordered brain function with Neuropsychiatric Inventory (NPI) or the Geriatric Depression Scale (GDS) tests.
- **Paralytic dementia (general paresis, general paralysis of the insane)**:
  It is a severe neuropsychiatric disorder that leads to cerebral atrophy in late-stage syphilis caused by chronic meningoencephalitis. There is a slow decrease in mental ability with symptoms of excitation of the central nervous system, leading to absolute dementia and paralysis.
- **Infective conditions**:
  Include cryptococcal meningitis caused by fungus in soil, AIDS, a chronic life threatening condition, Lyme disease caused by bacteria, progressive multifocal leukoencephalopathy caused by virus and a disease that affects white matter of brain, subacute sclerosing panencephalitis, a neurological disorder which affects central nervous system, syphilis, a bacterial infection that results in neurological problems, and Whipple disease, a bacterial infection that affects joints and digestive system.

11.5.2 Cognitive Testing

- **Mini-Mental State Examination (MMSE)**:
  Personality assessment by making a note on routine activities and an assessment on behavior is done in MMSE and is considered as a useful tool.
- **Montreal Cognitive Assessment Test (MOCA)**:
  An online test which is considered as the better one in analyzing mild cognitive impairment (MCI).
- **Self-Administered Questionnaire (SAQ)**:
  A person's daily cognitive functioning is prepared to support the information obtained from brief cognitive tests.
- **Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)**:
  In order to evaluate the dementia stage in elderly people, a short questionnaire is planned. It is a screening tool in which the details are filled by a relative or friend who has known the elderly person for 10 years or more. It is not known how precise the survey is for identifying dementia.
- **Alzheimer Disease Caregiver Questionnaire (ADCQ)**:
  Tool which helps to assess the chance that an individual has dementia suggestive of Alzheimer's disease. This test can be done online or in the office by a caregiver and has 90% accuracy.
- **General Practitioner Assessment of Cognition (GPAC)**:
  It was a tool designed for assessing cognitive impairment and can be done by primary care set.

11.5.3 Laboratory Tests

Certain cases that can be treated can be ruled by performing blood tests.
Tests include:

- Assessment of vitamin B12.
- Assessing folic acid.
- Estimating thyroid-stimulating hormone (TSH).
- Measuring the inflammation by C-reactive protein (CRP).
- Complete blood count which includes estimation of electrolytes, calcium, renal function, and liver enzymes.

11.5.4 Imaging Scans

Accurate diagnosis is done by brain scanning. Brain biopsy can also be conducted to get an accurate diagnosis which is usually not recommended.

- CT (computerized tomography), CAT (computerized axial tomography), and MRI (magnetic resonance imaging) scans are broadly used to study the brain which shows structural changes happening in the brain tissue.
- Changes in the brain can be analyzed by SPECT (single photon emission computerized tomography) and PET (positron emission tomography) scans (Fymat 2018a, b, c, d).

11.6 Nutritional Treatment

11.6.1 Polyphenols

In potentially functional foods, polyphenols have been found to have an important role as an anti-inflammatory and antioxidant property. Polyphenol compounds from various types of food intake have remarkable effects in protecting the metabolism especially in brain tissues. Now, there is a new dietary protocol available for polyphenol collection which helps people a lot (Burckhardt et al. 2016). Highest content of polyphenols in blueberries have strong antioxidative benefits which protect the function of mitochondria and decelerate the structure and function of neurons in PD (Knaze et al. 2018) and AD inhibiting amyloid-β aggregation. Blueberries, blackberries, grapes and apples, green and black tea, wine, coffee, cocoa and spices such as turmeric and curry have polyphenols and are found to have anti-inflammatory, antioxidant, and neuroprotective properties (Visioli and Burgos-Ramos 2016).

11.6.2 Resveratrol

Resveratrol content can be made available by taking adequate or reasonable intake of red wine (one glass per meal) that contributes one component which has a promising effect of Med Diet (Strathearn et al. 2014; Granzotto and Zatta 2014) that reduces the risk of dementia including AD (Bastianetto et al. 2015). Also, reasonable intake of alcohol that is around $\leq$12.5 g/day reduces the risk of dementia, while excessive drinking about $\geq$38 g/day increases the risk (Braidy et al. 2016).

11.6.3 Olive Oil

Olive oil helps in counteracting neurological diseases and this has been explored in an experiment with animal model and humans. Oleocanthal (phenolic compound) extract which is derived from extra-virgin olive oil was administered to C57BL/6 wild-type mice showed an increase in the β-amyloid clearance from the brain where

its accumulation is an important event in AD (van der Zwaluw et al. 2014). These data assist and support the preventive effect of extra-virgin olive oil on AD (Hubbard and Sinclair 2014), showing a balance in the antioxidant system with a positive effect on cognitive function (Abuznait et al. 2013). High rate of polyunsaturated omega-3 fatty acids in the olive oil helps in inhibiting β-amyloid accumulation and aggregation of a protein tau which is the main constituent of neurofibrillary tangles and helps the brain in efficient clearing, thus reducing the risk of AD (Hubbard and Sinclair 2014).

11.6.4 Fruit and Vegetables

Anti-inflammatory effect and increased immune cell response can be increased by taking lot of fruits and vegetables (Pang and Chin 2018; Hosseini et al. 2018). Stabilization of blood sugar can be achieved by consuming moderate amount of wine with a diet rich in protein, fruits, and vegetables that would protect against the development of ALS (Kang et al. 2005). Also care should be taken because a diet with higher intakes of fruits and vegetables enhances the immune cell profile and reduces pro-inflammatory mediators (Pang and Chin 2018). Along with the former, higher legume and fish intake were also considered to be associated with the larger cortical thickness (Okamoto et al. 2009).

11.6.5 Insulin Signaling and Calorie Restriction (CR) Effect

It is noted that hyper-caloric diet with a glycemic load (helps to know the amount of carbohydrate in the food with its raise in blood glucose levels)that is very high has a negative impact in patients with higher amyloid deposition in the brain (Staubo et al. 2017). Studies revealed that if the calorie intake is reduced it has a valuable effect on health that helps in increasing lifespan and improvement in neuroprotection (Taylor et al. 2017).

11.6.6 Ketogenic Diet and Brain Function

Ketogenic dietary intervention helps to replace carbohydrates with average amounts of proteins and high amounts of fats, that is, carbohydrates intake is reduced to 10% of daily calories, and fat content is increased to 90% of total calorie intake leading to ketones body formation (Perera and Turner 2016) that can be detected in the urine (Vining et al. 1998). When the protein intake is high or average it does not relate with ketones body formation (Westman et al. 2007). Thus, the ketogenic diet is said to be

effective in improving the control of epilepsy (Cassady et al. 2007; Villaluz et al. 2018), and motor control (McDonald and Cervenka 2017).

11.6.7 Traditional Medicines and Diets

***Ginkgo biloba* L.**: In earlier studies, *G. biloba* has been used to treat cognitive dysfunction, dementia, and AD by German physicians. Extracts of *G. biloba* leaves (EGb 761) were registered and the products developed from the same are patented and commercialized in the early 1970s (Wagner 1999). Currently, extracts from *G. biloba* leaves are widely recommended in Europe and USA for the treatment of AD and a nonspecific age-related deterioration of mental functions, and for the improvement of blood flow in the cerebral region and to improve memory (Birks et al. 2002).

***Panax ginseng*:** Ginseng root is found to contain ginsenosides (triterpenic saponins complexes) which is considered an adaptogenic herb that is found to elevate the body's resistance towards tension, shock, nervousness, and weakness by controlling the immune function. Moreover, it helps in increasing the memory, learning performance, and motor activity (Radad et al. 2006).

11.6.8 Ayurvedic Medicine

***Curcuma longa* L**: Previous studies have emphasized the wide use of *Curcuma* among Indians that explains their role in reducing the prevalence of AD in India compared to USA (Ganguli et al. 2000). Process of inflammation shows a major role in the pathogenesis of the most chronic illnesses, including neurodegenerative diseases. However, the therapeutic potential of curcumin as anti-inflammatory agent has been highlighted in the prevention and treatment of chronic disorders (Aggarwal and Harikumar 2009).

11.7 Supplements

11.7.1 Vitamin B12 and Folic Acid

Deficiency of both vitamin B12 and folic acid in the cases of dementia has proved that dietary and supplementary intake of these vitamins and iron do not help in the treatment of dementia (Nelson et al. 2009). In contrast, few studies have shown that supplemental intake (via parental substitution) of these vitamins and folic acid has helped in treating such as neuropsychiatric disease (Goebels and Soyka 2000; Stanger et al. 2009). However, in all the cases the dietary intake of vitamin B12

does not progress the dementia treatment as most of the older adults are found to have atrophic gastritis with altered production of intrinsic factor and decreased stomach acid excretion. Therefore it is highly suggested to take supplements and/ fortified foods like cereals with high vitamin B12 and folate content (Stover 2010).

11.7.2 Vitamin B1

According to the report published by University of Maryland and Medical Centre, and University of Michigan Health system, around 50 g of vitamin B1 per day can help in the treatment of dementia and also supports a few enzymes and cholinergic neurons which are responsible for transmission of nerves related to dementia and few other brain related issues. Grain products, nuts, seeds, pork, legumes, and organ meats are highly rich in vitamin B1. Regarding vitamin B1 intake, supplemental vitamins are good only for a few groups of people; however, for major people it is very hard to absorb and these multivitamin pills are also known to cause cancer in few people. And so, nutritionists highly suggest taking a healthy diet with more thiamine content. Taking a vitamin supplement may boost thiamine intake to help maintain a healthy brain but as a supplement intake thiamine is found to be poorly absorbed. Nutritionists suggest that healthy diet would be a better approach, because multivitamin pills may have increased risk of cancer in some people (Gibson et al. 2016).

11.7.3 Niacin

In general, vitamin B3 (niacin) deficiency leads to increased risk of dementia. However, a study was conducted to check whether the dietary intake of niacin was associated with cognitive neurological diseases related to dementia by Morris et al. (2004). The study was carried out in individuals with an age group of 65 and above for a period of around 5.5 years. They have identified that higher intake of niacin food was related to a slower annual rate of dementia. From the data they have concluded that dietary niacin acts against dementia related cognitive decline (Morris et al. 2004). In another study, Gregory administered large doses of intravenously supplemented niacin, in addition to dietary intake, they have successfully recovered from dementia and were suggested to continue the same for a period of time to protect themselves from this cognitive decline (Prousky 2011; Gregory 1952). High niacin foods include fish, turkey, pork, chicken, beef, brown rice, peanuts, mushrooms, green peas, and avocados.

11.7.4 Polyunsaturated Fatty Acids (PuFa)

A notable improvement has been reported in cognition and memory in healthy (Kuelzow et al. 2016; Witte et al. 2014) and AD patients after supplementation with eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) (Zhang et al. 2015; Kuelzow et al. 2016). Some studies showed that there is a reasonable effect of omega-3 fatty acids on brain atrophy where its effect is well seen in reducing the neurogenerative and inflammatory diseases but it is limited to patients with physiological B vitamin status that highlights the importance of finding out subgroups in clinical outcomes who are highly benefited (Kuelzow et al. 2016; Jernerén et al. 2015) to bring down the amount of the amyloid-β-induced toxicity (Regitz et al. 2016).

11.8 Conclusion

Nutrition represents the most promising approach to prevent the neuronal and cognitive decline in neurodegenerative and non-neurodegenerative diseases which may worsen with time and has no cure at all. Insulin action in brain is very well connected with decline in cognitive function. AD is more prevalent in high-glycemic diet, while a low carbohydrate-high protein diet supports the hormonal action and a diet with high-fat has control over neuro-inflammation in central and peripheral nervous systems. In support with the above said high-doses of B vitamin supplementation is found to show positive effects in patients with cognitive dysfunction. Also, the most analyzed nutrients like ω-3 and ω-6 polyunsaturated fatty acids from fish, poultry, nuts, and margarine, as well as, folic acid, vitamin C and E have given a better result. Along with the previous diet, intake of polyphenol-rich foods like blueberries, blackberries, grapes, apples, or beverages such as green and black tea, coffee, and red wine is proven to be beneficial and found to give promising results. General function of brain and its protection can be boosted by taking a Mediterranean diet. In addition, caloric restriction may be counterproductive in elderly. For the treatment of neurodegenerative disorders in future, plants with relevant medicinal and therapeutic activity may be exploited. Clinical effectiveness and potential toxicity of active plants and compounds isolated from them in larger trials require deep study and evaluation before recommendations is done. The use of a polyvalent "cocktail" of drugs can be advised in future which helps to boost different mechanisms such as antioxidant activity, anti-inflammatory activity, and the inhibition of the formation of fibrillary tangles and β amyloid plaques.

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Chapter 12
Nutrients' Role in the Treatment of Parkinson's and Alzheimer's Diseases

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Abstract Neurological illnesses disrupt brain function and are one of the primary causes of disability and mortality around the world. Nutritional factors have a significant impact on brain function. Some nutrients have been found to help prevent the onset of prevalent neurological illnesses like Alzheimer's and Parkinson's disease. Certain diets, such as carbohydrate-rich diets, can assist to prevent neurological diseases from developing. As a result, nutrition and neurological problems are linked, which could lead to the development of a novel treatment strategy that slows disease progression.

Keywords Amyloid plaque · Diet · Neuroinflammation · Nutrients · Omega 3 fatty acids

12.1 Introduction

Neurological disorders are a group of diseases that are known to affect the central and peripheral nervous systems and are considered a major health concern worldwide. The most common neurological disorders included in the Global Burden of Disease (GBD) report are Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, brain disease, and headache disorders (Murray et al. 2012). Neurological disorders were found to be the leading cause of disability and the second leading cause of death worldwide. It is estimated that at least one in three people have a chance of developing a neurological disorder during their lifetime (Feigin et al. 2019). The most important cellular and molecular effects that cause neurodegeneration are oxidative stress, abnormal protein accumulation, damaged mitochondrial function, and neuroinflammation (Hoglund and Salter 2013). Diet and nutrients have been shown to increasingly impact neurological function. The major types of nutrients are depicted in Fig. 12.1. Several diets and diet patterns are found

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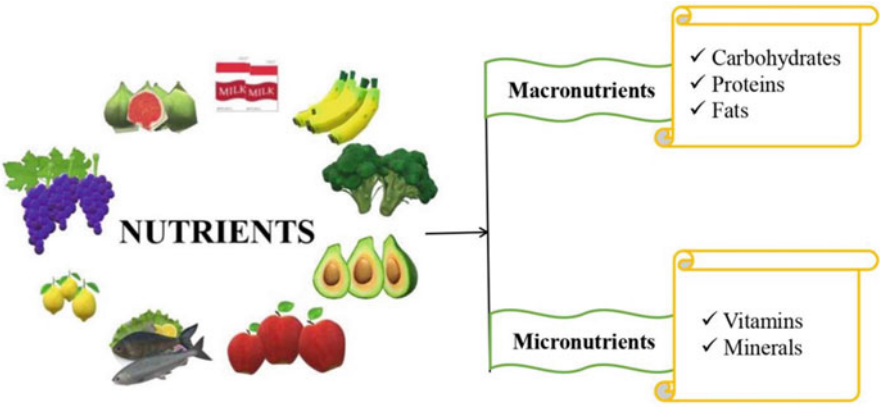

Fig. 12.1 Major types of nutrients

to be rich in antioxidants and anti-inflammatory properties, which play a protective role against the pathophysiology of the development of neurological diseases. The pathophysiological development of neurological diseases is highly influenced by diet (Francis and Stevenson 2018). Diet is crucial in the development of arteriosclerosis and other neurological ischemic diseases. The development of stroke is known to be highly influenced by high salt intake, low vegetable diet, and high-fat diet. Vegetables, fruit, and nutrient-rich diets have been shown to reduce the risk of PD development (Breton 2007). Hence, diet is known to play a vital role in neurological disorders, and this chapter focuses on the role of nutrients in major neurological disorders.

12.2 Alzheimer's Disease (AD)

Alzheimer's disease and other dementias were found to be more common among women than among men. AD and other dementias are among the three leading neurological disorders (Isik 2010). Cholinergic dysfunction, cognitive impairment, memory loss, neuronal death, and behavioral problems are all symptoms of AD. Complex mechanisms and deterioration of the memory-related neurological cascade are involved in the etiology of Alzheimer's disease. Early-onset of this disease has been identified in people under the age of 65. However, more than 90% of cases reported are due to late-onset AD, which affects predominantly people over the age of 65 (Olasehinde et al. 2019; Prince et al. 2019). Although so many studies have been conducted on neurological diseases, studies focusing mainly on AD are comparatively low.

AD is a sickness of early life. It affects one in four people at 85 years of age. Relative frequency is predicted in the coming years, with 131.5 million reckoning cases by 2050 (Harris 2012). The normal brain contains healthy neurons, but in the

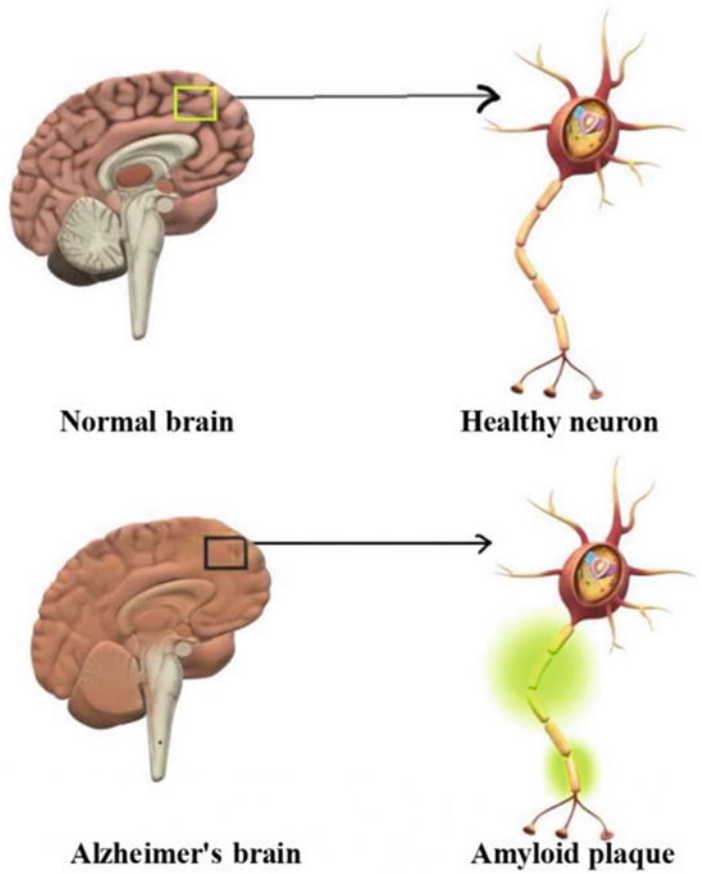

Fig. 12.2 Alzheimer's affected brain

AD-defined slowly progressive neurodegenerative disease, the amyloid plaque is the most affected area in the brain as shown in Fig. 12.2 (Rathmann and Conner 2007). The loss of physiological features can be caused by cerebral disorders like AD or other causes such as excitement, infections, slowness in the pulmonary and circulatory systems which cause a decrease in the oxygen supply to the brain, nutritional deficiency, vitamin deficiency, and others (Breijyeh and Karaman 2020; Blasko et al. 2000).

12.2.1 Complications of AD

Some of the AD cases are hereditary. There are many diseases and lifestyle causes that can lead to an increased risk of the development of AD, like diabetes, painful

brain injury, high blood pressure, obesity, and other metabolic syndromes associated with aging. Treatment focusing on these risk factors causing AD could help us to enhance our treatment strategy and develop more efficacious treatments for AD (Vauzour et al. 2015).

12.2.2 Polyunsaturated Fatty Acids (PUFAs)

Many studies have examined the effects of PUFAs in preventing or decreasing AD (Jicha and Markesbery 2010). When taken regularly, fish oil high in omega-3 fatty acids has been shown to reduce the frequency of Alzheimer's disease. Both the omega-3 and omega-6 polyunsaturated fatty acids are essential for the cell membrane and normal neuronal function (Zandi et al. 2004). The major types of nutrients are depicted in Table 12.1.

Table 12.1 List of some common nutrient-rich food

Sources	Nutrients
Salmon	Omega-3-fatty acid, animal protein, vitamins, minerals, magnesium, potassium, selenium, vitamin B
Kale	Vitamin C, vitamin A, vitamin K1, vitamin B6, potassium, calcium, magnesium, copper, manganese, fiber, protein
Seaweed	Calcium, iron, manganese, magnesium, phycocyanins, carotenoids, iodine
Garlic	Vitamin C, vitamin B1, vitamin B6, calcium, potassium, copper, manganese, selenium, sulfur rich allicin
Shellfish, clams, and oyster	Vitamin B12, vitamin C, vitamin B, potassium, selenium, iron, zinc, copper, vitamin B12, vitamin D
Potatoes	Potassium, magnesium, iron, copper, manganese
Liver of poultry animals	Vitamin B12, vitamin B5, vitamin B6, niacin, folate, vitamin B2, vitamin A, copper, iron, phosphorus, zinc, selenium, animal protein
Sardines	Omega-3-fatty acids
Blueberries	Antioxidants, anthocyanin
Egg yolk	Vitamin, minerals, choline, lutein, zeaxanthin, antioxidants
Cocoa	Fiber, iron, magnesium, copper, manganese, antioxidant
Beans	Proteins, low-fat, fiber, vitamin C, vitamin A, calcium, phosphorus, potassium
Yogurt	Protein, potassium, calcium, vitamin B12, riboflavin, phosphorus
Peanuts	Protein, carbohydrate, fiber, vitamin, polyunsaturated fatty acids
Mushrooms	Selenium, riboflavin, niacin, pantothenic acid, proteins

12.2.3 Vitamins

Vitamins are powerful antioxidants, and knowing that the brain is particularly vulnerable to oxidative stress damage increases their ability to maintain good knowledge and proper psychological characteristics. The brain consumes a lot of oxygen and has only a few antioxidant mechanisms to protect it. It also has a lot of polyunsaturated fatty acids and a lot of iron, both of which are antioxidants. The effect of vitamin E in protecting membrane phospholipids against peroxidation has been extensively researched. Supplementing with vitamins E and C and eating a healthy diet have been linked to a lower risk of AD (Dysken et al. 2014; Gentreau et al. 2020).

12.2.4 Carbohydrates

The development of AD was found to be associated with a carbohydrate-rich diet. A carbohydrate-rich diet is known to alter the brain's insulin signaling and cause memory impairment and increased amyloid deposits. A carbohydrate-rich diet is known to increase the risk of AD development (Grimm et al. 2017).

12.2.5 Role of the Nutrients in AD

Omega-3 fatty acids, vitamin E and B, choline, and uridine have supplied the principles for rising powerfulness in AD prevention and medical organization. Nonetheless, there is no clinical evidence that nutritional supplementation prevents the onset or progression of AD (Barbalace et al. 2019). Marine organisms provide a rich supply of natural chemicals, which have structural characteristics that differ from land. 20,000 species of algae have been known and they are classified into macroalgae (seaweeds) and microalgae-based on their size (Brown et al. 2014). Microalgae are single-celled marine plants, whereas macroalgae are multicellular marine plants. According to their colors, marine seaweed can be grouped into three groups: red seaweed, brown seaweed, and green seaweed, and shown in Fig. 12.3 (Newman and Cragg 2004). It represents the beginning of a large number of natural compounds. Some of the marine organisms have different structural characteristics from their aquatic origins and they produce different pharmacological effects like anti-diabetic, anti-inflammatory, antioxidant, anticancer, and anti-obesity activities. It is a way for the development of new drugs using natural compounds that have been approved for clinical use (Goo et al. 2013).

Carbohydrates are an important component of marine algae. Furthermore, polysaccharides are commonly the major constituents of brown, green, and red algae (Huang et al. 2019). Among marine organisms, algae are one of the richest resources

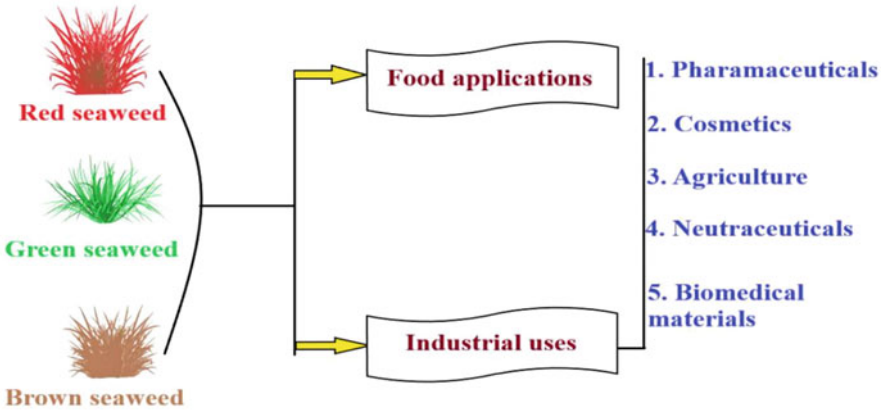

Fig. 12.3 Uses of seaweed

of the deep sea. Algae are satisfying sources of bioactive elements such as antioxidants, proteins, vitamins, minerals, soluble dietary fibers, polysaccharides, sterols, carotenoids, and polyunsaturated fatty acids (Jutur et al. 2016). Oxidative stress and inflammation are the leading agents in the progression of AD. Nutraceuticals protect against the formation of reactive oxygen species and consequent tissue damage. Seaweed polysaccharides are a good source of nutraceuticals (www.mayoclinic.org).

12.3 Parkinson's Disease

Parkinson's disease is a major neurological disorder that affects the nervous system that affects movement. PD involves the loss of dopaminergic neurons. Symptoms can be different for each individual and range from no symptoms to tremors. The most common symptoms of PD are tremors, slow movement, rigid muscles, impaired posture, loss of movement, speech changes, etc. (Murakami et al. 2010). Nutrition is known to play a vital role in the risk of PD and the progression of PD. Certain diets and nutrition are known to influence the risk of PD, and nutrition can either promote or slow the progression of the disease.

12.3.1 Carbohydrate

The high glycemic index (GI) and glycemic load (GL) reduce the risk of PD by increasing dopamine release in an insulin-dependent manner. Dietary GI was found to be inversely associated with the risk of PD. Dysregulation of insulin and insulin action increases the brain dopamine concentration and decreases PD risk (Cereda

et al. 2013). A high carbohydrate diet is associated with increased DM. But the association of DM with the development of PD remains contradictory (Noyce et al. 2012).

12.3.2 Lipids

Epidemiological studies have shown that dietary fat has been associated with PD. Increased fat intake is associated with increased PD risk. Saturated fats which are found in the diet are known to increase oxidative stress, thereby increasing the chances of PD, while the presence of PUFAs protects the brain against PD development by anti-inflammatory reaction (Kamel et al. 2014). A meta-analysis of nine studies indicates that dietary fat intake is known to affect Parkinson's disease. Higher PUFA intake reduces PD risk, whereas higher cholesterol and arachidonic acid intake increase PD risk (Qu et al. 2019).

12.3.3 Vitamin

Several vitamins are known to play a major role in PD. Vitamin D regulates calcium homeostasis, which is required for dopaminergic neuron regulation. Dietary intake of vitamin D has been shown to decrease the progression of PD (Holick 2007). Several vitamins were found to be associated with a reduced PD risk, but certain studies showed contradictory results. Hence, the role of vitamins in the progression or prevention of PD needs to be studied and analyzed.

12.4 Stroke

Stroke can occur when the brain's blood supply is interrupted and, thereby, the brain cells have low access to oxygen and nutrients. Brain cells begin to deteriorate, and early intervention is required to prevent this (www.mayoclinic.org). Nutrition is known to play a vital role in the development of strokes, and healthy lifestyle choices are known to reduce stroke risk by 80% (Spence 2019).

12.4.1 Carbohydrate

A case-control study has shown that individuals consuming high carbohydrate diets that contain high GI and GL are at an increased risk of developing stroke. Increased

GI and GL are known to increase the factors associated with insulin resistance and diabetes, which may lead to stroke (Hajishafiee et al. 2013).

12.4.2 Lipids

Even though dietary saturated fat was assumed to increase the risk of ischemic stroke, an observational study indicated that dietary saturated fat did not significantly increase stroke risk (He et al. 2003). No reliable study showed an association of PUFA with a decreased risk of stroke.

12.4.3 Vitamins

A meta-analysis of randomized control trials has concluded that vitamin C, vitamin E, and vitamin A are not associated with stroke development and prevention. However, the role of Vitamin B12 and folic acid in the development of stroke is still unknown (Hankey 2012).

12.5 Conclusion

Nutrition is known to play an important influence in the onset and course of a variety of diseases. Nutrition has an essential role in the prevention and development of neurological illnesses, which are the second leading cause of mortality worldwide. This study highlights how particular diets and nutrition might help prevent the onset of major neurological disorders like Alzheimer's, Parkinson's, and stroke. As a result, a well-balanced, nutrient-dense diet can help to delay the onset of neurological problems. The main benefit of employing nutrition as a therapy method is that it has little to no side effects. Therefore, further studies focusing on the role of nutrients in neurological disorders have to be done.

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Chapter 13
Novel Marine-Derived Natural Products for the Treatment of Depressive Disorder

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Abstract This chapter covers the research focused on and published with respect to the treatment of depressive disorder using marine-based products. Depression is one of the illnesses in which an individual feels irritable, guilty, unhappiness in life, sometimes suicidal ideation, and loss of pleasure in activities. So far, there are hundreds of millions of people suffering from this major depression disorder worldwide. To resolve this issue, there is a need to spend a large amount of money for drug every year, and it leads to a significant share of the economy going for the treatment. Therapeutic drugs are not very effective, and they also have side effects that compound the problem. Many studies have proved that marine-derived natural products show potential activities against many diseases including depression treatment. Over the last few decades, vitamins, amino acids, trace elements, and omega-3 polyunsaturated fatty acids from marine sources are used for the treatment of depression, and these compounds do not having any side effects, which merits utmost consideration for advanced research and development.

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13.1 Introduction

Marine realm is habitat to various organisms with distinct abilities for the survival and the biosynthesis of diverse metabolites. Conventional and synthetic drugs are not performing well like marine natural products (MNPs), which are highly potential in scientific medical research. These MNPs primary metabolites such as amino acids, glucose, and acetic acid are prototype substances where secondary metabolites of alkaloids, polyketides, lipids, etc., actively worked as antibiotics, hormones, and toxins. In addition, endometabolites and exometabolites were released into the environment by many influenced factors (Stonik 2009). The latest research techniques in new screening platforms, structural elucidation, analytical chemistry, synthetic biology, and genome mining have given the focus on production and transformation of marine metabolites. Over the past several decades various industries have proven the value of marine natural products based on their functional role and structural biology. In addition, 1554 new compounds were reported from marine source and 57 compounds structure had been revised. These compounds were reported from bacteria, fungi, archaea, cyanobacteria, dinoflagellates, tunicates, sponges, cnidarians, Bryozoans, Echinoderms, mangroves, algae, and seagrass (Carrol et al. 2019). Furthermore, the identified compounds have antimicrobial, anticancer, anticoagulant, antioxidant, anti-inflammation, antihistamine, antiviral, antiparasitic, and antihypertensive activities, but the findings are very limited to neuropathic studies. Hence, researchers started to investigate the role of marine natural products on neuropsychiatric disorders.

Obsessive completion disorder (OCD) is caused by external factors interfering through the people's quality of life (Nazeer et al. 2019). It is a psychological health problem described via uncontrolled repeated thought, forced recurring behaviors, irregularity of the central nervous system, and genetic factors (Lochner et al. 2004; Prajapati et al. 2011; Seibell and Hollander 2014; Zahra et al. 2019). As per some studies, OCD persists with various fears on cleanliness, hygiene, and other contaminations, the need for constant inspection, and concern about regular balance in their life (Milman 1961; Swedo et al. 1992; and Calles 2012; Boydston et al. 2015; Patel et al. 2017). People with OCD will be affected deeply by health-related risks resembling the COVID-19 pandemic. They fear about self-contamination, and they unwittingly think that spreading contamination to others and isolating themselves for 14 days without contact with anyone leads to severe mental illness. Furthermore, psychological treatment and other synthetic treatments are associated with adverse side effects. To resolve these kinds of issues, we spend a large amount of money on drugs. Therapeutic drugs are not very effective, and they also have side effects that compound the problem. In recent decades, marine natural products are considered novel therapeutic agents including for depression-related diseases.

Therefore, the present review aims to find active marine natural products for depression disorder.

13.2 MNP for the Treatment of Depressive Disorder

Marine organisms have various bioactive compounds like protein, taurine, fiber, polyunsaturated fatty acids, sterol, amino acids, pigments, trace elements, vitamins, and lipids (Food and Agriculture Organization of the United Nations, World Health Organization 2010). An epidemiological survey has revealed that lifestyle diseases are increasing due to improper nutrients in their diet (Story et al. 2008; Cerchietti et al. 2007). This review focuses on the nutrient supplement of seafoods and their active role in the treatment of neurological and other psychological diseases (Liao and Chao 2009).

13.3 Vitamins

Marine natural products are considered as nutritional-rich bases due to the presence of bioactive substances, i.e., protein, vitamins, carotenoids, essential amino acids, polyunsaturated fatty acids, and other metabolites (Gouveia et al. 2010; Barra et al. 2014; Wells et al. 2016; Galasso et al. 2017; Smerilli et al. 2017; Hippler 2017). This trait represents promising opportunities in biomedical application specifically in the treatment of neuropsychiatric disorders (Galasso et al. 2019). Few of the marine organisms were the source of exogenous B-vitamins for other organisms, and it is proven by genomic studies (Croft et al. 2005; LeBlanc et al. 2011; Sanudo Wilhelmy et al. 2014). Marine organisms contribute to various bioactive compounds and are used as nutraceuticals, food source, and food ingredients (Tseng 2001). Among them marine microalgae are known as a rich source of food nutrients and vitamins, which include vitamin C, E, H, B_1, B_2, B_6, and B_{12} (Grobbelaar 2004). The deficiency of vitamin B implies neuropsychiatric disorders; among them folate draws a special attention (Nanri et al. 2010, 2012; Beydoun et al. 2010). Early studies have shown that lack of B_6, B_9, and B_{12} has given more vulnerable symptoms in elderly peoples (Dimopoulos et al. 2007; Kim et al. 2008; Pan et al. 2012). Low level of folate (B9) level in pregnant women, creating the depression symptoms and its deferred clinical improvement also (Van Dijk et al. 2010). Red and brown seaweeds are fine source of vitamins, minerals, and essential fatty acids (Plaza et al. 2008; Gomez et al. 2010). The bioactive peptides from seaweeds are used to improve protein digestibility and antidepression activity (Kim et al. 2011).

Generally marine microalgae contain a large quantity of proteins in their biomass which is effective in treating antihypertensive, depression, cardiovascular disease, and other neurological disorders (Sheih et al. 2009; Kim and Kim 2013; Fan et al. 2014; Vo et al. 2013; Rizzello et al. 2016; Caporgno and Matthys 2018).

Epidemiological studies also revealed that the dietary intake of B_6, B_{12}, and folate can actively improve the symptoms of depression (Payne et al. 2009; Skarupski et al. 2010; Murakami et al. 2010; Watanabe et al. 2012; Miyaki et al. 2012; Yary 2013). Marine micro- and macroalgae contain water and lipid soluble vitamins, and it is considered as a conventional source of human nutrition through diet (Jaime and Herrero 1988). Following this study, Tolmunen et al. reported that dietary intake of folate may have a significant role against depression and less dietary intake is a risk factor for depression (Tolmunen et al. 2003). Similarly, Riboflavin shows improved effect on postpartum depression in Japanese patients (Miyake et al. 2006). Likewise various reports were obtained from Finnish, Japanese, and French cohort with respect to depressive disorder (Tolmunen et al. 2003; Astorg et al. 2008; Murakami et al. 2008; Lewis et al. 2012).

Microalgae are a significant source of vitamins: α and β carotene, and apocarotenoids (vitamin A), ascorbic acid (vitamin C), tocopherol and tocotrienols (vitamin E), thiamine (B_1), riboflavin (B_2), niacin (B_3), and cobalamin (B_{12}) have been revealed as nutritional supplements which may reduce aggressive behavior and other depressive disorders (Roeck Holtzhauer et al. 1991; Brown and Miller 1992; Brown et al. 1999; Japelt and Jakobsen 2013). A similar study has been conducted by Gesch et al. (2002) and revealed that nutritional supplements of vitamin B may reduce aggressive behavior in 231 adult convicts, and reduce the risk of neuropsychiatric disorders, vascular endothelium lesions, neurotoxicity, excitotoxicity, oxidative stress, and cell death (Miller 2008; Karakuła et al. 2009). *Spirulina* sp., *Chlorella* sp., and *Pleurochrysis carterae* are a well-known source of cobalamin (vitamin B_{12}), which act as anti-depressants through dietary supplement (Watanabe et al. 2002; Gruber 2016). Similarly, vitamin B_{12} producing marine bacteria up to 150 μg/ml (Burkholder and Burkholder 1956) and similar bacteria were isolated from seawater (Ericson and Lewis 1953) which produce 10 μg/ml of vitamin B_{12}. The role of vitamin B_{12} and folate is well known to take part in the synthesis of methionine and S-adenosylmethionine (Bottiglieri 1996). S-adenosylmethionine plays an important role in phospholipid and protein metabolism and the biosynthesis of dopamine, serotonin, and epinephrine (Bottiglieri 1996).

Water-soluble ascorbic acid (vitamin C) is an immunomodulatory agent that provides sedative effect to reduce anxiety and stimulate depression remedies (Padayatty et al. 2003; Knowles et al. 2003). A notable quantity of vitamin C was extracted from the diatom of Skeletonema marinoi and its showed potential activity against carcinogenesis and atherosclerosis disease (Smerilli et al. 2017; Roeck-Holtzhauer et al. 1991; Brown and Miller 1992; Brown et al. 1999; Sharma et al. 2008). Vitamin C is beneficial to human health to prevent the symptoms of OCD through the reduction of radical damage (Boyera et al. 1998; Nunes-Alves et al. 2014). *Nocardiopsis alba* and *Streptomyces coelicoflavus* isolated from mangrove sediment samples exhibited oxidation stress reduction potential (Janardhan et al. 2019; Kothagorla and Tamanam 2013). Early studies signify that the reduction of oxidation stress may lead to improvement in neuropsychological disorders (Olivieira et al. 2015). Oral supplements of vitamin C have shown a therapeutic role in the

reduction of anxiety level and have shown promising antidepressant activity (Moretti et al. 2014).

Vitamin D plays a significant role in antioxidant processes, proliferation, cell death, differentiation, inflammatory response and immunity modulations, neuroprotection, brain development, and neurotransmission (Cannell and Grant 2013; Eyles et al. 2013; Holick 2015). At the same time, the deficiency of vitamin D leads to major depressive disorder, autism, schizophrenia, and other neuropsychiatric diseases (Chiang et al. 2016; Wang et al. 2016; Parker et al. 2017). Generally, vitamin D is produced in the epidermis and it is assimilated as two forms (D_2, D_3) in the human body. Vitamin D, as well as reformed 25 OH-D_3 (25-hydroxyvitamin D) extracted from marine microalgae, have shown the potential result of hydroxylation in the liver and it turns into the active form of vitamin D (1, 25-dihydroxy-vitamin D3) in the kidney (Takeuchi et al. 1991; Sunita Rao and Raghuramulu 1996; Eyles et al. 2013). The active form of vitamin D_3 regulates the enzymes tyrosine hydroxylase and tryptophan hydrolase, which is the reason of OCD etiology (Cui et al. 2015; Kaneko et al. 2015). Marine fish tuna and mackerel and fish liver oil have the highest concentration of vitamin D (Japelt and Jakobsen 2013). In 2007, Lu et al. reported vitamin D_3 content in mackerel, salmon, blue fish, cod fish, and grey sole; in that, salmon has 245 IU of vitamin D_3 followed by mackerel with 241 IU of vitamin D_3. This study has suggested that marine fish salmon, mackerel, and blue fish are an excellent source of vitamin D.

Marine microalgal species *Chaetoceros calcitrans*, *Nannochloropsis oculata, Dunaliella tertiolecta*, *Porphyridium cruentum*, and *Tetraselmis suecica* are the best source of vitamin supplement to humans (Carballo-Cardenas et al. 2003; Durmaz 2007; Bong and Loh 2013; Mokronsnop and Zolotareva 2014; Santiago-Morales et al. 2018). The diet supplement of vitamin E will protect the cell membrane from lipid peroxidation and stop the reactive oxygen species (Corina et al. 2018). It is a chemoprotectant that reduces vascular damages and also recovers vascular heath and endothelial function (Ni et al. 2005; Corina et al. 2018).

13.4 Amino Acid

Marine fishes are a source of arginine, tryptophan, glutamine, methionine, glutamate, histidine, leucine, isoleucine, valine (branched chain amino acids), methionine, choline, and betaine (sulfur amino acids) and are needed to stimulate health, and they regulate optimal metabolism and other psychological illness (Anderssen et al. 2016). Likewise, *Chlorella vulgaris* isolated from marine samples produces bioactive peptides at the molecular weight of 7.5 μM and shows prolific activity on cell death and oxidative stress (Sheih et al. 2009). This peptide made-up of 2–20 amino acids has gastrointestinal enzyme resistance (Suetsuna and Chen 2001). Water-soluble amino acid mycosporine producing marine microalgae has photoaging protective formulation and oxidation stress (Lawrence et al. 2017) and prevents cell death in human cell lines B16-F1 murine skin melanoma at 3.2 mg/ml (IC_{50}) and

HeLa Cervical adenocarcinoma at 0.2 mg/ml (IC_{50}). Marine snail *Conus magus* has produced neuropathic pain-relieving compound conotoxin approved by FDA, and it is commercially known as ziconotide (Ana et al. 2014).

13.5 Trace Elements

The trace elements deficiency has combined with the pathophysiology of depression disorder, and a comparison study of 48 OCD patients with healthy control revealed low concentrations of serum iron, magnesium, and zinc and higher levels of manganese and calcium in OCD patients (Shohag et al. 2012). Zinc has significant trace elements, playing important role in enzyme catalysis, protein synthesis, and gene expressions (Takeda 2000). The antioxidant trace element zinc is present in cerebral cortex, central nervous system, and pineal gland (Peters et al. 1987; Sayyah and Olapour 2012). The antioxidant activity of trace elements controls the oxidation mechanism in OCD pathogenesis (Karciand Celik 2020).

Selenium is an important micronutrient in humans which has antioxidant properties of glutathione peroxidase (Wolonciej et al. 2016). Ozdemir et al. reported that OCD patients have lower levels of selenium (Ozdemir et al. 2009). In humans, selenium is present in the form of selenoprotein as a factor in the function of thyroid gland (Holben and Smith 1999). Selenium deficiency may cause obsessive compulsive disorder along with renal and cardiovascular diseases (Holben and Smith 1999; Tilami and Sampels 2017). According to the USDA National Nutrient Database, seafoods are a good source of selenium and other trace minerals (Ralston 2008). The World Health Organization (WHO) has recommended 400–500 mg of calcium per day for adults for metabolic activity and skeleton rigidity (Ghosh and Joshi 2008). In general, fish and molluscs have 14–26 mg/100 g and crustaceans have 68 mg/100 g of dietary calcium, and fish bones are suggested as natural calcium sources to use in functional food (Malde et al. 2010; Tacon and Metian 2013). Similarly phosphorous is also needed for bone development, fabrication of cellular membrane and membrane lipid layer in humans. Overall the human body contains 700 g of phosphorous which is bound to the skeletal muscle (9%), viscera (10%), and bones (80%) (Martınez-Valverde et al. 2000). Low phosphorous content leads to metabolic acidosis, muscle disorder, encephalopathy, cardiac and neurological disorders (Ghosh and Joshi 2008). The phosphorous content of seafoods ranged between 204 and 230 mg/100 g in fish, molluscs, and crustaceans (Tacon and Metian 2013). So that, seafoods are finest source of phosphorous, calcium, selenium, and other trace minerals.

13.6 Omega-3 Polyunsaturated Fatty Acid

The omega-3 polyunsaturated fatty acid plays a role in the regulation of membrane fluidity, neuroinflammation, hypothalamic pituitary and adrenal axis, signal transduction, modulation of dopamine, serotonergic transmission, and cell survival (Liperoti et al. 2009; Shei et al. 2014; Abozid and Ayimba 2014). Neurodegenerative and neuroinflammatory diseases in humans were developed by the deficiency of omega-3 polyunsaturated fatty acid (Logan 2003; Bourre 2004; Young and Conquer 2005; Freeman et al. 2006). A recent study revealed that omega-3 fatty acid plays a crucial role in depressive disorder (Chang et al. 2009). The PUFA-prostaglandin E2 cascade represents a regular connection between omega-3 polyunsaturated fatty acids and depression, and cardiovascular diseases (Chang et al. 2009). These results proven by the epidemiological study of post-mortem brain tissue have exhibited inverse relationship and oxidative stress and inflammation biomarker (Tiemeier et al. 2003; Rees et al. 2009; Yary and Aazami 2011; Jiang et al. 2012; Jadoon et al. 2012; Miyake et al. 2013; Park et al. 2011; Baek and Park 2013; Grosso et al. 2014). The blue mussel (*Mytilus edulis*) intake has improved the erythrocyte fatty acid composition and plasma phospholipids and serum metabolites in women rheumatoid arthritis. This study concluded that the omega-3 fatty acid must be the reason for this potential effect on 23 patients (Helen et al. 2019).

The different studies in the past evaluated the effectiveness of omega-3 fatty acid in six psychological patients who reported estimable improvement from daily stress, suicidal thoughts, depression, and aggression, and they remain stable after 84 days of treatment (Hallahan et al. 2007; Martins 2009; Mozaffari Khosravi et al. 2013). Furthermore, experimental analysis has shown that omega-3 polyunsaturated fatty acids from seafoods have potentially prevented psychological symptoms including the risk of suicide (Tsai et al. 2014; Helen et al. 2019), impulsivity, depression behavior, and hostility (Silvers et al. 2005; Danthiir et al. 2011; Stafford et al. 2013; Rice et al. 2014).

13.7 Expert Opinion to Improve the Efficiency of MNPs

Marine natural products have received special attention in the field of medicine and other applications by the successes and their new molecular entities (Perira 2019). In addition, Shang et al. (2018) revealed that more nitrogen, halogen, bromine atoms, and few oxygen atoms are the reason for the synthesis of diverse biosynthetic pathways of marine natural products (Shang et al. 2018; Peraria 2019). Still, various restrictions are restraining the progress of drug from marine natural products due to these three factors: on the one hand complication in the collection of drug source material (Day et al. 2018) and on the other hand organic synthesis of drug and less machine learning approaches (Coley et al. 2018, Szymku et al. 2016). Experts also recommend that computer-based synthetic pathways are able to design

de-replication of the compound and their organic synthesis which will make it easy to predict reaction conditions, ligand based as well as structure based analysis (Shang et al. 2018; Peraria 2019). Also, it is used to find the mechanism of action and reaction types. Thus, computational methodologies will be essential to simplify the identification, design, chemical synthesis, elucidation, and prediction of bioactivity and rationale of biological target of marine drug discovery (Perira and De-sousa 2018).

13.8 Conclusion

In the modern society, people have to develop awareness about the nutritional value of seafoods. Various studies suggest that regular consumption of seafood will create affirmative health impact, but it took some time to realize (Daar et al. 2007). In addition, marine micro- and macroalgae are a source of natural stress hesitant and best food supplement. The single cell protein *Spirulina* has enormous health benefits followed by *Chlorella, Dunaliella, Haematococcus*, and *Tetraselmis*. It enhances the bioactive molecule in the cell and reduces the risk of neuropsychological disorders. Seafoods are not much expensive than high sugar instant foods, saturated fatty acids, and soft drinks, so people have to realize which is good for health. Apart from this the selected marine organism should be identified correctly because misidentification may compromise the entire research work which could not repeat again. But it is unfortunate to mention that taxonomical knowledge on marine organisms is still inadequate and most of the species are undescribed. The taxonomical lack of knowledge has to be solved by upgrading technology. Further, marine-derived sources help to treat depression, and those compounds do not have any side effects, which merits highest deliberation for improvement of research and development.

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Chapter 14
Nanoceuticals as Theranostics Against Neurodegenerative Diseases

Prabhakar Mishra and Santosh Anand

Abstract Nanoceuticals, also referred to as nutraceuticals, are pharmacological molecules or natural supplements fabricated employing nanotechnology-related approaches. Recently, application of these nanoceuticals has been established as a novel paradigm shift helping in modulating the properties of potent compounds at the molecular level in terms of enhanced solubility, permeability, systemic availability, and with reduced adverse effects. These nanosized molecules are designed using various fabrication methods, namely nanocapsules, micelles, nanoemulsions, nanocochleates, nanoparticles, and nanocrystals for their target-oriented delivery. Owing to these benefits, nanotechnology finds a huge prospect in improvising safety as well as quality of human lives. Several studies have witnessed the advantages of nanoceuticals in health-promotion or disease-prevention attributes against numerous ailments like cancer, diabetes, cardiovascular, and neurodegenerative diseases. Although nanoceuticals cannot be considered as a replacement to pharmaceuticals, but can act as an alternate indispensable tool in the treatment and prevention of diseases. This chapter provides a systematic review of the application of nanoceuticals as a therapeutic or pharmacological intervention towards the management of neurodegenerative diseases.

Keywords Nanoceuticals · Nutraceuticals · Health · Neurodegenerative diseases

14.1 Introduction

Neurodegeneration is linked with the progressive damage of neuronal tissues resulting in irrecoverable loss of neuronal function and subsequent decline in motor activity and cognitive function (Uddin et al. 2020a). It is involved in various central nervous system (CNS) disorders, namely Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease,

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amyotrophic lateral sclerosis (ALS), and epilepsy, each of which is distinguished by pathological etiologies and clinical management (Rogers and Cahill 2020; Tanaka et al. 2020; Uddin et al. 2020b). The origin of neurodegenerative diseases (NDs) as a cluster of heterogeneous ailments has not been fully understood. However, enhanced oxidative stress, aggregation of peptides, chronic neuroinflammation, protease resistance misfolding have been regarded as general mechanisms of most NDs (Huang et al. 2019). Although aging by far has been considered as the chief risk factor for the prevalence of NDs, the underlying molecular mechanisms of age-associated brain alterations still remain unclear, especially the switching from normal healthy brain aging to pathological brain aging (Moreno-Garcia et al. 2018).

Owing to the augmented prevalence of NDs among the elderly population, it warrants effective therapeutic strategies (Hou et al. 2019; Huang et al. 2019). So far, a broad range of synthetic drugs for the prevention and treatment of NDs are in clinical use, but the outcomes remain unsatisfactory. The administrations of these existing drugs have been found to be associated with adverse side effects (Sharma et al. 2018; Sharifi-Rad et al. 2020). In addition, their exorbitant prices make them unaffordable by a vast majority of vulnerable population (Dehghani et al. 2017). To address these shortcomings of conventional drugs, the scientific communities in the recent years have been inclined towards the exploration of potential bioactive candidates from natural sources for the control and management of NDs.

Phytochemicals and its derivatized nutraceuticals are basically plant derived heterogeneous compounds. They are non-nutritive and possess various bio-beneficial properties, if utilized in proper manner (Amorati and Valgimigli 2018). Plants are used as the major source of phytochemical drugs and form the backbone of Ayurveda and traditional medicine (Mukherjee et al. 2017). Phytochemicals have been widely classified into phenolic, flavonoids, alkaloids, sulfur, and nitrogen containing compounds (Velu et al. 2018). Ancient medicinal systems of India, China, Babylonia, Greece, and Egypt have widely exploited phytochemicals in treatment of numerous diseases and disorders (Jamshidi-Kia et al. 2018). Unlike minerals and vitamins, phytochemicals have important roles in protecting cells from harmful effects of stress leading to various neurological disorders and neuroinflammation.

The current scenario of enormous burden linked with neurological diseases and disorders brings the urge for a transition of traditional to novel drug delivery strategies, which has mechanistic approach via targeting explicit molecular pathways towards mitigation of these ailments (Javed et al. 2019). This necessity of novel drug delivery brings the role of nanometric structures, which can serve as a vector for essential plant based/herbal drugs and other biomolecules (Mishra et al. 2018; Rodriguez-Nogales et al. 2018; Sharma et al. 2018; Pottoo et al. 2020). These nano-based drugs have superior bioavailability, protracted stay in the blood, and negligible side effects. They accomplish these activities by modifying intrinsic assets of drugs like drug release kinetics, solubility, diffusivity, immunogenicity, and bioavailability (Poovi and Damodharan 2018; Barkat et al. 2019). As per the nanotechnology, the particles attaining size lesser than 100 nm favor better permeability with high surface-to-volume ratio, distinguishably unlike its bulk counterpart (Alam et al. 2017).

The current chapter provides an illustration of the efficacious role of nanometric nutraceuticals and other phyto-derived molecules that can become potential therapeutics against various neurological disorders like Alzheimer's, Parkinson's, and other neuropathy disorders with greater specificity, target approachability, bioavailability, and safer to the host.

14.2 Pathophysiology of Neurodegenerative Diseases and Their Clinical Manifestations

NDs are the consequence of progressive decrement of neurons and axons in the CNS, resulting in cognition and motor dysfunction during the aging process. CNS inflammation and immune activation have major contribution towards the pathophysiology of NDs. The advancement in neuroprotective interventions has been always challenging due to the inadequacy of consistent and sensitive biomarkers and because of limited understanding of the disease pathogenesis (Fakhoury 2015; Marek et al. 2018). Figure 14.1 represents the various clinical interventions towards the treatment of NDs.

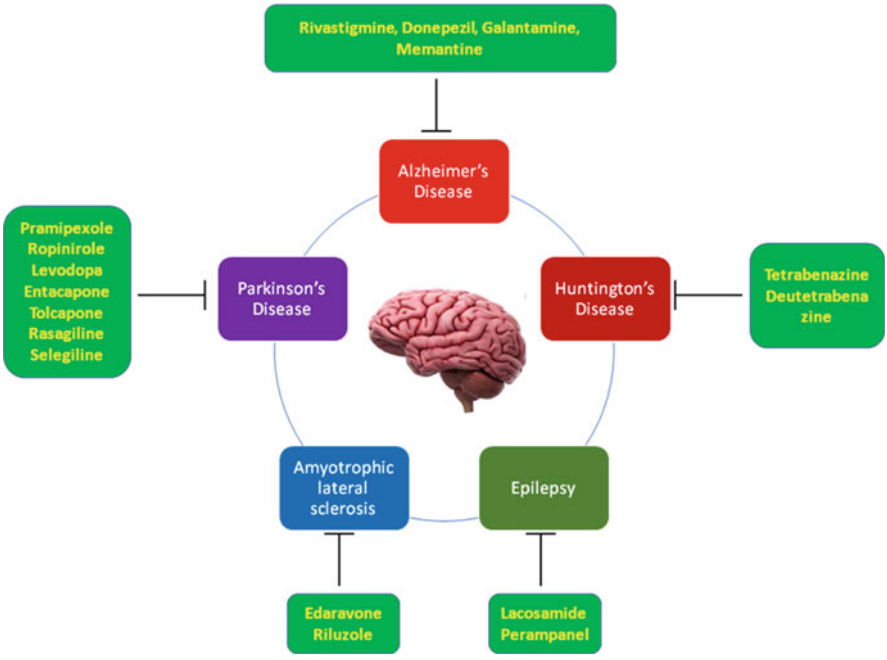

Fig. 14.1 Schematic representation of approved clinical candidates for the management of neurodegenerative diseases

14.2.1 Alzheimer's Disease (AD)

AD is reported as the most common ND accounting for >80% among the dementia cases globally in the elderly population. It leads to the progressive decline in motor, cognitive, and learning abilities. The prominent clinical hallmarks of AD include the accumulation of β-amyloid peptides and the development of neurofibrillary tangles because of the hyperphosphorylated Tau aggregation (Kumar et al. 2015; Dos Santos Picanco et al. 2018). Although these features have been reported extensively in postmortem AD brains and relevant in vitro and in vivo model systems, the complete understanding of AD pathogenesis is still in its infancy, predominantly in the early period of the ailment wherein the therapeutic interventions would really be most efficacious (Mufson et al. 2016). The advancements in imaging technologies and their diagnostic accuracy to understand the AD pathophysiology have provided avenues for deciphering the relationships between the two key regulatory proteins (β-amyloid and Tau) that get deposited gradually during the progression of the disease (Jagust 2018).

Owing to its increased prevalence, AD is presently one of the biggest healthcare concerns, especially in the developed countries. According to the existing hypotheses like cholinergic, amyloid cascade, mitochondrial cascade, dendritic, metabolic, neuroinflammation, and oxidative stress with regard to the origin of AD, several treatment strategies have been adopted in the recent years (Folch et al. 2016). Currently, cholinesterase inhibitors, namely rivastigmine, donepezil, and galantamine are clinically recommended for patients having mild-to-severe AD dementia. Additionally, memantine which is a dopamine agonist and *N*-methyl-D-aspartate receptor opponent has been approved for the strategic management of moderate-to-severe AD (Howard et al. 2012; Weller and Budson 2018).

14.2.2 Parkinson's Disease (PD)

Parkinson's disease also known as "shaking palsy" is a progressive, chronic neuropathology associated with motor and nonmotor attributes. The motor features of PD are characterized by the decrease in the number of striatal dopaminergic neurons, while the presence of nonmotor features is attributed to the loss of neurons in the non-dopaminergic sites. Cardinal motor PD symptoms include rigidity, rest tremor, and bradykinesia that are evident in the early phases of the ailment. PD has a remarkable clinical impact not only on the patients but also on the families and caretakers by its progressive deleterious consequences with respect to mobility and muscle coordination (DeMaagd and Philip 2015; Magrinelli et al. 2016; Schneider et al. 2017).

Accumulating evidence and understanding pertaining to PD etiopathogenesis has led to the development of potent neuroprotective approaches that when administered at the early stages may positively combat the disease progression. Currently, various

clinical candidates, namely pramipexole and ropinirole (dopamine agonists), entacapone and tolcapone (catechol-*O*-methyl-transferase inhibitors), rasagiline and selegiline (monoamine-oxidase type B inhibitors), and levodopa are routinely used for the clinical management of PD. Besides treating the pathological symptoms of PD, these molecules exhibit several side effects like dyskinesias, nausea, dizziness, vomiting, insomnia, hallucination, diarrhea, leg swelling, dry mouth, and abdominal pain (Stoker et al. 2018; Jankovic and Tan 2020).

14.2.3 Huntington's Disease (HD)

HD is a genetic autosomal dominant neurodegenerative ailment distinguished by progressive cognitive, behavioral, and motor decline (Dayalu and Albin 2015). It is a fatal disorder caused by extended cytosine-adenine-guanine trinucleotide repeats in the Huntingtin (HTT) gene. Although the association of HTT gene with HD has been discovered two decades ago, a complete understanding of the correlation of the gene with the progression of the disease is still in its infancy (Mattis and Svendsen 2017).

The clinical strategies towards HD undertaken currently are therefore aimed at reducing the HTT protein levels to slow down or stopping the disease related pathologies (Mestre 2019; Leavitt et al. 2020). In recent years, several lead candidates are under investigation for their safety, efficacy, and with reduced adverse effects in the ongoing clinical trials towards the management of HD. Tetrabenazine and deutetrabenazine (specific inhibitors of vesicular monoamine transporter) are the only FDA approved drugs so far for the treatment of chorea in HD patients (Richard and Frank 2019; Rodrigues and Wild 2020).

14.2.4 Amyotrophic Lateral Sclerosis (ALS)

ALS is a fatal, idiopathic neurological disorder characterized by motor neurons degeneration in the spinal cord and motor cortex and consequently by muscle deterioration (van Es et al. 2017; Hulisz 2018). Numerous studies have documented the linking of gene mutations to both familial and sporadic ALS, but the development of suitable therapeutic pharmacological intervention by various clinicians and researchers so far has not proven successful in mitigating ALS. The complications and diverseness in the pathophysiology of ALS, wherein irrespective of neurons, other cell types also play a significant role through non-cell autonomous effect predominantly worsens neuronal characteristics (Filipi et al. 2020).

Majority of the clinical candidates developed towards ALS management have failed to respond positively at phase III in larger cohorts. Up to now, only two drugs, edaravone and riluzole although with modest effects, have successfully cleared the clinical trials for the treatment of ALS (Jaiswal 2019; Hergesheimer et al. 2020).

14.2.5 Epilepsy

Epileptogenesis, a multifaceted process resulting in acquired epilepsy can be induced by diverse acute brain insults. It is characterized by various brain alterations like blood–brain barrier disruption, astrocyte dysfunction, neuroinflammation, neuronal loss, altered neuronal excitability, receptors and ion channels dysfunction, and gliosis (Klein et al. 2018). Regardless of the progress in understanding the underlying mechanisms of epileptogenesis, no approved treatment still exists either to prevent the progression or development of epilepsy in subjects at risk (Loscher 2020).

The mainstay of epilepsy management relies on antiseizure medications. Therapies adopted presently are directed towards epilepsy etiology and are reported to control seizures in two-thirds of the patients. Lacosamide and perampanel are emerging drugs in the treatment of tonic–clonic seizures in generalized epilepsy. However, major group of clinical candidates as antiseizure therapeutics are under clinical development targeting mainly gamma-aminobutyric acid, 5-hydroxytryptamine, T-type calcium, and potassium channels (Manford 2017; Steriade et al. 2020).

14.3 Phytoceuticals: Potent Therapeutics and Theranostics Towards Neurological Disorders

Phytoceuticals are also beneficial for the management of immune and hormonal responses. They can also stimulate the production of enzymes that help in several neurological processes and maintenance (Farooqui 2012). As plant compounds help fight against oxidative stress and inflammation, they also regulate angiogenesis, redox imbalance, and ionic homeostasis through controlled network signaling (Kapoor et al. 2019). Various factors such as age, genetic disposition, exposure to radiation, and protein processing can affect the development and appearance of neurodevelopmental disorders. These disorders lead to loss of synapse, ion homeostasis, and abnormalities in neurotransmission (Madabhushi et al. 2014). It is widely known that age-related changes in the physiological function of the brain and its metabolites are linked to various diseases and conditions. Table 14.1 describes the therapeutic efficacy of various phytoceuticals against NDs.

Several factors including age, unhealthy lifestyle, family history, and exposure to hazardous environmental factors result in induction of several neurological diseases and disorders (Dewhurst et al. 2013). In neurological illnesses, these mentioned causative agents contribute to aberrant protein modifications, which results in changes in proteins conformation, excess production of reactive oxygen species, development of neuroinflammation, and apoptosis (Ferraiuolo et al. 2011). The intervention of dietary naturally occurring phytochemicals exhibits their effects by curtailing, repairing, and reducing the injury caused by oxidative stress and

Table 14.1 List of phytoceuticals and their role as therapeutics against the NDs

Phytoceuticals	Plant source	Neurological disorders	References
Curcumin	*Curcuma longa*	Stroke	Kalani et al. (2015)
Resveratrol	*Vitis vinifera*	Alzheimer's disease	Sawda et al. (2017)
Baicalein	*Scutellaria baicalensis*	Brain ischemia	Liang et al. (2017)
Wogonin	*Scutellaria baicalensis*	Neural inflammation	Huynh et al. (2020)
Shogaol	*Zingiber officinale*	Dementia	Moon et al. (2014)
Trigonelline	*Trigonella foenum-graecum*	CNS injury	Priya et al. (2011)
Caffeine	*Coffea arabica* and *Coffea canephora*	Parkinson's disease	Negida et al. (2017)
Ginsenoside	*Panax ginseng*	Huntington's disease	Cho (2012)
Tanshinone	*Salvia miltiorrhiza*	Ischemia	Adams et al. (2006)
Picroside	*Picrorhiza kurroa*	Memory impairment	Kim et al. (2020)
Parthenolide	*Tanacetum parthenium*	Pediatric headache	Moscano et al. (2019)
Withanolide	*Withania somnifera*	Lateral sclerosis	Rao et al. (2012)
Acetylbetulinic	*Eucalyptus globulus*	Hypertension	Trabolsi et al. (2021)
Nuciferols	*Cocos nucifera*	BDNF stimulant	Lima et al. (2016)
Limonoids	*Azadirachta indica*	Parkinson's disease	Sandhir et al. (2021)
Sesamin	*Sesamum indicum*	Neuroprotection	Park et al. (2010)
β-Sitosterol	*Tripterygium wilfordi*	Multiple sclerosis	Li and Hao (2019)
Phlobatannin	*Baccopa monnieri*	Excitotoxicity	Kiani et al. (2020)
Bilobalide	*Ginkgo biloba*	Alzheimer's disease	Singh et al. (2019)
Quercetin 3-*O*-hexose coumaric ester	*Lycium barbarum*	Ocular hypertension	Chan et al. (2007)
Anthraquinone	*Justicia gendarussa*	Hypnotic disorders	Subramanian et al. (2014)
Picrinine	*Alstonia scholaris*	Alzheimer's disease	Bhowmik et al. (2015)
α-Humulene	*Bauhinia acuminate*	Brain dysfunction	Mondal et al. (2019)
Mimosine	*Mimosa pudica*	Alzheimer's disease	Duyu et al. (2020)
Piperine	*Piper longum*	Depression	Lee et al. (2005)

neuroinflammation resulting in neurohormetic response (Santoro et al. 2020). This response leads to the genes expression that helps the antioxidant enzymes regulation, BDNF complex, and protein chaperones (Son et al. 2008). Based on stimulation of stress-resistance genes and signal transduction network, it has been hypothesized that the use of phytochemicals and regular exercise helps towards onset of age-associated neurological risks (Farooqui 2012). While phytonutrients have nil impact on any factors like family history or age, gender, long-tenure consumption may help to mitigate the effects of an unhealthful lifestyle through delaying or reducing the inception of neurological risk and disorders. These procedures may improve one's health and quality of life as they get older (Son et al. 2008).

Through their capability to act together with the brain cells and their molecular biology for memory formation, phytoceuticals may be able to halt and partially repair age-related memory deterioration. These interfaces involve their ability to regulate growth factors in distinctive regions of brain regions towards upregulation of signaling cascades critical for regulating and enduring synaptic activities (Candore et al. 2010). The ability of phytochemicals to counter toxic production of free radicals, as well as the enzymatic regulation vital genes such as hemeoxygenase-1 and sirtuin related genes, that are linked to their ability to prevent neurodegenerative, oxidative stress-interceded neuronal diseases, and disorders (Calabrese et al. 2004). Phytochemicals modulate neural cell function by intermingling with a wide range of targets through cell-signaling machinery and various enzymatic pathways like iNOS and COX-2 (Spencer 2007).

Phytoceuticals supplementation of the diet is now the most effective strategy for extending the healthy life span and deferring the onset of chronic disorders linked neuronal system (Minor et al. 2010). Because most of these evidence-based studies are preclinical, more clinical trials are needed to reinforce this process and make it more effective. Because chronic neurodegenerative illnesses might take 40–55 years to appear, designing and organizing medications for clinical trials can be challenging (Graham and Sharp 2019). As previously noted, it is unknown what levels of phytoceuticals are required and for how long, as well as whether phytochemicals should be consumed in food or if supplements will suffice (Farooqui 2012). The evidence that phytochemicals are safe, multi-targeted, therapeutic, and cost-effective necessitates additional research into their application in chronic neurodegenerative disorders. Although the molecular mechanisms for many phytochemicals beneficial effects have yet to be discovered, it is clear from the above discussion that phytochemicals protect against oxidative stress and neuroinflammation by inhibiting oxidative/inflammatory stress signaling, increasing neuroprotective signaling, and inducing neurohormetic effects.

14.4 Nano-Derived Phytoceuticals: A Promising Aid Against Neurological Disorders

Nanotechnological developments provide various strategies towards material fabrication at nanometric enabling the properties of specificity and targeted delivery attainment. This requirement results in development of nanosized materials like

metals nanoparticles (NPs); polymeric NPs such as polymeric conjugated nanomaterials, polymer nano-encapsulates, micelles, etc. Other derivatized structures include inclusions and chelates and lipid-based nanocarriers (Hasnain et al. 2019; Barkat et al. 2019). Examples of the nanometric formulations are metal NPs and oxides of metal; nanostructured polymeric materials and lipid-based nanostructures like liposomes, solids-lipid nanoparticles (SLNs), nano-lipid carriers (NLCs), niosomes, ethosomes, etc. (Hasnain et al. 2019; Barkat et al. 2019). Consequently, these explicitly altered nanoparticles provided efficacious applications for loaded drugs to targeted site with bio-benign feature (Patel et al. 2012; Javed et al. 2019; Alam et al. 2017). The largest part of the drug delivery nanometric carriers investigated in latest years for neurological theranostics are centered to lipid-based or lipo-polymeric materials.

Polymeric nanocarriers and NPs and lipid-based nanocarriers are under the explicit focus of neuroscientists, as they attain the promising attributes and vast efficacy towards neurological diseases and disorders (Agarwal et al. 2017). Surface alterations of nanometric vehicles with proper targeting portion or covering with surfactants stimulate the collaboration of these nanometric particles to the cellular moiety of neurological system like endothelial cells which help in easy passage of nanometric carriers to the brain (Jimenez et al. 2014).

Hence, these unambiguously modulated nanosized carriers enable carriage of stacked medications to seek out towards at action site with enhanced kinetics and its therapeutic efficiency with negligible adverse complications (Patel et al. 2012; Alam et al. 2017; Javed et al. 2019). For example, the employment of polymers like resomer is one of the recent strategies towards the development of drug-loaded polymeric nanoparticle system, which provides add-on property to the nanoparticle to get avoided by the antagonistic process of phagocytic macrophages erstwhile to enter the cellular compartments. Therefore, these nanostructures like lipid-based nanoparticles and lipid nanocarriers provide a better biocompatibility of used materials; better porousness attaining to particle sizes ranging between 50 and 300 nm, enhanced stability and shelf life due to integration of combined stabilizers, amended bioavailability, and control and safe delivery of therapeutic agents (Alam et al. 2013; Shrestha et al. 2014; Naseri et al. 2015; Nabi et al. 2019).

SLNs have been established and are recognized as an alternative towards conventional colloidal drug delivery systems and carriers, i.e. liposomes, microemulsions, and nanoemulsion and microparticles (EzzatiNazhadDolatabadi and Omidi 2016; Khan et al. 2013). As an alternative to liquid lipid of emulsion systems, incorporation of solid lipids, for example, fatty acids (stearic acid or palmitic acid), triglycerides (tri-stearin), and waxes cetyl palmitate provides the constitution of the lipophilic core which enables better solubility of the drug compound and delivers the stability to systems through emulsifying the active molecule and nanometric level (i.e., 20–200 nm) range, solid lipid nanoparticle systems. Henceforth the SLNs are being contemplated as current generation innovative lipid drug delivery agents.

Despite efficacy and stability of SLNs compared to liquid state lipid-based formulations such as nanoemulsion, the SLNs encounter challenge with respect to

proper gelation time, competence towards drug-loading feature, greater probability of drug outflow during loading as well other unsought penalties such as change in the state of the immobilized drugs (Uprit et al. 2013). Therefore, to enhance the effectiveness and benefits mutually, these colloidal suspensions should have a balanced methodology to adopt and overwhelm these shortcomings of colloidal suspension of these lipid-based nano-formulations.

The matrix utilized for the nano-lipid carrier formulations allows superior load of drugs as well as starts demonstrating characteristics of both SLNs and liquid emulsions type of delivery techniques. Based upon the formulation methodologies, NLCs are categorized into (1) Fallible type NLC, (2) amorphous form, and (3) multiple type (Jaiswal et al. 2016). Therefore, these NLCs are second-generation lipid-constituting novel medicine and drug delivery systems with enhanced biocompatibility, greater stability, higher drug-loading capacity, and extensive interaction time with the target site when compared to solid lipid nano-formulations (Muller et al. 2002; Kumbhar and Pokharkar 2013; Saupe et al. 2005; Li et al. 2010).

Even though both SLNs and NLCs are advantageous towards improving the solubility of pharmacological entities with targeted release and delivery in the brain further studies are warranted to validate their usage as a treatment strategy against various neurological diseases and disorders. NLCs are being recent formulations which tend to provide add on support to the novel drugs and herbal formulations to be delivered to the specific site of action in the brain with maximum efficacy and negligible side effects. Nanometric formulations of eco-friendly and biocompatible natural polymers can load lipophilic and lipophobic neuro-pharmaceutical agents in either solid or liquid state and protect them from biochemical hazards complications such as denaturation and degradations (Rahman et al. 2019). Nano-formulations, for neuro-therapeutic drug conveyance, entailing of polymeric or lipid ingredients offer exclusive benefits like assorted size distribution and structural characterization, surface inflection by targeting medieties and surfactants, abundant pathways of transport, and impetuses subtle drug release behaviors (Rassu et al. 2017). Table 14.2 describes the various forms of nanoformulation based mechanistic approaches which enable the nanoformulation to become superior drug delivery compounds.

14.5 Mechanistic Understanding of Nanoceuticals Against Neurological Disorders

Among various therapeutic approaches against neurological disorders, the novel treatment strategies focusing on the role of nanotechnology as nanoceuticals provides a latent beneficial agent, which has a proficiency to curb the pathophysiology or indulgence the neurological disorders and brain related diseases. These novel nanostrategies can become a futuristic medication which will have higher potency and in nontoxic way, due to the encumbering action of biological barriers such as

Table 14.2 Nano-formulations, their merits and mechanism/s of action against the NDs

Nano-formulations	Merits	Mechanism/s	References
Nanoemulsion	Physiochemical, morphological, and surface modification properties	Adsorptive mediated endocytosis	Jiang and Gao (2017)
Polymeric NPs	Physiochemical, morphological, and surface modification properties	Receptor mediated endocytosis, carrier mediated transport	Cruz et al. (2016), Cano et al. (2018), Saucier-Sawyer et al. (2015)
Liposomes	Higher shelf life, BBB permeation capability, multi-targeting property	Receptor mediated endocytosis, carrier mediated transport	Edelmann and Maegawa (2000)
Solid lipid nanoparticles	Ease to produce at large scale, BBB permeation capability, multi-targeting property	Receptor mediated endocytosis, carrier mediated transport	Graverini et al. (2018)
Micelles	Ease to produce at large scale, BBB permeation capability, multi-targeting property	Adsorptive mediated endocytosis, carrier mediated transport	Yang et al. (2020)
Nanogel	Biocompatible. BBB permeation capability, multi-targeting property	Adsorptive mediated endocytosis	Cruz et al. (2016), Wadajkar et al. (2017)
Carbon nanoparticles	Photothermal properties, hollow core, good drug delivery tool	Receptor mediated endocytosis, carrier mediated transport	Kuang et al. (2013), Koffie et al. (2011)

blood–brain barrier (BBB). These lipid-derived nanoceuticals have potential of incapacitating the bio-chemicals barriers and defending drug from efflux to endorse the optimal therapeutic drug concentration sections of brain like parenchyma tissues (Sun et al. 2017). Nanometric vector for the drugs and phytochemicals are the most extensively premeditated delivery vehicles for BBB translocation with the competence of exploiting essential biotic molecules, carriers, and receptor mechanisms of the brain. In this current situation, highly efficient, BBB porous, and potent chemotherapeutical agents distributed via innovative nanometric system are instantly demanded with no fringe toxicity and bio-benign profile (Cruz et al. 2016).

14.6 Conclusion

The neurological ailments affect people globally. The currently applicated therapeutics and theranostics are symptomatic and often the drug delivery is constrained by a specific group of layers of endothelial cell. In current years, developments in nanotechnology-based medicine study have directed to treatments that target central nervous system pathobiology through changing the signaling mechanisms. Often such connections are constrained by inadequate concentrations of medications attaining to neuronal tissues and/or inadequate welling time of drug/s with the

receptor of the respective cell. Hence, nano-formulations like liposomes, SLNs NLCs nanoemulsion, etc. have arisen to overcome these challenges by exploiting the biological transport mechanisms transversely to the blood–brain barrier, such as drug-loaded lipid nanoparticles and nanoemulsion results in adsorption of apolipoproteins, completing the circulation and are taken up by endothelial cells through receptor facilitated endocytosis and subsequently targeting the drugs at specific site. This phenomenon displayed by these polymeric and lipid-based nanoparticles conveys selectivity, target specificity, and bio-benign feature, making these nanoceuticals to be futuristic medicine to combat the problem of neuro-disorders.

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Chapter 15
Role of Antioxidant Nutraceuticals in Neurodegenerative Diseases

Rajadurai Murugan, Anand Paramasivam, and Lokesh Adhappa Chandrashekar

Abstract Neurodegenerative diseases are characterized by progressive dysfunction and death of neuron. Neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, etc., are diverse in their pathophysiology—with some causing memory and cognitive impairment and others affecting person's ability. Free radicals are considered as a major causative factor for neurodegenerative disease. Nutraceuticals are derived from natural sources that are purported to provide additional health benefits alone with basic nutritional value. Antioxidant nutraceuticals possess several pharmacological activities including neuroprotective action. This chapter focused on the neuroprotective role of antioxidant nutraceuticals and their health benefits.

Keywords Nutraceuticals · Antioxidants · Multiple sclerosis · Free radicals

15.1 Introduction

Neurodegenerative diseases (NDD) are considered as a heterogeneous group of disorders, which is characterized by progressive degeneration of the structure and function of the central nervous system (CNS) or peripheral nervous system. They are various in their pathophysiology, some of them cause memory and cognitive defects, whereas the others affect a person's ability to move, speak, breathe, etc. (Abeliovich

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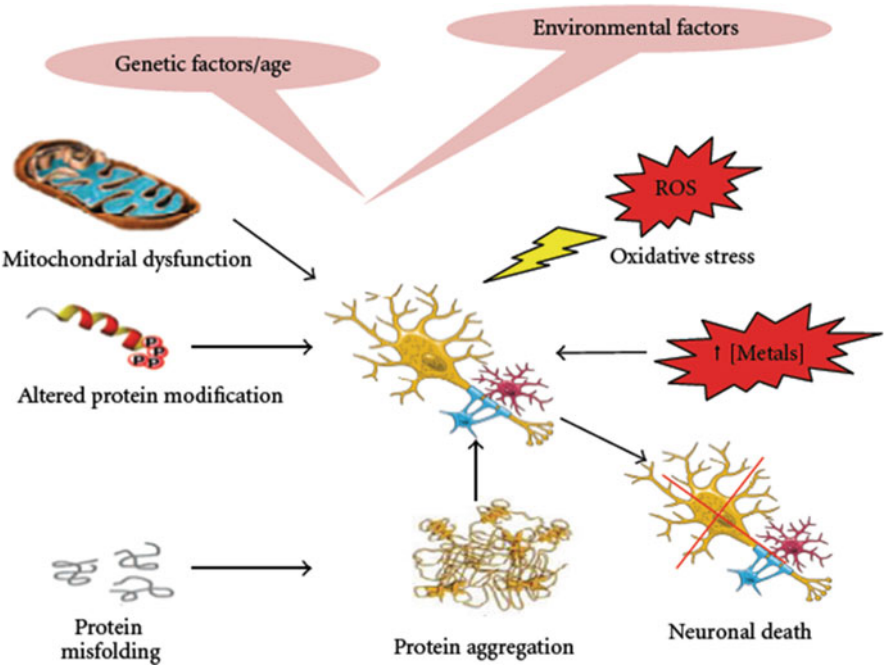


Fig. 15.1 Different factors associated with neurodegeneration

and Gitler 2016; Canter et al. 2016; Taylor et al. 2016; Wyss 2016). NDD represent a major threat to human health including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's diseases (HD) and amyotrophic lateral sclerosis (ALS), etc., all the above NDD make up a cluster of pathologies categorized by distinct etiologies with several morphological as well as pathophysiological features (Liu et al. 2017).

Neurodegenerative diseases arise due to genetic mutations and/or environment factors, which are intensely associated with increasing age (Sheikh et al. 2013). Reason for the progression of NDD by multifactorial circumstances such as (a) abnormal protein dynamics with deficiency in functional protein degradation and aggregation, (b) oxidative stress (OS) and the formation free radical (FR), (c) diminished mitochondrial dysfunction and overall cellular metabolism, (d) toxic metals and pesticides exposure (Fig. 15.1) (Sheikh et al. 2013). Cellular proteins must adopt and must maintain their 3D conformations, to be functionally and biochemically active. Just an improper or partial folding or misfolding is responsible for protein to become functionally inactive, which may lead to the protein as a cellular toxic one. Misfolding of protein followed by self-assembly and successive deposition and aggregation of proteins observed in NDD patients brain (Dobson 2003; Hartl and Hartl 2009).

In all the NDD, one or more lipid peroxidation (LP) markers of oxidative stress (OS), demonstrated as oxidation of proteins, reactive oxygen species (ROS)

generation, a DNA oxidation, have been described (Browne et al. 1999; Butterfield and Kanski 2001). Henceforth, one of the major therapeutic strategies in NDD has been to use approved antioxidants to determine if amelioration of signs and symptoms occurs. This review focused to describe the role as well as the recent developments of antioxidant nutraceuticals for the treatment of NDD (Butterfield and Kanski 2001).

15.1.1 Brain: The Target Organ

The important organ of our body, the one can be judged based on the brain, which is particularly susceptible to oxidative damage by ROS/reactive nitrogen species (RNS), because of the high quantity of oxygen utilization, as well as presence of high amount of oxidizable polyunsaturated fatty acid (PUFA) and of redox-active transition metal ions (Casetta et al. 2005). Consumption of antioxidant nutraceuticals has been proposed and considered as another form of management and treatment of age-related disorders. It is recognized well that the increase OS during aging can be considered as an important age-dependent factor for making the brain more susceptible to several NDD (Casetta et al. 2005).

15.1.2 Developmental Stages of Neurodegenerative Diseases (NDDs)

This section in the review describes three development stages and their symptoms that appear at different stages of NDD.

15.1.2.1 Retrogenesis

The commencement of NDDs is the defective functioning of the cholinergic system in the basal forebrain that promotes to the entorhinal cortex (EC) and the Hippocampus that are responsible for short-term and long-term memory. Usually, this kind of transform in the brain starts 10–20 years in advance and the first observable symptom of NDDs is forgetfulness or short-term memory problems (Jellinger 2009; Fadaka et al. 2019). This stage is connected with the diagnosis of NDDs in patients which include confusion among the familiar places, loss of decision-making power, misplacing of things, mood and personality variations, childish actions in working place, anxiety, and loss of spontaneity and sense of initiatives (Waring and Rosenberg 2008).

15.1.2.2 Cognitive Dysfunction

There is an association between NDD and toxic proteins. These toxic proteins play a critical role in the development of NDDs, leading to degeneration of neurons and cognitive dysfunction, AD affects EC part of brain. It has been proved that, if any trouble between these two regions, that disrupts the circuit and leading to memory disorder and memory damage (Sierpina and Kreitzer 2012).

15.1.2.3 Gait Abnormality

Forecasting the disruption in gait activity indicates a disorder in cognitive functions. The term "Last-in-First-out" refers to the phenomenon in which the neural circuits mature late in the developmental life cycle, which are more susceptible to NDD, which will help in early diagnosis of NDD (Scherder et al. 2011).

15.2 Nutraceuticals

The term "Nutraceutical" was coined from "Nutrition" and "Pharmaceutical." A nutraceutial is defind as "a food (or a part of food) that provides medical or health benefits, including the prevention and or treatment of a disease" (Padmavathi 2018). The antioxidant phytochemical works, any one of the following ways: Act as substrate for biochemical reactions, used as cofactors of enzymatic reactions, inhibits some enzymatic reactions, act as an absorbent, that bind undesirable constituent and helps to eliminate from the intestine, helps to enhance the absorption and/or stability of essential nutrients, support for the selective growth of beneficial bacteria, used as fermentation substrate for beneficial bacteria, selectively inhibits the growth of harmful intestinal bacteria, helps to scavengers of reactive oxygen species (ROS) or toxic chemicals, act as ligands (agonize or antagonize) for cell surface or intracellular receptors(Padmavathi 2018). Nutraceuticals are categorized based on sources, mechanism of action, chemical nature. They are categorized as: (1) Dietary fiber. (2) Probiotics. (3) Prebiotics. (4) Polyunsaturated fatty acids (PUFA). (5) Anti-oxidants. (6) Polyphenols (Skylar et al. 2018).

15.3 Classification

To understand the applications, the nutraceuticals are needed to be classified depending on their usage. They are: *Traditional nutraceuticals:* This category of nutraceutical does not undergo manual changes, the components are considered as natural and having some potential, which provide health benefits, e.g., lycopene, a

constituent of tomatoes (Ruchi et al. 2017). *Nontraditional nutraceuticals:* Nutritional content can be enhanced by the addition of nutrients or dietary components to improve the quality of nutrition, e.g., Beta carotene enriched rice (Sapkale et al. 2012). *Fortified nutraceuticals:* Fortification of food constituents by micronutrients (essential trace elements and vitamins) addition to enhance the effectiveness and nutritional value, e.g., milk fortified with cholecalciferol (Casey et al. 2010; Singh and Sinha 2012). *Recombinant nutraceuticals:* Genetic engineering used in the production of energy providing foods such as yoghurt and cheese or used for the extraction of bioactive components by fermentation technology or by enzymatic method, e.g., genetically modified (gold kiwifruit) fruit for high level of ascorbate, carotenoids, and lutein content (Beck et al. 2011; Singh and Sinha 2012). *Phytochemicals:* Plant chemical constituents with distinct biological action, these active constituents exert their action on metabolism and biochemical reactions, thus provide health benefits (Singh et al. 2012). *Herbals:* Plant products and/or any part of the plant such as dried leaf, fruit, stem, seeds, roots, or concentrated extract is considered as herbs. These herbs have various pharmacological properties associated with the treatment and prevention of several diseases (Singh et al. 2012).

It is not possible to discuss the pharmacological role and neuroprotective action of all the nutraceuticals. Hence, we have chosen to describe the role of only polyphenolic compounds in this review. The details are given in Table 15.1.

15.4 Advantages of Nutraceuticals

Due to the following reasons, people are moving towards nutraceutical products nowadays. They are listed as follows: (a) Concerned about healthcare costs, (b). disappointed with pharmaceutical agents in promoting health, (c). highly processed food supply, coming from agriculture land grown with excessive fertilizers, pesticides, herbicides, and often genetically modified seeds, lacks sufficient nutrients necessary for optimum Health, (d). people believing more in prevention than a cure, (e). chronic diseases have found no solution in allopathic medicines, (f). economically challenged patients (Shahidi 2012).

15.5 Free Radicals

Free radicals (FR) are having one or more unpaired electrons, which are highly active with the neighboring molecules, which have been implicated in the pathogenesis of NDD. FR damage and defective mitochondrial oxidative phosphorylation are more common in PD than control. Neuronal tissue is particularly sensitive to oxidative stress, due to high content of PUFA, high oxygen consumption, and weak antioxidant defense (Casetta et al. 2005). Imbalance in the levels of prooxidant and antioxidant in CNS results in the production of numerous harmful toxic ROS, which

Table 15.1 Polyphenolic compounds used in nutraceuticals and their biologic effects (Jain and Ramawat 2013)

Active polyphenolic compounds	Source	Biologic effect
Quercetin	Citrus fruits, apples, onions, parsley, tea, and red wine	Potent antioxidant, anti-inflammatory, anti-allergic, anticancer, inhibits mitogen activated protein (MAP) kinase in human epidermal carcinoma cells, inhibits tumor growth
Ellagic acid	Pomegranate, raspberries, cranberries, *Terminalia chebula* fruit, pecans, and walnuts	Strengthens the immune system, anticancer, induces apoptosis of cancer cells, and suppresses angiogenesis, prevents heart disease and liver fibrosis, promotes wound healing, prevents the binding of carcinogens to DNA
Luteolin	Thyme, peppermint, basil herb, celery, and artichoke	Possesses free-radical scavenging activity, protects human single-cell DNA from oxidative attack
Curcumin	Turmeric roots	Suppresses the production of cytokines such as IFN-g, interleukins, and TNF; inhibits the inducible nitric oxide synthase (iNOS)
Resveratrol	Grapes, raisins, berries, peanuts	Anti-aging, anti-carcinogenic, anti-inflammatory, and antioxidant properties; improves insulin sensitivity in type 2 diabetic patients
Apigenin	Parsley, thyme, peppermint, red wine, and tomato sauce	Antidepressant, anticancer, antitumor, anti-inflammatory
Ferulic acid	Rice, wheat, oats, coffee, apple, peanut, orange, and pineapple	Provides neuroprotection, against oxidative stress-related apoptosis by inhibiting ICAM-1 mRNA expression after cerebral ischemia, hypotension, and hypoglycemia
Caffeic acid	White grapes, white wine, olives, spinach, cabbage, asparagus, and coffee	Exerts anti-depressive and anxiolytic-like effects through indirect modulation of the alpha1A-adrenoceptor system
Catechins	Tea, chocolate, red wine, apples, and berries	Prevents human plasma oxidation by delaying the consumption of endogenous lipid-soluble antioxidants and inhibiting lipid oxidation

includes both radical and non-radical species, that usually participate in the initiation and/or propagation of FR chain reactions. ROS are generally classified as FR (superoxide radical, hydroxyl radical, hydroperoxy radical, alkoxyl and peroxyl radicals) and non-radicals (hydrogen peroxide, nitric oxide, and singlet oxygen). In NDD, oxidative damage has been found in every class of biological molecules within neurons, covering from lipids to DNA including proteins (Mc Lennan and Esposti 2000).

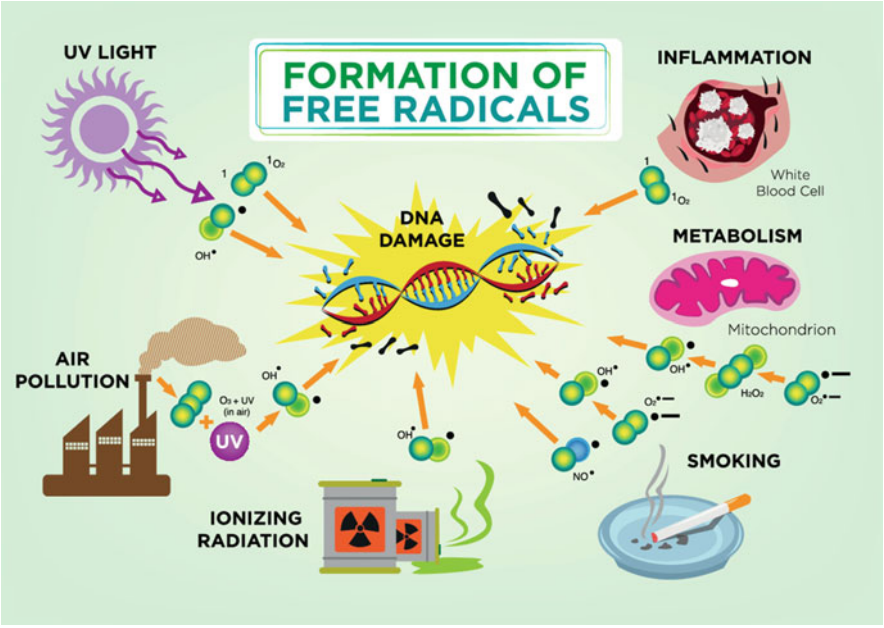


Fig. 15.2 Sources of free radicals

Apart from exposure of external factors like UV rays, X-ray, air pollution, ionizing radiation and toxins, internally inflammation, metabolism, mitochondrial dysfunction, etc., are being the major reasons for FR formation. There is a relation between ROS production and induction of necrosis or apoptosis and the pathogenesis of NDD, also evidences showed that neuronal death in PD occurs primarily by apoptotic mechanisms (Vajda 2002) (Fig. 15.2).

15.6 Oxidative Stress and NDD

Oxidative stress occurs, when ROS gets accumulated in the cell, either from excessive production or insufficient neutralization, causing damage to biomolecules like DNA, lipids, and proteins (Rajadurai and Stanely Mainzen Prince 2007b, c). Brain contains high level of PUFA, which are more susceptible to peroxidation that consumes a maximum amount of total oxygen (20%) consumption for its relatively small weight (2%). Brain is lower in antioxidant activity in comparison with other tissues, e.g., liver (10%). Presence of higher concentration of oxidizable PUFA, highly susceptible to lipid peroxidation (Floyd and Hensley 2002; Valko et al. 2007). Moreover, the brain energy metabolism completely depends on glucose utilization and its complete oxidation in the mitochondrial region via the tricarboxylic acid (TCA) cycle and electron transport chain (ETC). Around 95–98% of ROS are

produced by the ETC during aerobic metabolism (Grivennikova and Vinogradov 2006; Vaishnavi et al. 2010). Mitochondrial complexes (I and III) are principal sites for the production of FR, and damaged complexes (II and IV) also generate ROS under pathological conditions (Albarracin et al. 2012; Muller et al. 2004).

15.7 Mitochondrial Damage and NDD

Mitochondria is an important cellular organelle and powerhouses of the cell; they are the predominant source and target for ROS and have the essential function of generating ATP. Cells produce ATP through the oxidative phosphorylation via ETC (Md. Torequl Islama 2017). The accidental leakage of electrons and their actions with molecular oxygen mainly contributes in the production of ROS. Besides, production of ROS in mitochondria subsequently targets several components of the ETC (complexes I and III), resulting in boosted ROS generation, severe ATP depletion, and cell death (Castro et al. 2012; Wei et al. 2001).

During ETC in mitochondria, electrons are captured by oxygen to produce superoxide radicals (O^{-2}) further converted into hydrogen peroxide by the action of antioxidant enzyme Mn-superoxide dismutase (SOD). Also, hydrogen peroxide can be broken down by glutathione peroxidase (GPx). Inhibition of enzymes in ETC causes increased ROS, which decreases loss of ATP, alters mitochondrial membrane potential, energy collapse, and subsequent cell death (Lee et al. 2012; Nicolson 2014). Mitochondrial dysfunction is also responsible for the dysregulation calcium levels, membrane depolarization, and impairment of mitochondrial functions, which have been recognized as common feature of most of the NDD (Fadaka et al. 2019).

Along with mitochondrial calcium dysregulation and higher levels of ROS, mitochondrial DNA (mtDNA) mutation, and diminished mitochondrial respiration have been reported in various NDD (Meraz-Rios et al. 2014; Sochocka et al. 2013). Calcium homeostasis are interrupted by the hyperactive action of *N*-methyl-D-aspartate (NMDA) receptors. These hyper activation increases Ca^{2+} concentration, which induces the mitochondrial transition pore (MTP) to open. This event leads to osmotic swelling and alteration in the outer mitochondrial membrane. MTP open permits the release of pro-apoptotic proteins, like cytochrome c and apoptosis inducing factor (in the cytoplasmic region), which activates the apoptotic cascade (Zlokovic 2014) (Fig. 15.3).

15.8 Antioxidants

Our mother nature have gifted with adequate protective mechanism against harmful effects of FR. Antioxidants are substances that neutralize free radicals or their actions and can act at different stages of lipid peroxidation (Halliwell and Gutteridge 1989). FR scavenging enzymes such as SOD, catalase, GPx, and glutathione

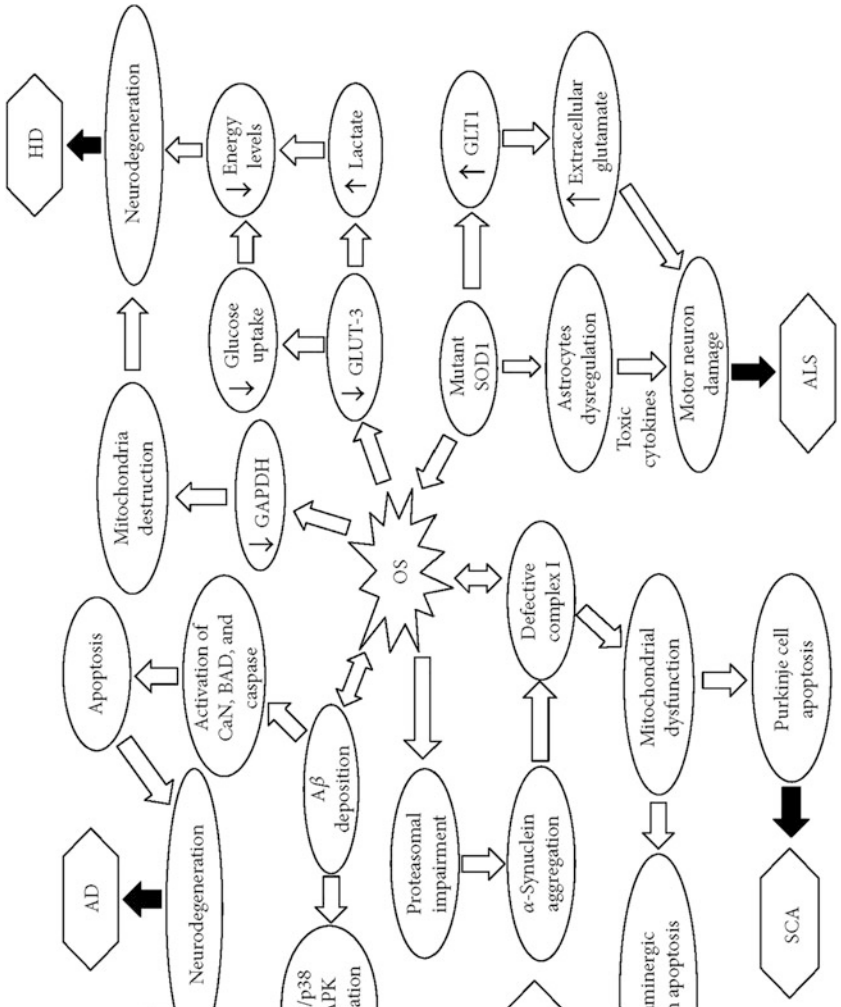
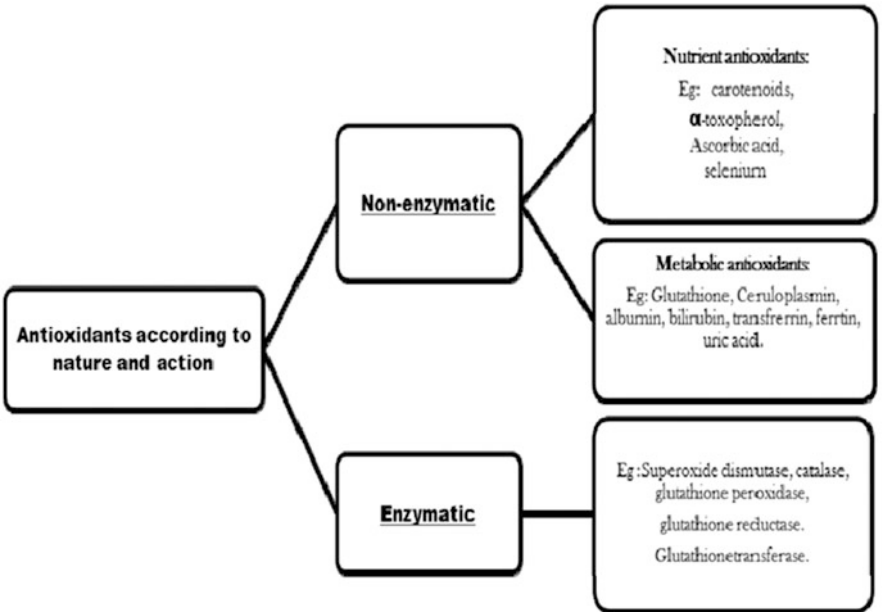


Fig. 15.3 Schematic illustrating the key roles of OS in the development of AD, HD, PD, ALS, and SCA. *AD* Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *Aβ* amyloid beta, *BAD* Bcl-2-associated death promoter, *CaN* calcineurin, *GAPDH* glyceraldehyde-3-phosphate dehydrogenase, *HD* Huntington's disease, *JNK* c-Jun N-terminal kinase, *MAPK* mitogen-activated protein kinase, *NFT* neurofibrillary tangle, *OS* oxidative stress, *PD* Parkinson's disease, *SCA* spinocerebellar ataxia, *SOD* superoxide dismutase. (Adopted from Liu et al. 2017)

S-transferase (GST) are the first line of cellular defense against oxidative injury. The non-enzymatic antioxidants and other small molecules with antioxidant property include GSH, ascorbic acid (vitamin C), and alpha-tocopherol (vitamin E) (Yadav et al. 2016). Antioxidant neutralizes FR directly or indirectly, equilibrium between these antioxidant enzymes is an important event to neutralize OS in intracellular organelles (Rajadurai and Stanely Mainzen Prince 2006a).

A dietary antioxidant significantly decreases the adverse effects of ROS, RNS, or both on normal physiological function in human (Rajadurai and Stanely Mainzen Prince 2006a). Plant-based antioxidant especially that can target mitochondria will be a perfect treatment for NDD. Numerous studies are in progress most especially, energy production, scavenging ROS, and in the prevention of oxidative damage (Castro et al. 2012). It is also reported that treatment with antioxidants has the capacity to prevent or slow down disease progression in NDDs (Ghosh et al. 2011).



15.9 Treatment for NDD

There are several therapies to control the NDD including gene transfer therapy, stem cell therapy, nanotechnology based treatment, and multitarget directed ligands that have been developed as encouraging new therapies for the treatment of NDD (Moosmann and Bhel 2002). Even though the available therapies are effective in controlling NDD, due to the high cost it is not possible for everyone to afford.

Whereas antioxidant nutraceuticals are proven as an effective remedy for the treatment of NDD and minimum cost. It is not possible to describe the role of antioxidant nutraceuticals for all the NDD; however, some selected NDD are discussed in this review. Whenever people consume food stuffs, they not only focused on the supply of nutrients, but also concerned about the health benefit out of it. Nowadays along with the balanced diet, people started to give importance for nutraceuticals based diet. The purpose is along with supply of energy, it also provides health benefits, particularly in the prevention/and/or treatment of metabolic disorders. It is also evident that consumption of pure antioxidant too not possible, because of less availability, high cost, and scarcity in the market. So, along with our life style modification, dietary changes with rich antioxidants play a crucial role in controlling NDD.

15.10 AD and Nutraceuticals Antioxidants

Along with several other risk factors, age is one of the main and important risk factors for AD. After the age of 65, the frequency rate of AD gets double every 5 years. An estimated amount of 1300 new cases are identified annually, per 100,000 people over the age of 65 (Shelat et al. 2008). AD is the most predominant NDD, which is categorized by the progressive decline of behavior, cognition, and functionality, which considerably impairs day-to-day activities including difficulty in remembering things, inability to solve problems, misplacing the valuable things, mood and personality changes, poor decision-making capacity, struggling with conversations, etc. (Zuo et al. 2015).

The pathophysiology of AD is primarily associated with the extracellular deposition of amyloid beta (Aβ) (peptide derived from amyloid precursor protein, which is cleaved by beta secretase to yield Aβ) plaques and intracellular accumulation of tau neurofibrillary tangles (NFT) (Butterfield 2014). Aβ plaques have been reported to deplete the intracellular Ca^{2+} storage in endoplasmic reticulum (ER), where Ca^{2+} storage occurs generally, resulting in cytosolic Ca^{2+} overload. Due to increased cytosolic Ca^{2+} concentration, with subsequent decrease in the levels of endogenous GSH, ROS get overaccumulated inside the cells (Ferreiro et al. 2008). ROS-induced OS is an important feature in pathogenesis of AD as ROS overproduction is supposed to play a critical role in Aβ accumulation and deposition in AD (Bonda et al. 2010).

Additional important role of Aβ deposition, which results in microglial activation. Extended activation of microglia promotes the release of pro-inflammatory cytokines molecules, thus commencing a pro-inflammatory cascade reactions, and contributing damage and loss of neurons (Wang et al. 2015). Also, elevated levels of ROS responsible to stimulate the pro-inflammatory gene transcription and release cytokines, i.e., tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, 6, and the chemokines lead to neuroinflammatory processes (Liu et al. 2017).

AD treatments generally rely on combinations of active constituents, which contain neuroprotective, anti-inflammatory, and antioxidant properties. According to epidemiological data, the Mediterranean diet (rich in antioxidants) is effective in the prevention of AD (Dumont and Beal 2011). Medications (e.g., rutin, resveratrol, and vitamin E) that are capable of targeting ROS mediated chain reactions like JNK and NF-κB have been reported to produce positive results both in vitro and in vivo against NDD. It also suggests that dietary habits, with intake of vitamin rich foods, play an important role in brain aging, impairment of cognitive function, and AD development (Martin et al. 2002; Youdim and Joseph 2001). It is possible to control NDD by altering the dietary consumption, when the diet is rich in antioxidant nutraceuticals, which shows beneficial effects on controlling NDD. Important features such as bioavailability (digestion, absorption, distribution, transport, and retention in the targeted area) and the reaction kinetics must be considered while using antioxidants (Dumont and Beal 2011).

Curcumin is a chief polyphenol derived from turmeric, widely used for the treatment of AD. It is a well-known antioxidant and reported to possess anticancer, anti-viral, anti-bacterial, hepatoprotective, neuroprotective, nephroprotective, and cardioprotective properties (Menon and Sudheer 2007). Both in vivo and in vitro investigation describe the mechanisms of action of curcumin, where curcumin modifies AD pathology (Goozee et al. 2016; Tang and Taghibiglou 2017). The usage of curcumin has same as therapeutic drug are characterized by its pharmacokinetics profile and the low bioavailability after oral administration (Serafini et al. 2017). Tang and Taghibiglou (2017) have been reported that curcumin has the capacity to inhibit the formation as well as promotes amyloid-β plaques disaggregation and reduces the tau protein hyperphosphorylation, then improves its clearance, binds with copper, lowers cholesterol levels, modifies microglial activity, inhibits the activity of acetylcholinesterase (mediates the insulin signaling pathway).

Rutin (quercetin-3-*O*-rutinoside) is a naturally occurring flavonoid glycoside, due to the ability to cross the blood–brain barrier (rutin and/or its metabolites), it has also been shown to modify the cognitive and several behavioral symptoms of NDD. Therapeutic potential rutin for AD is evaluated through various cellular and molecular targets of NDD. Among the targets, the effect on amyloid beta (Aβ) protein processing, aggregation and action; modification of the pro-oxidant-antioxidant balance, which is associated with loss or damage of neurons; removing the inflammatory component of neurodegeneration, etc. were predominant (Habtemariam 2016). Apart from curcumin and rutin, several polyphenols including punicalagin, resveratrol, macranthoin G, salidroside, pterostilbene, genistein, lycopene, and gallic acid were reported for the treatment of AD. Numerous alkaloids such as berberine, glaucocalyxin B, oridonin, tetrandrine, galantamine, anatabine have been reported to show anti-inflammatory effects in in vitro and in vivo AD models. Natural products from plants sources are considered as interesting candidates for the treatment of AD (Seo et al. 2018).

15.11 PD and Nutraceuticals Antioxidants

PD is the second most predominant NDD, characterized by dopaminergic neuron (DN) loss in the substantia nigra pars compacta of the brain (play a significant role in reward and movement) (Qin et al. 2017). About 1–2% of the entire population over 65 are affected by PD and the rate of incident increases up to 4% in individuals above the age of 85 years (Bekris et al. 2010). PD incident usually higher in masculine compared to feminine. The lower effect in females could be due to elevated levels of estrogen (Klepac et al. 2007). A lot of evidences from post-mortem reports demonstrated that numerous processes are accompanying with apoptosis or necrosis in PD, including accumulation of misfolded proteins, OS, mitochondrial dysfunction, neuroinflammation, and excitotoxicity (Ciancarelli et al. 2015). Production of these FR is provoked in PD due to degradation of dopamine, dysfunction of mitochondrial region, neuroinflammation, aging, GSH depletion, and higher levels of iron or Ca_{2+}contents (Meiser et al. 2013). Furthermore, along with the above internal factors, ROS accumulation is aggravated in PD subjects, when individuals are exposed to environmental related factors such as pesticides, neurotoxins, etc. (Gangemi et al. 2016).

Excessive ROS/RNS with a downregulated expression of cellular antioxidant (both enzymatic and non-enzymatic) such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione (GSH) causes selective loss of neurons in the PD. In this context, dopamine (DA) neurons are more susceptible to ROS/RNS. Currently, nine nuclear genes have been recognized in PD patients, like *α-synuclein, parkin, phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1),* etc., There are reports showing that *PINK1* protects the cell against OS induced apoptosis by suppressing the release of Cyt-*c* from mitochondria, whereas mutation in *parkin* alters the mitochondrial quality control (Liu et al. 2017).

Fisetin has been reported to enhance learning and memory capacity, decreases neuronal cell death, and suppresses OS. Nabavi et al. (2016) addressed the beneficial effects of fisetin on NDD, especially AD and PD. Additionally, they provided information regarding the chemistry, sources, bioavailability, and clinical impacts of fisetin, as a new approach to the treatment of AD and PD. Resveratrol is a natural polyphenol that possesses multiple biological activities, which exerts neuroprotective effects on several NDD. Resveratrol treatment improved motor activity and cognitive deficits in A53T α-synuclein mouse model of PD. The beneficial effects of resveratrol against PD have been reported by inhibiting α-synuclein aggregation and cytotoxicity and lowering the levels of total α-synuclein, oligomers, reducing neuroinflammation and OS (Zhang et al. 2018).

Leem et al. (2014) have demonstrated that naringin could increase the level of GDNF (expand) in DA (expand) neurons, contributing to its neuroprotective properties in the MPP(+) rat model of PD, with activation of mammalian target of rapamycin complex 1. Additionally, naringin (a citrus fruit flavonoid) could decrease the level of TNF-α in microglia, increased by MPP(+)-induced neurotoxicity in the substantia nigra region. This evidence suggests that naringin is a beneficial natural

product for the prevention of DA degeneration in the adult brain (Rajadurai and Stanely Mainzen Prince 2006a, b, 2007a, b, c; Leem et al. 2014).

Jung and Kim (2018) reported that baicalein, luteolin and apigenin, nobiletin, tangeretin, quercetin, isoquercitrin, rutin, troxerutin, kaempferol, myricitrin, myricetin, naringin, naringenin, hesperidin, hesperetin, and epigallocatechin-3-gallate possess protective and controlling effect in PD. Their beneficial effects could be due to any one or more of the reasons like decreased dopaminergic neuronal loss and dopamine depletion, reduction of neuroinflammation, improved antioxidant capacity, mitochondrial dysfunction, activated anti-apoptotic pathways, induction of neurotrophic factors, and the inhibition of a-synuclein aggregation.

15.12 HD and Nutraceuticals Antioxidants

Huntington's disease is a genetic disorder triggered by an unusual expansion of polyglutamine (polyQ) repeat in Huntingtin (Htt) protein. HD results in the death of brain cells, which affects muscle coordination leading to mental decline and behavioral changes. HD is characterized by motor dysfunction, including emotional disturbances, chorea and dystonia, memory, and weight loss (Hammond and Tatum 2014). It usually occurs from the age of 35. HD occurs due to protein misfolding, where Htt protein interacts with about hundreds of other proteins and interferes with usual biological functions of these proteins (Goehler et al. 2004). ROS-induced protein misfolding leads to formation of inclusion body, which clumps together with each other at neuronal axons and dendrites and inhibits the transmission of nerve impulses through neurotransmitters (Rubinsztein and Carmichael 2003).

New mechanism of mitochondrial damage in HD was proposed, which suggested that OS has the capacity to inactivate the catalytic action of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which are accompanying with mitochondrial damage and performances as a signaling molecule towards selective degradation via lysosome engulfment. iGAPDH, leading to abnormally interaction with the long polyQ of mHTT at the mitochondrial outer membrane, which blocks the iGAPDH signaling for degradation. Therefore, impaired mitochondria cannot be engulfed by lysosome, generally called as suicide bags and harmfully accumulate in the mHtt-expressed cells, leading to cell death (Liot et al. 2017). It is well known that oxidative damage is associated with diminished expression of glucose transporter (GLUT)-3 protein, resulting in decreased glucose uptake and increased accumulation of lactate (Pinto et al. 2015). ATP synthesis occurs due to proton motive force generation during ETC (Bonora et al. 2015). The inhibition of the mitochondrial ETC results in elevated levels of ROS and decreased ATP production (Wetzel et al. 2008).

Decreased activity of the ETC complexes (II, III, and IV) is linked with increased lactate levels in HD patients. HD subjects are associated with OMM (expand) is evident to release cyt-*c* and cause cell death through apoptosis (Liu et al. 2017). The

mutation in *HTT* genesis is found to affect mitochondrial transport and dynamics. Excitingly, the *HTRA2* expression was decreased under the expression of mutant *HTT* in striatal neurons in HD patients (Filosto et al. 2011).

Curcumin is a commonly used ingredient in Asian food has a wide spectrum of antioxidant, anti-inflammatory and anti-fibrilogenic properties. Chongtham and Agarwal (2016) have provided the evidence that curcumin significantly ameliorates disease symptoms in a Drosophila model of HD by suppressing cell death, which could play a key role to halting the progression of HD with fewer side effects. Mehan et al. (2017) has reported that forskolin exhibits neuroprotective effects on 3-nitropropionic acid-induced Huntington's disease-like NDD.

15.13 Multiple Sclerosis and Nutraceuticals Antioxidants

Multiple sclerosis is a demyelinating disease categorized by damage in insulating covers of nerve cells in the brain and SC (infiltration, demyelination, and axonal pathology). The damaged insulating cover disrupts the ability of the nervous system to transmit signals, triggering the signs and symptoms, including physical, mental as well as psychiatric problems. More precise symptoms like double vision, blindness in one eye, muscle weakness and trouble with sensation or coordination. Female gender is more susceptible to MS than men, which begins between the age of 20 and 50 years. Even though the MS is one of the most common autoimmune disorders of CNS, the actual causes could be due to iron overload OS, excessive protease and glutamate production may link in promoting myelin sheath breakdown (Ward et al. 2015).

The event of demyelination and axonal damage could be initiated by the activation of microglia, which release nitric oxide (one of the free radicals, produce nitrosative stress) and show enhanced production of glutamate (a major excitatory neurotransmitter), leading to injury of nerve fibers by prompting the accumulation of intracellular Na^+ and/or Ca^{2+} concentration (Berer and Krishnamoorthy 2014). Elevated concentration of these cations induces a change in membrane permeability, followed by mitochondrial swelling and rupture of the mitochondrial membrane. The deadly superoxide radical and nitric oxide via cyt-*c* pathway may attribute to apoptotic cell death and an impaired mitochondrial respiration. Moreover, FR and cytotoxic CD8+ cells damage the nerve tissue, injured and nude axons lead to neurological impairment in MS patients (Rottlaender and Kuerten 2015).

Naturally occurring antioxidant nutraceuticals like xanthines, isoflavones, organosulfurs, anthocyanins, glucosinolates, steroid glycosides, and alkaloids have been reported to show significant protective effects in the treatment of MS in animal models. Studies with vitamins (A, B12, D, H) and minerals (selenium and lithium), as well as PUFA, marijuana, lipoic acid, statins, resveratrol, EGCG, and some probiotics have shown significant beneficial role in MS by preventing or delaying the onset of disease (Sanadgol et al. 2017). Beta-sitosterol is effective in controlling the secretion of pro/anti-inflammatory cytokines, a potential factor in MS

management without the side effects (Desai et al. 2009). Also the phytochemicals like apigenin, coumestrol, chrysin, baicalein, daidzein, cyanidin, sulforaphane, flavone glycoside, bee venom and huperzine A are the candidates for more prospective investigations in controlling and management of MS.

15.14 Summary and Conclusion

Though various therapies are available to control the NDD, due to economic reasons it is not possible for everyone to afford. While looking for the alternate, antioxidant nutraceuticals are proven as an effective one for the treatment of NDD with reasonable cost. During consumption of food, apart from supply of energy, also concerned about the health benefit out of it. Based on various reasons, people are moving towards nutraceutical products currently. It includes healthcare costs, unsatisfactory results from available pharmaceutical agents in the market, foods consist of excessive fertilizers, pesticides, herbicides, and often genetically modified seeds, several chronic diseases found no solution in allopathic medicines, but effectively controlled by alternative medicine. So, along with our life style modification, dietary changes with rich antioxidants play a crucial role in controlling NDD. Days are far away, very soon we can expect the antioxidant nutraceuticals in the market to control and treat NDD, because several studies reported that it has proven effect to control NDD.

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Part III
Herbal Remedies for Neurological Disorders

Chapter 16
Herbal Drugs: Its Mechanism to Prevent Alzheimer's Disease with Special Reference to Non-phenolic Secondary Metabolites

Kamsala Venkata Ratnam, Lepakshi Md. Bhakshu, and Rudraraju Reddy Venkata Raju

Abstract Alzheimer's disease (AD) is recognized as complex neurological disease marked by gradual dementia and deterioration of cognitive function. As per World Alzheimer Report (2015), 46.8 million individuals have mental illness and the number will increase twofold every 20 years. Synthetic drugs used to treat cognitive loss in AD patients are tacrine, donepezil, rivastigmine, and memantine. They improve overall memory temporarily, but cause other side effects. Medicinal plants used in traditional medicinal systems have been used to treat progression of disorders of neurons like memory deficits, i.e., amnesia, dementia, and AD many years ago. Natural compounds isolated from plant sources, like phenolics, terpenoids, and alkaloids have been recommended to have the potential to cure AD because of their inflammation/oxidative stress reducing capacity and anti-amyloidogenic properties. In the present review, we discussed the mechanism of neuroprotective effect of medicinal plant extracts and non-phenolic compounds, i.e., Bacoside A (*Bacopa monnieri*), acetyl-11-keto-β-boswellic acid (Indian Frankincense), caffeine (*Coffea arabica* and *C. canephora*), Galantamine (*Galanthus nivalis*), ginkgolide B and bilobalide (*Ginkgo biloba*), Hederacolchiside E (*Hedera colchica*), Huperzine (*Huperzia serrata*), and Withanolide-A and Withaniferin-A (*Withania somnifera*).

Keywords Alzheimer's disease · Acetylcholinesterase inhibition · Anti-amyloidogenic · Alkaloids · Saponins · Terpenoids

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16.1 Introduction

Neurological diseases are increasingly recognized as major causes of death and disability worldwide. The most prevalent neurological diseases are Parkinson's (PD), multiple sclerosis (MS), AD, and Huntington's disease (HD). The most important pathological symptoms of neuro degenerative diseases are mitochondrial dysfunction, synapse loss, elevated oxidative stress, protein abnormalities, decreased neuronal survival, and nitrosative stress (Winner et al. 2011). It is accepted that among neurodiseases, AD is most complex neurological disease characterized by gradual dementia and failure of cognitive function. The prevalence of AD accounts for about 60% of all cases (van Marum 2008). As per World Alzheimer Report (2015), 46.8 million individuals have mental illness and the number will increase twofold every 20 years. The disorder is typified by variations in different genes, such as the β amyloid precursor protein (APP) and persenilins (PS1, PS2), proteins such as BACE (Aβ cleaving enzyme), APOE, PS1/2, and APP, tau and secretases play a crucial role in the immunopathology of AD.

The approved medicine used to treat cognitive impairment in AD patients are tacrine, donepezil, rivastigmine, galantamine, and memantine. They improve overall memory temporarily, but cause gastrointestinal complexity, such as diarrhea, hepatotoxicity, nausea, weight loss, etc. (Kim et al. 2010). Herbal recipes used in traditional medicinal systems are fundamentally preventive, protective, nutritive, and curative. These traditional herbs have been used to treat progression of disorders of neurons like abstraction and AD since years ago. Because these traditional herbs and isolated chemical components may be less toxic than synthetic drugs. The herbal drugs used in medicinal systems of Indian tradition to cure AD are *Centella asiatica* (Apiaceae), *Bacopa monnierii* (Scrophulariaceae), *Curcuma longa* (Zingiberaceae), *Withania somnifera* (Solanaceae), *Celastrus paniculatus* (Celastraceae), *Nardostachys jatamansi* (Caprifoliaceae), *Tinospora cordifolia* (Menispermaceae), *Morinda citrifolia* (Rubiaceae), etc. Natural compounds such as alkaloids, terpenoids, and phenolic components of plant origin have been proved to have the potential therapeutic value to prevent AD because of their inflammation/oxidative stress reducing capacity and anti-amyloidogenic properties (Kim et al. 2010).

The present work is concentrated on the role of the potential traditional herbal extracts and their active principles in the prevention of AD with special reference to non-phenolic compounds of the herbal drugs to understand its possible mechanism.

16.1.1 Bacopa monnieri *(L.) Wettst.*

B. monnieri (L.) Wettst. (Family: Scrophulariaceae) is known as Brahmi (Telugu) or Aindri (Sanskrit). Medhya rasayana is a popular brain tonic prescribed by Ayurveda practitioners for intellectual, cognition rejuvenation and in memory loss conditions

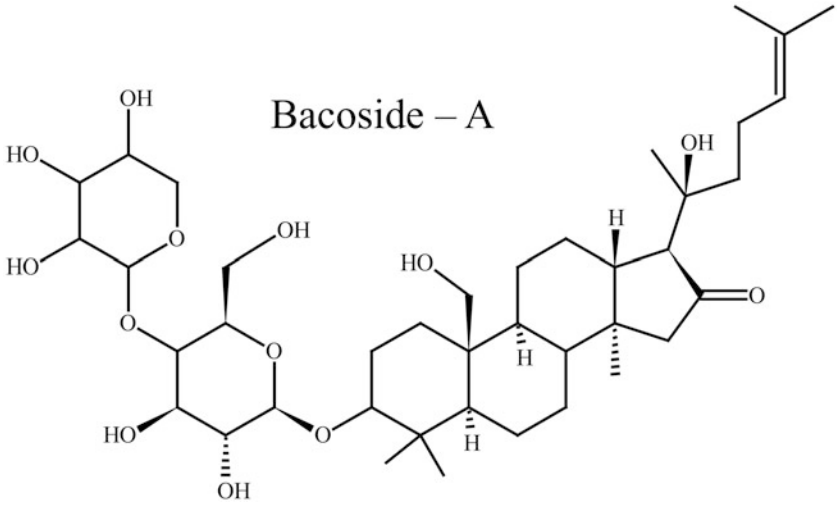


Fig. 16.1 Bacoside structure

(Vishnupriya and Padma 2017). Studies on standardized extract of *B. monnieri* revealed that the extract significantly reversed scopolamine induced impaired the acquisition and recapture of memory producing both retrograde and anterograde amnesia in Morris water maze mice model (Saraf et al. 2011). Further, Holcomb et al. (2006) evaluated the efficacy of *B. monnieri* extract on expression studies of M146L presenilin-1 mutations and Swedish amyloid precursor protein in PSAPP mice. The results showed that *B. monnieri* extract has downregulated amyloid (Abeta) gene expression 60% and reversed behavioral changes in incessant locomotion and Y-maze performance in PSAPP mice. Bacosides (Fig. 16.1), isolated from *B. monnieri*, significantly reduced stress in adult male Sprague Dawley rats via modulating the expression levels of Hsp 70 and activities of superoxide dismutase and cytochrome P450 (Chaudhari et al. 2017).

B. monnieri extract significantly decreased glutamate- and β-amyloid protein (25–35) challenged toxicity in cortical neurons by reducing intracellular oxidative stress and by inhibiting lipid peroxidation in neuronal cells (Limpeanchob et al. 2008). Amyloid-beta (Aβ42) polypeptide plays remarkable role in AD development due to neuronal dysfunction. Bacoside A, saponin isolated from *B. monnieri* significantly reduced toxicity of cells and suppressed fibril formation both in membrane vesicles and in buffer solution (Malishev et al. 2017). Methanolic extract of *B. monnieri* significantly inhibited *S*-nitroso-*N*-acetyl-penicillamine (SNAP) induced generation of free radical and damage of DNA in concentration-dependent manner in isolated rat astrocytes (Russo et al. 2003). In a double-blind placebo and randomized experiment, BacoMind, a standardized phytochemical enriched *B. monnieri* extract, improved cognitive functions such as attentiveness and

remembrance in patients (Barbhaiya et al. 2008), in AD patients (Goswami et al. 2011) and in medical students (Kumar et al. 2016).

Further, Usha et al. (2008) conducted a clinical experiment on efficiency of BacoMind on cognitive enhancement in children. The results showed that BacoMind at 225 mg/day for a span of 4 months, significantly increased working memory and short-term verbal memory in 28 children volunteers. Rai et al. (2015) evaluated protective effect of CDRI-08, a special extract of *B. monnieri* in scopolamine-induced neurotoxicity amnesic mice. In results, pretreatment of CDRI-08 to amnesic mice treated with scopolamine bring back the spatial memory. The mechanism of action the drug found to be enhancing the expression levels of GluN2B subunit and decreased levels of acetylcholinesterase activity prefrontal cortex and hippocampus, similar to the normal mice. Oral administration of Medhya Rasayana, an Ayurvedic drug prepared from *B. monnieri* significantly reduced anticholinesterase activity and secured the cholinergic neurons than the standard drugs rivastigmine, donepezil, and galantamine. It further reduced the deposition levels of β-amyloid proteins in hippocampal and stress-induced damages in hippocampal regions of rat models in in vivo study (Chowdhuri et al. 2002). Peth-Nui et al. (2012) investigated the effect of standardized *B. monnieri* extract on brain function and remembrance in 23 males and 37 female healthy elders for a period of 12 weeks and concluded that the *B. monnieri* extract improved attention, cognitive processing, and working memory partly by inhibiting the activity of acetyl cholinesterase (AChE) activity.

16.1.2 Boswellia serrata *Roxb.*

B. serrata Roxb. (Family: Burseraceae) is known as olibanum or Indian Frankincense. Its oleo gum resin is traditionally used in Indian traditional systems (Ayurveda or Unani or ethnomedicine) to treat several types of human ailments like pain and cardiac debility, inflammatory health ailments, blood disorders, rheumatism, urinary disorders, and corneal ulcer (Paranjpe 2001; Khan 1885). Nrf2, a transcription factor, plays a main role in regulation of antioxidant genes/proteins such as heme oxygenase-1 (HO-1). Dysregulation of HO-1 is connected to pathogenesis of variety of neurodegenerative diseases including AD (Habtemariam 2019). Medication with acetyl-11-keto-β- boswellic acid (AKBA, Fig. 16.2) resulted noteworthy reduction in the volume of infarcts and number of apoptotic cells and upregulated expression amounts of HO-1 and *Nrf2* in brain tissues of tested animals.

Further, AKBA increased the expression of HO-1 and Nrf2 expression in oxygen and glucose deprivation induced oxidative stress in primary cultured neurons (Ding et al. 2014). In another experiment, *B. serrata* at 50 mg/kg significantly improved memory retrieval and step-through latency in streptozotocin-induced Alzheimer disease in rat models (Zaker et al. 2015). Medication with water extract of *B. serrata* gum resin for 42 days of experimental schedule, significantly decreased streptozotocin-induced Alzheimer disease symptoms, i.e., decreased step-through

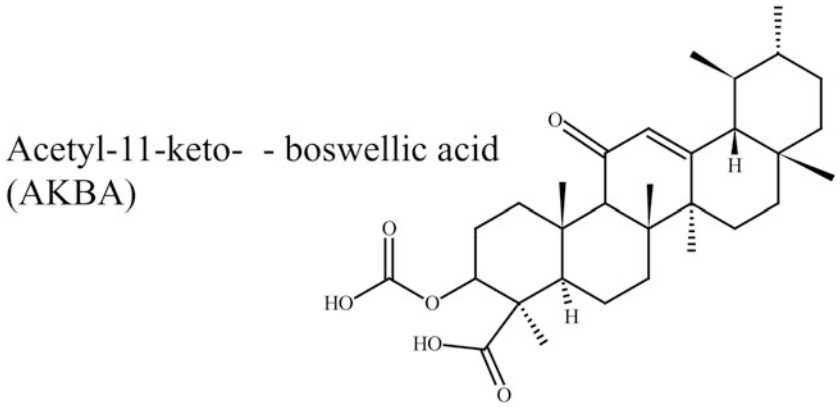
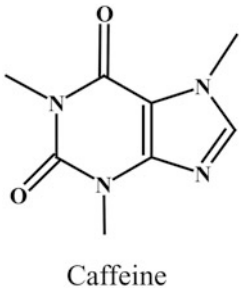


Fig. 16.2 Acetyl-11-keto-β- boswellic acid structure

Fig. 16.3 Structure of caffeine



latency, increased the decimal of step-through into the dark compartment and increased the spending time in the dark compartment (Beheshti and Aghaie 2016).

16.1.3 Coffea arabica *L.*

Methylxanthines isolated from the coffee (*Coffea arabica* L. and *C. canephora* L.) reported to have antagonists on adenosine-receptors. Caffeine (Fig. 16.3) a indifferent, competitive inhibitor of A2A and A1 receptors of adenosine, diffused in CNS. General depressant reaction is due to binding of adenosine to specific targets, lowering blood pressure and slowing rate of hart beat (Gu et al. 1992). As per epidemiological reports, caffein and A2A receptor inhibitor contribute a crucial role in delaying and avoidance of the emergence of AD. Maia and de Mendonca (2002) case study results demonstrated that people consumed two cups of coffee per day for 20 years have low risk for onset of AD than the people consumed less coffee. Systematic review on case control and prospective studies on efficiency of coffee on AD, concluded that coffee has therapeutic effects (Barranco Quintana et al. 2007).

These consequences were in line with previous reports in which consumption of coffee was regularly protective against PD for women and men without estrogen therapy (Ascherio et al. 2001, 2004; Ascherio and Chen 2003).

16.1.4 Galanthus nivalis *L.*

G. nivalis L. (Family: Amaryllidaceae) known as snowdrop, is widely grown in gardens and naturalized particularly in northern Europe. The active principle isolated from this plant is an alkaloid, galantamine. Galantamine is commercially accepted as AChEi drug to treat AD patients at different stages in many countries. Castillo (2017) assessed the efficiency of galantamine on beta-amyloid peptide-challenged damage of DNA and cell viability in SH-SY5Y neuroblastoma cell lines of human in vitro studies. The results revealed that treatment with galantamine exhibited noteworthy recovery of cell longevity, reduced the death of necrotic cells and exerted anticancer effects. Lopes et al. (2013) assessed the neuroprotective activity of galantamine alone or in mixed with memantine, an *N*-methyl-D-aspartate (NMDA) receptor inhibitor, in rat primary cultures of cortical neurons. Galantamine exhibited its neuroprotective effect via activation of α7 and α4b2 nicotinic acetylcholine receptor at a concentration of 5 μ mol/L.

Prins et al. (2014) conducted a clinical, placebo-controlled, randomized, double-blind trial experiment to investigate the neuroprotective effect of galantamine in 364 mild cognitive impairment patients for a time schedule of 1 year at 16–24 mg flexible-dose every day. They concluded that patients received galantamine showed a lower rate of whole brain atrophy than patients received placebo. In another experiment, galantamine significantly attenuated β-amyloid1–40 and thagapsigarin challenged cell toxicity of SH-SY5Y cell lines and bovine chromaffin cell. The mechanism related to neuroprotective effect of galantamine was by activation of levels of α7 nicotinic receptors and enhancing the expression levels of Bcl-2, the antiapoptotic protein (Arias et al. 2004). In in vitro study, galantamine significantly modulated regulation of signal transmission via intracellular cascade implicated in rat hippocampal slices of brain ischemia-reperfusion model put through glucose and oxygen deprivation (OGD) subsequently reoxygenation. Galantamine expressed its neuroprotective mechanism by reducing the induction of iNOS and secretion of NO caused by OGD via Jak2. It also decreased ROS generation by NADPH oxidase (NOX) activation (Egea et al. 2012). Kihara et al. (2004) investigated the efficiency of galantamine on β-amyloid-increased glutamate toxicity using cortical neurons of primary rat cultures. The defensive effect of galantamine was expressed by partial inhibition of α7 nAChR antagonists.

16.1.5 Ginkgo biloba *L.*

G. biloba L. (Family: Ginkgoaceae), known as the maidenhair tree or Ginkgo, belongs to Gymnosperms. The usage of *Ginkgo biloba* L. to treat neuro diseases was started by German physicians in 1965. EGb 761, a patented and commercialized extract of *G. biloba* leaves was developed in the early 1970s (Wagner 1999). The standardized products of Ginkgo extensively prescribed in Europe and the USA to treat various types of neurodegenerative diseases. EGb 761 extracts rich in flavonoids and terpenic lactones may be responsible for its therapeutic action. The terpenoid fraction consists mainly diterpenic lactones, sesquiterpene trilactone, the bilobalide, and the ginkgolides A, B, C, J and M (Birks and Grimley 2009).

G. biloba extract and active ingredient ginkgolide B (GB), a terpene trilactone solution reduced the endothelial permeability coefficients and upregulated ZO-1 and occludin expression, the tight junction proteins in endothelial cells (Fang et al. 2010). Administration of ginkgolide B demonstrated that GB reduced the neurological deficits core and enhanced the amount of nestin, mRNA expression levels of neurotrophic factor derived from the brain and growth factor of the epidermis. Further, it enhanced brain-derived neurotrophic factors expression levels in animal models with middle cerebral artery occlusion (MCAO) (Zheng et al. 2018). Further, ginkgolide B derivative, 10-*O*-(*N*, *N*, dimethyl aminoethyl)-ginkgolide B methane sulfonate, (XQ-1H) significantly reduced high lipid profile, cerebral infarct size and improved Blood–Brain Barrier (BBB) permeability in hyperlipidemic rats (Fang et al. 2015). Pretreatment with ginkgolide K (GK) reduced mitochondrial fission, modulated mitochondrial dysfunction and inhibited mitochondrial permeability transition pore opening through a GSK-3β-dependent mechanism of action in both MCAO mice and OGD/R neuroblastoma cells (Zhou et al. 2017).

EGb 761 and its component, ginkgolide A, modulated Aβ-induced disease symptoms such as reduced chemotaxis behavior, 5-HT hypersensitivity and paralysis in a transgenic *Caenorhabditis elegans* (Wu et al. 2006). In in vitro study, ginkgolide B attenuated pro-oxidant Aβ25–35 peptide induced oxidative stress symptoms such as higher amount of ROS/RNS and decreased concentration of mitochondrial Apurinic/apyrimidinic endonuclease 1 (APE1) in human neuroblastoma SH-SY5Y and IMR-32 cells (Kaur et al. 2015). Bilobalide, diterpene constituent of *G. biloba,* showed neuroprotection in ischemia-induced neurotoxicity in mice model. The mechanism involves drug reversed ischemia-induced brain damage, mitochondrial dysfunction, leading to reduction in the release of glutamate amount (Schwarzkopf et al. 2013).

16.1.6 Hedera colchica *(K. Koch) K. Koch*

H. colchica (K. Koch) K. Koch (Family: Araliaceae) commonly called ivy/Persian ivy, is an evergreen woody vine, native to Turkey. Hederacolchiside E, saponin, active principle isolated from *H. colchica* reported to have antioxidant activity (Gülçin et al. 2004). Neuroprotective efficiency of hederacolchiside E, isolated by bioactivity-guided fractionation from root extract of *Pulsatilla koreana*, was studied in in vivo and in vitro methods (Han et al. 2007). Hederacolchiside E reversed scopolamine-challenged cognitive impairment in rats and reduced amyloid-beta peptide (1–42) induced cell toxicity in human SK-N-SH cells. Hederacolchiside E and its 11 derivative compounds were assessed for neuroprotective effects against H_2O_2- and $A\beta_{1-42}$-induced neurotoxicity using cell-based assays (Li et al. 2018). Compound 1 and 7 exhibited noteworthy reduction in LDH release levels, amount of intracellular ROS, and extent of malondialdehyde (MDA) enhancement in $A\beta_{1-42}$-induced cells.

16.1.7 Huperzia serrata *(Thunb. ex Murray) Trevis.*

H. serrata (Family: Lycopodiaceae) known as the club moss, has been used by tribes of China to treat strain, swellings, contusion, and schizophrenia. Liu et al. (1986) isolated active chemical constituent, the alkaloid (−)-huperzine A, reported to possess AChE inhibition, which was associated with the traditional uses of this plant.

Huperzine A significantly modulated the D-galactose (D-gal) induced neurodegenerative disease symptoms such as increased cellular senescence and auditory brainstem response (ABR) threshold and reduced neurofilament in the cochlear tissues in Sprague Dawley rats. Further it also suppressed expression levels of NF-kB in Schwann cells and notably blocked D-gal-stimulated expression amounts of pro-inflammatory markers such as IL-1b, IL-6 and TNF-α (Li and Shi 2019). Huperzine A attenuated beta-amyloid protein, H_2O_2, ischemia, glutamate, and staurosporine-induced cell toxicity and programmed cell death in animal models. The protective mechanism of Huperzine A involved in restoring the oxidative stress controls the expression levels of apoptotic markers i.e., *Bcl-2,* caspase-3, *P53,* and Bax, mitochondrial protection and interferes with APP metabolism (Wang and Tang 2005).

In in vivo study, Huperzine A exhibited noteworthy reduction in pathological symptoms, i.e., memory deficiency and neurodegeneration, induced by Aβ1–40 in both hippocampus and cortex of animal models, and inhibited amyloid deposits formation in cortex (Wang et al. 2001). Additionally, huperzine A also reported that it can directly process the amyloid precursor protein (Peng et al. 2006). With regard to cell culture studies, treatment with (-)-huperzine increased the secretion levels of α-APPs, and inhibited Aβ in embryonic kidney 293 cells of human, transfected with the Swedish mutation (Peng et al. 2006, 2007). Acetylcholinesterase (AChE)

inhibitory potential and attenuation of Aβ-induced toxicity in NG108-15 and PC cells were studied (Zhang et al. 2002).

Receptors of glutamate play crucial role in the alteration of synaptic plasticity and play noteworthy roles in learning and memory (Contractor and Heinemann 2002). Cells treated with huperzine-A (100 nM) significantly modulated the glutamate (100 μM) induced morphological changes, such as reduction of axon-like processes and diffusion of cell aggregates and cell viability of cell cultures of rat cerebellum (Ved et al. 1997). Huperzine A at 10 μM concentration attenuated *N*-methyl-D-aspartate (NMDA) challenged cell viability in neuronal cultures in concentration-dependent manner. The binding capacity of huperzine A to proximal to the phencyclidine binding sites and MK-801 is the diagnostic feature in the process of NMDA receptor modulating activity (Gordon et al. 2001). Neuroprotective effect of huperzine A and enantiomers of huperzine A demonstrated by inhibiting the MK-801 binding capacity in the cerebral cortex of animal models was studied (Zhang et al. 2000). Huperzine A was identified as an efficient drug in pre- and post-treatment experiments, against *N*-methyl-D-aspartate induced seizures and epilepsy (Coleman et al. 2008).

In a placebo-controlled, double-blind, parallel, multi-centered clinical experiment, it showed noteworthy developments in behavior, cognition and daily living activities than patients given with placebo was studied in China (Xu et al. 1995, 1999; Zhang et al. 2002a). Similarly, the efficiency of huperzine-A on learning and memory enhancement clinical experiment in school students with 34 pairs was studied in double-blind method in China (Sun et al. 1999). They conclude that huperzine A-treated students group showed better performance in Chinese-language lesson quizzes than the placebo-treated group. A multi-centered, randomized, prospective, double-blind, three-arm, dose-escalation clinical experiment was conducted to assess the neuroprotective effect of huperzine A in 210 patients with AD in the USA. Patients treated with 400 μg of huperzine A demonstrated a 2.27-point enhancement in the Alzheimer's Disease Assessment Scale-Cognitive Subscale, while 0.29- point decline was observed in the after 11 weeks treatment period (Rafii et al. 2011).

16.1.8 Withania somnifera *Dunal.*

W. somnifera Dunal. (Family: Solanaceae) is locally called as Aswagandha (Sankskrit). In Ayurveda, the root of Ashwagandha has been used as a Rasayana and it is used as stimulant, diuretic, tonic, aphrodisiac, narcotic, astringent, and thermogenic (Singh et al. 2011). *W. somnifera* root extract showed a noteworthy improvement in the gripping ability, motor movement patterns and restored tyrosine hydroxylase and antioxidant enzyme activity in paraquat (PQ) and maneb challenged nigrostriatal dopaminergic neurodegeneration in mice models (Prakash et al. 2013). Withanolide-A (Fig. 16.4), a major chemical constituent of *W. somnifera* root showed neuroprotective ability by modulating brain damage, morphology of brain

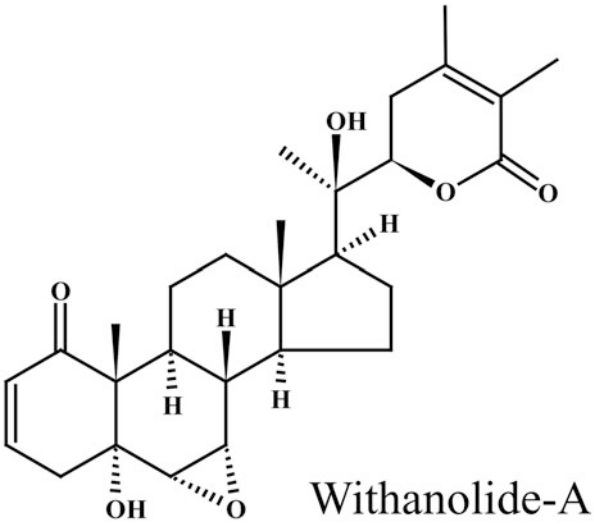


Fig. 16.4 Withanolide-A structure

tissue, levels of neurotransmitter in cerebral and brain tissue morphology in mice (Mukherjee et al. 2020). Banu et al. (2019) investigated the neuroprotective efficiency of withaniferin-A, steroidal lactone characterized from roots of *W. somnifera* on aging induced oxidative stress in substantia nigra (SN) and striatum (ST) of aged rat brain. In conclusion, withaniferin-A significantly modulated the aging induced oxidative stress biochemical changes such as reduced motor activity, increased free radical concentration, reduced antioxidant enzyme levels, increased active caspase-3 activity, enhanced apoptotic nuclear morphology in striatum and substantia nigra of aged rat. Further, Rabhi et al. (2019) studied the neuroprotective activity of CR-777, a glutathione derivative of withaferin A (Fig. 16.5), neurotoxicity caused by 6-hydroxydopamine (6-OHDA), α-synuclein (α-Syn) and 1-methyl-4-phenylpyridinium (MPP+), in rat dopaminergic neuron cells. In 6-OHDA-treated neurons, CR-777 at nanomolar concentrations enhanced neurite network and cell survival and reduced the expression levels of α-Syn in rat dopaminergic neurons.

16.2 Perspectives

Medicinal plants used in traditional medicinal systems have been used in the prevention of neurological diseases since long time. Natural compounds isolated from plant sources such as terpenoids, alkaloids, and phenolic components have been reported to have the potential therapeutic value to prevent AD because of their anti-amyloid genic, reduction capacity of oxidative stress and inflammation properties. Some of the potential medicinal plant extracts and its chemical constituents scientifically proved its intellectual, cognition rejuvenation and memory enhancing power in AD patients, such as *Bacopa monnieri* extract and its active principle

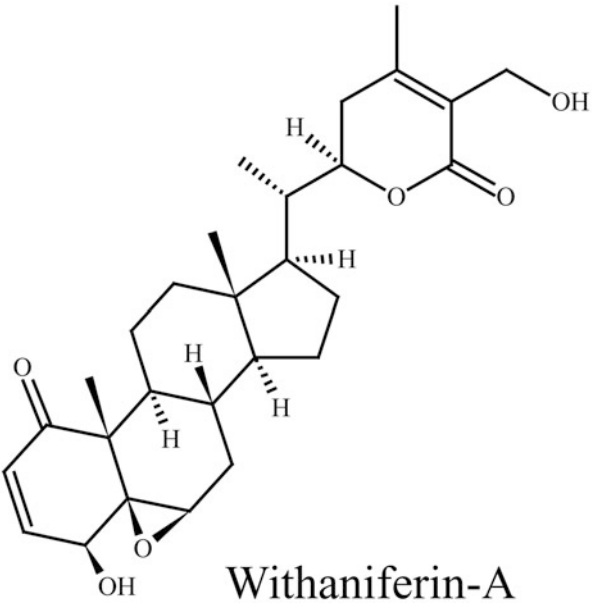


Fig. 16.5 Withaniferin-A structure

bacoside A, ginkgolides from *Ginkgo biloba*, withanolides and withaniferin from *Withania somnifera*, huperzine from *Huperzia serrata*, etc. Extensive research studies are to be conducted in order to establish the long-term usage and efficacy of using phytochemicals as potential therapeutics for neurological diseases and sustainable utilization of drug yielding plants by using biotechnological interventions.

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Chapter 17
Preventive Role and Mechanism of Herbal Medicine in Alzheimer's Disease with Special Reference to Phenolic Compounds

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Abstract Alzheimer's diseases (AD) is prevalent and is characterized by memory deficits/loss which became prevalent in age old persons and much research is focused to develop new inhibitors for pathogenic marker proteins in the treatment. The scientific evidence strongly supports that the herbal medicine is highly effective on the AD and much research is in advancement on the cholinesterase inhibitors and their usage. Since the dawn of civilization, many plants were used for nervous disorders as memory boosters and rejuvenator even as aphrodisiacs in treatment of epilepsy, weakness, anxiety, etc.. The advent of scientific methodologies the natural medicaments were studied and evaluated scientifically and developed as potential pharmaceuticals and commercialized. The present review emphasizes the phytochemicals, especially the phenolic compounds which include flavonoids, coumarins, lignans, polyphenolics and its glycosides. These compounds exert preventive mechanism in age-related disorders by involving antioxidant activity or signaling cascades. The phenolics of *Camellia sinensis*, (Tea), *Curcuma longa* (Turmeric), *Vitis vinifera* (grape), etc. were taken directly as ingredients in the food, whereas the other plants were given as medicaments. Among these, Epigallocatechin gallate from Tea, curcumin from the turmeric, resveratrol from grape, baicalin from *Scutellaria baicalensis*, caffeoylquinic acids from *Centella asiatica*, rosmarinic acid from *Melissa officinalis,* etc. were well established and studied to prove its molecular mechanisms, which were discussed in detail.

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Keywords Alzheimer's disease · Herbal medicine · Neurodegenerative disorder · Phenolic compounds · Molecular mechanism · Acetyl cholinesterase inhibition

17.1 Introduction

The herbal medicines became popular which are used in traditional Ayurvedic as well as the Chinese systems of medicine possess multiple secondary metabolites or phytochemicals that may have a neuroprotective capacity and proved that they are beneficial in different neurodegenerative and neuropsychiatric disorders, among which Alzheimer diseases (AD) is prevalent in the old age group above 60 years. It is characterized by the loss/deficit in the memory during aging.

Plants are rich source of secondary metabolites and the phytochemical components identified such as alkaloids, flavonoids, lignins, polyphenols, sterols, triterpenes, tannins, etc. have pharmacological effects on the memory retaining capacity including anti-cholinesterase and anti-amyloidogenic. The phytophenolic compounds serve as important antioxidants and inhibitory molecules in several drug targets including acetyl cholinesterase (ACHase) which is one important enzyme found in hippocampus resulting in the reduced level of Ach (acetyl choline a neurotransmitter) in cerebrum. Regaining the Ach levels in brain has been empathetically utilized therapeutically, introduced in recent decades, to accomplish symptomatic treatment in AD (Bhattacharjee 2018). The plant extracts and its constituents make them an important well-spring of novel leads for the medications in the treatment of AD. The search for the novel secondary metabolites in AD is being thrust area. The phenolic compounds such as "Apigenin-8-*C*-*β*-boivinopyranoside," "Apigenin-8-*C*-*β*-digitoxopyranoside," and "luteolin-8-*C*-*β*-boivinopyranoside" from the leaves and stems of *Passiflora edulis* reported to inhibit nitric oxide-mediated pathogenesis, which can be beneficial in neuritogenesis, anxiolytic, neuroinflammation, and neuroprotection (Xu et al. 2013). The available allopathic medicines for AD are donepezil, galantamine, rivastigmine, tacrine, and memantine. They improve overall memory temporarily, which are reported for certain cross effects, such as gastrointestinal disturbances, nausea, hepatotoxicity, diarrhea, weight loss, etc. (Kim et al. 2010) with reference to rational traditional medicines which may not have side effects and considered as safe and potential resources.

The treatment of AD became inadequate and has multiple adverse effects and requires a safest and alternative treatments to retain the memory loss. A plethora of medicinal plants are being used to improve the memory might be applied to improve memory in AD patients (Xu et al. 2009). In this context, many reports on the claims on usage of medicinal plants and its active principles along with explanation of mode of action related to molecular approach in the treatment has been advanced in the research of natural products and its chemistry. The review on the neurodegenerative disorders and its prevention mechanism revealed that there are good number of medicinal plants used in traditional systems on the name of Medha-rasayanas (Ayurveda) and among which *Centella asiatica* (Apiaceae), *Bacopa monnieri*

(Scrophulariaceae), *Curcuma longa* (Zingiberaceae), *Withania somnifera* (Solanaceae), *Celastrus paniculatus* (Celastraceae), *Nardostachys jatamansi* (Caprifoliaceae), *Tinospora cordifolia* (Menispermaceae), *Morinda citrifolia* (Rubiaceae), *Convolvulus pluricaulis* (Convolvulaceae), etc. are proved the potentiality in prevention of AD or PD and other age-related disorders (Kim et al. 2010; Singh et al. 2011; Bhattacharjee 2018). The present study is focused on to review the role and possible mechanism of phenolic components, a major group of secondary metabolites in AD or age-related nervine disorders. The study emphasized on the phenolic group of secondary metabolites (polyphenols, flavonoids, coumarins, lignans, etc.) from the plethora of medicinal plants has been enlighted up to its possible molecular mechanisms as discussed below.

17.1.1 Camelia sinensis *L. (Family: Theaceae, Common Name: Tea)*

The green tea is rich source of catechins with maximum antioxidants which are igniting wide range of neuroprotective cascade in the cellular metabolism in the nerves. The antioxidative mechanism includes the scavenging of free radicals, iron binding, activating beneficial signaling and regulating the mitochondrial function, prevents the excessive generation of free radicals, plays important role in prevention of damage to biological membranes including the brain tissues and nerve cells and thereby helps in maintenance and curing of AD and PD during the aging process. The "epigallocatechin-3-gallate" (EGCG; Fig. 17.1) has been demonstrated to function as an iron chelator, binding and removing the iron, thus attenuating it from the generation of charged free radicals in the brain. In addition, EGCG also enhances the activity of major antioxidant enzymes such as superoxide dismutase (SOD) and catalase and further prevents the damage by free radicals (Mandel and Youdim 2004; Reznichenko et al. 2006; Weinreb et al. 2004). Another active compound epicatechin (EC; Fig. 17.2) of green tea decreases the secretion of

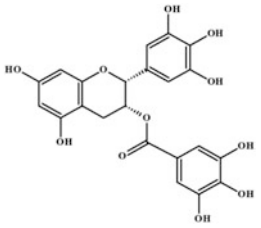


Fig. 17.1 Epigallocatechin gallate

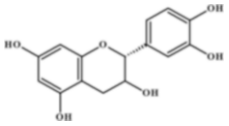


Fig. 17.2 Epicatechin

β-amyloid particles and of the consequent plaque depositions in the brain characteristic pathogenetic feature of AD (Hsu et al. 2013). Similarly, the black and green tea extracts and their main constituents (epigallocatechin gallate and epicatechin gallate) were demonstrated in an in vitro system of cultured neurons and its protective effects. Moreover, the presence of the extracts improved the neurons survival against the toxicity of β-amyloid (Reznichenko et al. 2006). Green tea polyphenols have potentially affected the oxidative stress mediated cell signaling of the MAPK pathways in brain cells and are believed to play a crucial role in neuro-depressant diseases (Mandel and Youdim 2004). The L-theanine, an active compound of tea plants and some mushrooms may directly promote the relaxation effect through the production of alpha brain waves, calming the body (Gray 1998; Haque et al. 2006). Since tea leaves are rich in polyphenols such as EGCG, they play an important role through interacting with membrane receptors or transporters and trigger downregulation of intracellular signals to prevent neuronal disorders (Huh et al. 2004).

17.1.2 Centella asiatica *(L.) Urban*

It belongs to the botanical family "Apiaceae" and popularized as Gotu Kola, Indian pennywort, and Asiatic pennywort. In Ayurveda, (Sanskrit name: Mandukaparni, brahmi) it has been used as memory enhancing herb and in treating of skin and neurological diseases (Jamil et al. 2007). The aqueous extract of *C. asiatica* and its compounds, caffeoylquinic acids (Isochlorogenic acid A (Fig. 17.3) and 1,5-dicaffeoylquinic acid (Fig. 17.4)) inhibited the β-amyloid (Aβ)-induced oxidative stress, mitochondrial dysfunction, and calcium imbalance in MC65 and SH-SY5Y neuroblastoma cells in in vitro studies (Gray et al. 2014, 2015). In vivo experiments conducted in animal models revealed that *C. asiatica* extract significantly improved behavioral deficits (Soumyanath et al. 2012) and changed the antioxidant and mitochondrial cascades besides improvement in cognitive function

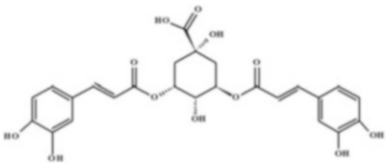


Fig. 17.3 Isochlorogenic acid A

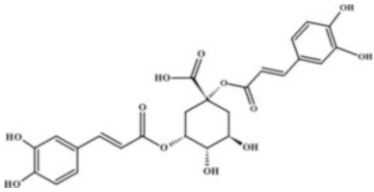


Fig. 17.4 1,5-dicaffeoylqunic acid

(Gray et al. 2016) in addition to prevention of the outgrowth of dendrites and spines developed due to Aβ exposure in "Tg2576 neurons" and behavioral changes of mice besides proving its molecular mechanism in mice (Gray et al. 2017, 2018).

17.1.3 Curcuma longa *L.*

It is a rhizomatous perennial herb and prime source of turmeric and belongs to the family, Zingiberaceae, and the dried ground flour of rhizome is a spice widely used in curry or dishes for its flavoring in variety of foods and recipes besides its yellowish dye. The wide usage of turmeric in Indians might be the cause of lower prevalence of AD when compared with the USA (Ganguli et al. 2000).

The curcumin (Fig. 17.5) is one of the phytoconstituents of turmeric and its effect on an animal model of AD, for 6 months treatment (160 ppm), decreased the incidence of inflammatory response and oxidative stress correlated with the decreased expression of proinflammatory cytokines, oxidized proteins and of β-amyloid in a significant rate (Lim et al. 2001) besides curcumin also showed anti-amyloidogenic activity in in vitro and animal models (Ganguli et al. 2000; Lim et al. 2001; Kim et al. 2001a, b, 2005; Ono et al. 2004; Ringman et al. 2005; Yang et al. 2005) in addition to chelating effect in animal models (Baum and Ng 2004). Curcumin along with NSADs (non-steroidal anti-inflammatory drugs) inhibited the oxidative damage, deterioration of cognition and Aβ deposition in both cell cultures and animals in addition to the anti-inflammatory effect (Cole et al. 2004). The inflammation plays a major (detrimental) role in the disease prognosis in most of the chronic illnesses, including neurodegenerative diseases which provide evidence for the therapeutic potential of curcumin (Aggarwal and Harikumar 2008). The curcuminoid compounds reported inhibition of nitric oxide generation through LPS-mediated microglia in the experimental rats (Zhang et al. 2008). Intraperitoneal injection of curcumin in cerebral ischemia induced Mongolian gerbils attenuated the neural death and improvement in lipid peroxidation, mitochondrial functions besides glial activation (Wang et al. 2005).

17.1.4 Ginkgo biloba *L.*

For the long time, the German physicians have included *Ginkgo biloba* L. (Family: Ginkgoaceae) to treat conditions and symptoms dementia, cognitive failure, and

Fig. 17.5 Curcumin

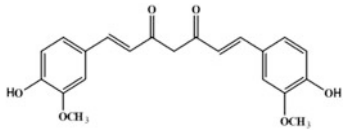


Fig. 17.6 Quercetin

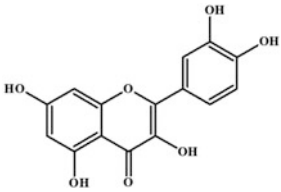


Fig. 17.7 Kaempferol

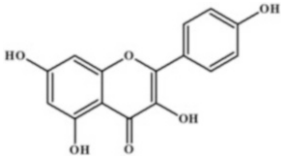
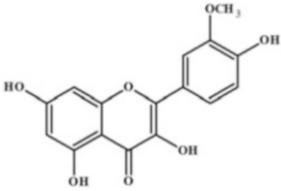


Fig. 17.8 Isorhamnetin



AD. The standardized extracts were possessing 24% of flavonoids and 6% of terpenic lactones, giving this extract its unique polyvalent pharmacological action. The extracts with the flavonoids have three prime flavonols, such as quercetin (Fig. 17.6), kaempferol (Fig. 17.7), and isorhamnetin (Fig. 17.8) in addition to terpenes (Birks and Grimley 2009).

17.1.5 Scutellaria baicalensis *Georgi*

The extract obtained from the root of *S. baicalensis* (Family: Lamiaceae; Chinese skullcap), rich in bioactive components such as wogonin (*O*-methylated flavone (Fig. 17.11) is used to treat different neuro/inflammatory diseases (Wakabayashi and Yasui 2000; Park et al. 2001; Nakamura et al. 2003; Suk et al. 2003). The constituents of *S. baicalensis* were acted as antioxidants when tested in various cells and animal models, exhibited the quenching of ROS and protected the neurons from the oxidative damage in cerebral ischemia/reperfusion (I/R) injury, besides protecting from peroxidation of lipid of neuronal membranes and the toxic effects initiated by glutamate (Hamada et al. 1993; Gao et al. 1996, 1998, 1999, 2001; Shieh et al. 2000; Kim et al. 2001a, b; Lee et al. 2003; Cho and Lee 2004; Son et al. 2004). The secondary metabolites such as "baicalein" (5,6,7-trihydroxyflavone; Fig. 17.9), "baicalin" (baicalein 7-*O*-glucuronide; Fig. 17.10), and wogonin (5,7-dihydroxy-8-methoxyflavone) are flavonoids which were isolated from its roots, assayed for numerous potential benefits (Lai et al. 2001) and they protected the neurons when

Fig. 17.9 Baicalein

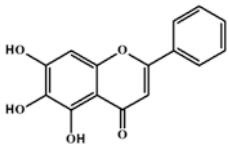


Fig. 17.10 Baicalin

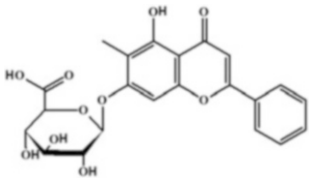
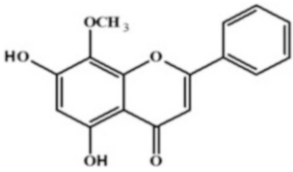


Fig. 17.11 Wogonin



tested in in vivo or in vitro models (Lin 2009). Kim et al. (2001a, b) reported that the wogonin inhibits the inflammation in central nervous system and reported to suppress the nitric oxide production including iNOS genes in astrocytes of rats and cultured microglia cells (in vitro). Besides this, wogonin also inhibited the LPS stimulated inflammation and cytokines such as IL (interleukin)-1β and TNF (tumor necrosis factor)-α and the NF (nuclear factor)-κB (Lee et al. 2003; Piao et al. 2004) and its related regulatory path of inflammatory cascade (ONeil and Kaltschmidt 1997). Further the inhibition of inflammatory stimulation of microglia by wogonin reduced cytotoxicity in co-cultured PC12 neurons, provided the supporting its neuroprotective role in in vitro model (Lee et al. 2003) (Fig. 17.11).

Similarly, Baicalein a flavonoid also reported to attenuate the nitric oxide secretion by inhibiting iNOS, in microglial cells stimulated LPS studied in "BV-2" mouse, in addition to decreasing apoptosis and activation of NF-κB (Suk et al. 2003). Finally, baicalein and baicalin reported for protecting the neurons from β-amyloid triggered toxicity and inhibition of the fibrillation of α-synuclein and disaggregates existing fibrils (Lebeau et al. 2001; Zhu et al. 2004; Heo et al. 2004). The presence of baicalin in the plant reported ten times more than baicalein and baicalin transforms into baicalein in the intestine through bacteria and enters the brain as baicalein which is an active form within 20 min (Tsai et al. 2002; Zhang et al. 2005, 2007).

17.1.6 Vitis vinifera *L. (Family: Vitaceae)*

Grapes are important dietary agent worldwide and act as a neuroprotective agent. The major polyphenolic components are resveratrol (Fig. 17.12), quercetin and catechin (Fig. 17.13). They proved to decrease the cytotoxicity in cultured glial/neuronal cells of hippocampus of the rats. The treatment with grape polyphenols effectively inhibited the cytotoxicity and intracellular ROS and nitric oxide accumulation which provide beneficial roles in AD or PD (Bastianetto et al. 2000a, b). Consumption of red vine (Cabernet Sauvignon) delayed secretion of β-amyloid in Alzheimer's mouse (Wang et al. 2006), the extracts also attenuated the cognitive deterioration effect in in vitro or in vivo models such as Tg2576 mice.

17.1.7 Lead Neuroprotective Molecules

Some of the plants are reported for neuroprotective effects which are mainly based on their strong antioxidative properties as discussed below.

Melissa officinalis (*Rosmarinus officinalis*), commonly called Lemon balm which is rich in rosmarinic acid (Fig. 17.14) is being used traditionally due to its antioxidative and neuroprotective effects. It exhibits regeneration effect in PC12 cells and enhances cholinergic property (Omri et al. 2010). In addition, it contains

Fig. 17.12 Resveratrol

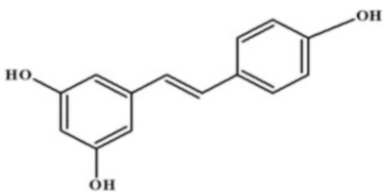


Fig. 17.13 Catechin

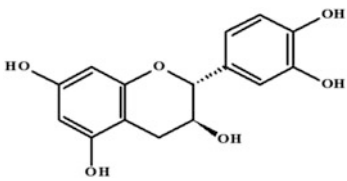
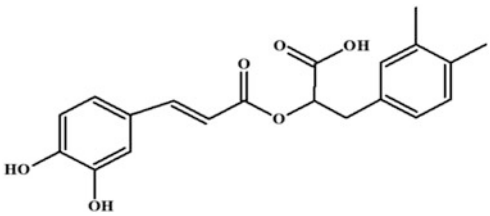


Fig. 17.14 Rosmarinic acid



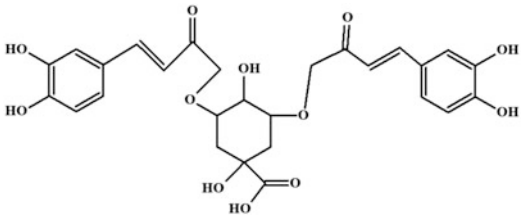


Fig. 7.15 (−)-3,5-dicaeoyl-muco-quinic acid

ursolic and oleanolic acids reported for promotion and differentiation of neuroblasts in the dentate gyrus by modulating serum corticosterone, GABA (γ-aminobutyric acid) and trans-aminase (Yoo et al. 2011).

McGee (2004) studied that 6-shogaol is a product of zingerone when the ginger is dried or cooked. It reported to inhibit the hydrogen peroxide (H_2O_2) induced in neuronal apoptosis of astrocytes, it decreases the apoptosis through inhibiting ROS, caspase 3 and Bax and upregulating "GDNF, BDNF, NGF, Bcl-2, and Bcl-xL" through "ERK1/2" mediated signaling (Kim et al. 2010). Shim and Kwon (2012) studied the effect of hydrogen peroxide induced ROS production in "HT22 hippocampal" neuronal cells and the 6-shogaol reported a notable enhancement in acetylcholine transferase, BDNF expression, choline transporter and decreased ROS.

Pimpinella brachycarpa (Apiaceae) and *Aster scaber* (Asteraceae) are source of caffeoylquinic acid which increased the survivability of C6-glioma cells through antioxidative property (Soh et al. 2003). Further, (−)-3,5-dicaffeoylmucoquinic acid (Fig. 7.15) reported for the affecting "ERK1/2" and "PI3K" through "TrkA" signaling cascade activation and subsequently affected neurite outgrowth (Hur et al. 2004; Kim et al. 2005). Quinic acid normalizes neurodegenerative effects through improving the free radical quenching system and protects neurons and potentiates "neurite outgrowth."

17.1.8 Miscellaneous Phenolic Compounds as Neuroprotective Agents

Passiflora alata and *P. edulis* flavonoids have proved for improvement in behavioral progress in rats (Barbosa et al. 2008). The *Passiflora* possess the flavonoids such as "apigenin-8-*C*-*β*-igitoxopyranoside," "apigenin-8-*C*-*β*-boivinopyranoside" (Fig. 17.16), and "luteolin-8-*C*-*β*-boivinopyranoside" (Xu et al. 2013), which might be the active constituents exerting antioxidant, anti-inflammatory, and anticarcinogenic effects. The treatment with apigenin in "APP/PS1 mice" model downregulated BACE, *β*-CTF, and *β*-amyloid deposition and restored BDNF expression leading to enhanced memory and synaptic plasticity ensuring prevention of AD (Zhao et al. 2013).

The lignans of Abies holophylla reported for decrease in nitric oxide generation in C6-glial cells (Kim et al. 2013), Apigenin on LPS induced microglia inhibited the

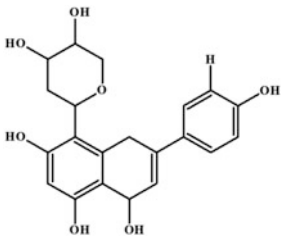


Fig. 17.16 Apigenin-8-C-β-boivinopyranoside

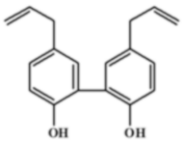


Fig. 17.17 Magnolol

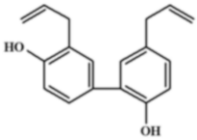


Fig. 17.18 Honokiol

production of nitric oxide and PGE2 through its scavenging role and found effective at molecular level in treatment of neurodegenerative diseases (Yang et al. 2005). Sanka et al. (2018) discussed and reviewed that polyphenolic compounds Magnolol (Fig. 17.17) and Honokiol (Fig. 17.18) from the stem bark of Magnolia officinalis show "peroxisome-proliferator activated receptor gamma agonistic" property (PPAR-γ) and effects like GABA modulator in addition to decreasing the precursor of amyloid and its products. Hence it is effective in the treatment and prevention of AD and the potential molecule for neuroprotective therapeutics. Oral administration of Magnolol (Fig. 17.17), (30 mg/kg) to mice model (C57BL/6N) once a day for 4 or 5 days along with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) a neurotoxin, treatment significantly attenuated the MPTP initiated decrease in dopamine transporter and tyrosine hydroxylase levels in the striatum without affecting GFAP levels. In addition, magnolol significantly inhibited MPTP-induced peroxidation of lipids, toxicity, and generation of ROS in human neuroblastoma cells, which indicates its beneficial role in Parkinson's disease (Muroyama et al. 2012).

17.2 Perspectives

Increasing demand for the natural anti-aging products from medicinal plants were more focused on the development of CNS active substances. Though the synthetic medicine/compoenets showed adverse side effects and non affordable. In this context, the natural substances which are having rational basis and scientific support are

being propagated for its wide usage as a preventive mechanism. The plants such as green tea, grape juice, *Ginko, Scutellaria*, Turmeric, *Centella asiatica,* etc. were investigated and revealed the molecular mechanisms which strongly suggests its benefits and opens new frontiers of research to further develop the commercial scaling and may be improved with content of bioactives. The bioactive plant phenolics characterized from above plants such as resveratrol, curcumin, epigallocatachins, flavonoids, coumarins or phenolics using molecular farming.

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Chapter 18
Herbal Remedies for Autism

Mukundan Chilambath and Geethalakshmi Sundararaman

Abstract The fundamental features of autism spectrum disorders (ASD) are long-term deficiency of interaction and social communication, repetitive behavioural patterns and impaired development. It comprises a group of neurodevelopmental abnormalities that begin in early childhood. The exact reason for autism is unclear but the immunological, genetic, psycho-social and biological factors are involved. Children with autism will be having delayed brain and body development due to lack of nutrition because of less nutrient intake and selective eating, so nutrition and balanced diet is important. The antisocial and repetitive behavioural patterns and communication disabilities can be reversed by proper education and behaviour therapy. Although there is no medicine to treat autism, risperidone is the only drug which is approved by FDA for treating children affected with autism spectrum disorders. Medicinal plants with neuroprotective effects on autism have been reported. Medicinal herbs such as *Zingiber officinale, Camellia sinensis, Piper nigrum, Curcuma longa, Bacopa monnieri, Glycine max, Prunus dulcis, Ginkgo biloba, Arthrospira platensis* and *Chlorella vulgaris* have been claimed for neuroprotective effects and might be useful in treating the problems associated with autism spectrum disorders. Herbal medicines are promising treatment or remedies for reducing symptoms of autism and improving memory, cognition and behaviour.

Keywords Autism · Neuroprotective effects · Medicinal herbs · Risperidone · Cognition

18.1 Introduction

Brain is the most vital organ in the human system and is the central organ of nervous system. It acts as a command and control system of body. It regulates the voluntary activities, balancing of body and functioning of other important involuntary organs

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of body. Also it regulates the body temperature, digestion, hunger, thirst, activities of endocrine glands and human behaviour. Brain processes the vision, hearing, speech, memory, intelligence and emotions and thoughts. As brain is a vital organ in human body with numerous functions, any disorders affecting brain may result in improper functioning of body and internal organs. Thus the brain should be supplied with vital nutrients which are essential for effective functioning of the body.

18.1.1 Autism

Autism is commonly a brain-based disorder which is strongly genetic in nature. **Autism or autism spectrum disorders (ASD)** is defined as a broad range of neurodevelopment disorders characterized by challenges with social skills, repetitive behaviour, speech and nonverbal communication and impaired social functioning. Several types and subtypes of autism are there, affecting children, most influenced by combination of environmental and genetic factors.

People with autism have trouble with communication and in understanding the feelings and thinking of others. Thus it makes them hard to express their feelings and expressions through words, gestures, facial expressions and touch. Also they have problems with learning and the development of various skills in them might be in an uneven pattern. This could be trouble in communications skills but be unusually good at music, arts or any other specific skills (Bahmani et al. 2016).

18.1.2 The Brain and ASD

Children affected by autism have excess synapses and connections between the brain cells. This is mainly because of the lack or sometimes sudden shutdown of the normal pruning process that occurs during brain development. A typical pruning process will be happened in an individual at late adolescence, which is actually the elimination of about half of the cortical synapses. Cortical synapses are found in the cerebral cortex, which plays a vital role in receiving and processing the information from various senses. Some children affected by autism are seen to be having a larger brain than normal. However, the role of brain in autism is not clearly understood.

Neuroimaging studies in ASD shows the abnormalities in different parts of brain such as frontal cortex, cerebellum, hippocampus and cerebello-thalamo-cortical pathways in autistic patients. One of the ASD studies' findings are presence of focal cortical dysplasia due to the heterochronic division of germinal cells leading to abnormal migration of the daughter cells to their target regions. Abnormal neuronal migrations lead to the circumscribed foci of thin cortical area of ASD brain especially in frontal lobe which contains smaller pyramidal neurons and interneurons. These findings attribute the sensory and motor deficit and impaired functions in ASD patients. The increased size of brain in autistic children is due to autism-epilepsy or

autism associated with macrocephaly, which is a condition of accelerated brain growth in early developmental stage.

18.1.3 Symptoms and Signs of Autism

- Lack of eye contact.
- A narrow range of interests and showing more interest in certain topics.
- Highly sensitive to sounds, touches and smells.
- Not looking and listening to other people.
- Doing certain tasks or activities over and over. Repeating certain words or phrases and rocking back and forth.
- Abnormal tone of voice.
- Learning disabilities and deficit in language comprehension.
- Lack of empathy and self-abusive behaviour.
- Affected children will not smile or laugh in response to others' activities (Klein and Kemper 2016).

18.2 Pathophysiology of ASD

The pathophysiology of autism spectrum disorders involves the defects in several genes and most of them are involved in neuronal synaptogenesis. Along with these genetic factors, many environment factors, associated conditions such as gastrointestinal (GI) abnormalities and immune balance are also the pathophysiological conditions of ASD. Although there is a strong genetic base for ASD, several other factors could have direct link and impact to the pathogenesis of ASD. In many children, these external factors act as modifying factors of these genes in aggravating the disorders.

Many children affected by autism have GI problems such as abdominal pain, chronic diarrhoea, constipation, vomiting, gastro-esophageal reflux, intestinal infections, etc. The gastrointestinal tract is having a direct connection with immune system of body; mucosal layer and Peyer's patches on GI tract have profound effect on immune responses and reactions. Thus children suffering from ASD will be having immune response imbalance due to gastrointestinal problems.

Immune system imbalance is also a condition seen in ASD due to the neuroinflammation; it causes abnormalities in activating microglial cells and innate neuroimmune system. Because of the neuroinflammation, immune dysregulation and increased inflammatory cytokines in brain alter the structure and functions of blood–brain barrier (BBB) causing imbalance in brain metabolism and dysregulation of brain homeostasis. Along with this, maternal infections and autoimmune disorders also cause immune imbalance in ASD patients (Brondino et al. 2015).

18.2.1 Genetic Factors

Genetics also plays a major role in autism. Autism occurs more frequently in patients and in certain families with some other genetic disorders such as fragile X syndrome, tuberous sclerosis, congenital syndrome and untreated phenylketonuria. There is not a single gene, which is responsible for autism but there tends to be a pattern of autism and other genetic disorders in families. Some children are born susceptible to autism spectrum disorders and the factor which triggers it to cause autism is unknown.

Even though the exact pathophysiological mechanism of autism is unknown, it is evident from several studies that genetic factors have a great impact on the aetiology of ASD. For instance, tuberous sclerosis, fragile X syndrome and Rett syndrome are some conditions which are associated with ASD. It is also seen that the siblings and twins of autistic children have a higher chance of getting autism. Thus, it says the strong role of inheritance of autism. There is a wide range of phenotype but more genetically homogeneous ASD patients present are with less phenotypic heterogeneity. It was found that the de novo copy number mutations and rare variant mutations wish is resulting in abnormal alleles in the affected person or close ancestry that influence neuroanatomical and behavioural traits. This is because of the dysregulation in genes which are involved in synapses functions. It is also evident from studies that the abnormal combination or structure of several transmembrane and scaffolding proteins involved in synapsogenesis and its maintenance, dysregulation of genes involved in signal transduction mechanism of synapse formation, which are some of the common and major genetic abnormalities of ASD.

The mutations in mitochondrial DNA also have a role in ASD, because several neurological disorders are having a condition of mitochondrial dysfunction. Mutations in mitochondrial DNA lead to impairment of energy metabolism. Mitochondria itself has antibacterial immunity and if mitochondrial dysfunction happens due to mutations, it leads to greater GI tract infections in autistic children (Bastaki et al. 2020).

18.2.2 Non-genetic Factors

The exact reason or causes of autism spectrum disorders are unknown, but majorly autism features abnormalities in brain structure or functions. Non-genetic factors are also having a great impact in the aetiology of ASD. It is evident that gastrointestinal problems such as abdominal pain, constipation, diarrhoea and vomiting are seen in autistic patients due to GI infections and gut leaks. Due to leaky gut or intestinal epithelium, the gluten and casein or digested products leak out to the bloodstream, which causes immunogenic response in brain. Thus GI abnormalities are very common in autistic children which affects the gut–brain interaction and thus leads to pathogenesis and severity of ASD (Mulloy et al. 2010). Apart from this, several other factors like stress, inflammation, toxins or drugs like valproic acid or

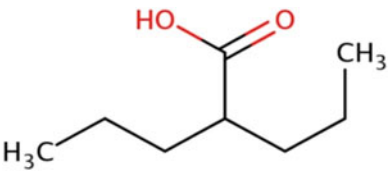

Fig. 18.1 Structure of valproic acid

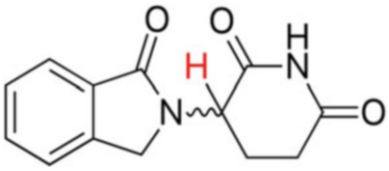

Fig. 18.2 Structure of thalidomide

thalidomide and even infection exposure during pregnancy may also increase the risk of autism spectrum disorders in children (Theoharides and Asadi 2012) (Figs. 18.1 and 18.2).

18.3 Screening and Diagnosis of ASD

Early diagnosis of autism spectrum disorders in children is very difficult as it does not have any medical tests to diagnose. Many children are not diagnosed early because ASD ranges from mild to severe and this may cause delay in treatment for years. The following are the common methods used in diagnosis of autism in children (Filipek et al. 1999; Kabot et al. 2003; Sharma et al. 2018).

- **Developmental Screening:**
  Developmental screening is an efficient test in diagnosing autism, in which a paediatrician would be testing the learning skills of a children and observing the learning process, speaking skills, behaviour and movements.
- **Observation of Speech problems:**
  This helps in the evaluation of speech and hearing developments in child. During this test, doctor will be observing how a child respond and react to the parent's smile, voice and activities. The communication skills are also observed here.
- **Evaluation of Social skills:**
  Determining the social skills is very important in diagnosing autism. Children with autism are not able to look into others' face or eyes. The do communicate without expressions and gestures and repeating certain words. This evaluation helps in finding of children's communication, gross motor, fine motor, problem solving and personal adaptive skills.
- **Comprehensive Diagnostic Evaluation:**
  A comprehensive diagnostic evaluation helps in diagnosing children with autism by observing child's behaviour, development and by interviewing parents.

Screening of vision, speech, communication, genetic screening and neurological testing.

ASD is diagnosed in children early by evaluating the impairment in social interaction, communication and a restricted and repetitive behavioural patterns, interests and activities (Page 2000).

18.4 Treatment for ASD (Pellow et al. 2011; Sze and Wood 2008; Akins et al. 2010)

18.4.1 Behaviour Programmes

Behavioural therapy programmes are offered by several government organizations to help people in improving communication, social interaction with other people, positive reinforcement and social training for improving behaviour and communication.

Applied behavioural analysis (ABA) and Treatment and education of autistic and related communication handicapped children (TEACCH) are treatment available for children affected with autism.

18.4.2 Education

Educating children with autism spectrum disorders is also a better mode of treatment for improving their skills and various abilities. The individuals with disabilities education act (IDEA) determines about providing of education to children affected by autism.

18.4.3 Medications

Although there is no proper treatments or medication for autism spectrum disorders, there are treatment for symptoms of autism.

Medications and therapy should be given under the proper advice of a paediatrician. Antipsychotic agents such as risperidone, aripiprazole and drugs such as methylphenidate, fluoxetine, anti-seizure medications are used commonly (Calarge et al. 2014).

18.4.4 Sensory Integration

Children with autism are very much sensitive to external stimuli such as sound, texture, taste, odours, etc. Some children may become agitated by touching, hearing or seeing certain things, tasting certain tastes and smelling certain odours. Training to adapt to these may improve behaviour.

Sensory integration therapy assesses how an autism affected child's brain is processing various sensory inputs. A physiotherapist or an occupation in this field evaluates the autistic children and creates a plan which matches the sensory stimulation and physical movement, which can improve the brain in processing and organizing sensory information.

18.4.5 Assistive Technology

This type of treatment involves use of technology in improving nonverbal, communication disabilities and functional incapability of severe autistic children. It involves the use of computer, mobile or any mobile applications with programmes designed to engage children with autism. Children with severe communication disabilities and hearing impairment can be treated using technology to improve their communication skills.

18.4.6 Balanced Diet

A balanced diet and supplementation of vitamins is advised and prescribed by clinicians for autistic children. Improvement in symptoms is seen in autistic children who are given with a proper balanced diet. Some autistic children show symptoms such as constipation and habit of eating in an unusual manner. These symptoms can be reduced by a keeping a proper diet.

Children with autism may have an allergy or high sensitivity to food containing gluten or casein. Autistic children's body processes peptides and proteins in food containing gluten and casein in a different way than other people. Thus gluten-free, casein-free (GFCF) diet is provided for children with autism. The diet eliminates all gluten containing food (wheat, barley, etc.) and casein (milk and dairy products).

Benefits of GFCF diet are improved social interaction, improved speech and language, decreased self-injurious and antisocial behaviour, improved focus and awareness, and increased immune function (Johnson 2006).

18.5 Treatment and Herbal Remedies for Autism Spectrum Disorders Treatment

Although no specific medicines has been recognized to treat autism, risperidone is the only drug approved by the FDA used in children affected with autism spectrum disorders. Other pharmacological treatment methods are adopted to reduce the signs and symptoms such as sleeping disorders, self-abusive and harmful activities, repetitive behaviour, etc. Plants having neuroprotective effects on autism have been recognized and can be used as herbal remedies for autism (Sharma and Chouhan 2016; Saki and Nadari 2018; Selvakumari et al. 2021). Complementary alternative medicine therapy (CAM) is the most effective treatment method for autism. They are of two types:

- Biologically based CAM.
- Non-biologically based CAM.

18.5.1 Biologically Based CAM Treatment

(a) **Balanced diet**
One of the popular and effective treatment method is the elimination diet, that is the gluten-free, casein-free (GFCF) diet as gluten and casein protein may originate opiate-active metabolites in the gut that could reach the systemic circulation because of gastrointestinal problems in ASD. In addition to this, low carbohydrate, high fat-ketogenic diet is administered to children with refractory epilepsy, this dietary regimen determines a better seizure control and has an effect much comparable to antiepileptic drugs.

(b) **Vitamins**
Vitamin supplementation is another CAM therapy for ASD. Dietary deficiency of important vitamins and micronutrients is observed in autistic children. It has been reported that autistic children are introduced with vitamin-D, K, A, E and vitamin B6 in lesser than recommended amount. These deficiencies are resulting in food selectivity and altered gastrointestinal absorption. This can be reduced to great extent by providing proper vitamin and nutrient supplementation (Rezapour et al. 2016).

(c) **Nutraceuticals**
Nutraceuticals are food substances which provides good health and medical benefits including disease prevention and treatment. It consists of dietary supplements such as vitamins, minerals, amino acids, etc. Providing nutraceuticals is a potential treatment for autism with limited and no side effects (Brown and Patel 2005).

18.5.2 Non-biologically Based Treatment

The National Center for Complementary and Alternative medicine (NCCAM) categorizes the non-biologically based CAM therapy into three Categories. They are:

(a) **Mind-body medicine**
Prayer, yoga, music, dance, meditation and arts
(b) **Manipulative and body based practices**
Acupuncture and massage
(c) **Energy medicine**
Homoeopathy

18.6 Herbal Remedies

The trend and practice of usage of medicinal plants as a source for preparation of new drugs for treating various diseases are emerging. Medicinal plants are herbs which contain active compounds or ingredients in their tissues and are effective against a wide range of diseases. Medicinal herbs used as medicinal source for preparation of drugs are available, effective and inexpensive. It is having a very fewer or no adverse effect than a chemical drug or compound. Different medicinal plants have different properties and various active compounds in them which are having effect on human body (Bang et al. 2017; Mourão-Miranda 2018; Selvakumari et al. 2021).

Recently, it was found that certain medicinal plants can be used for treating autism spectrum disorders. The neuroprotective activity of phytochemicals in plants is having a promising effect on autism (Al-Askar et al. 2017).

*18.6.1 Ginger (*Zingiber officinale*)*

Zingiber officinale Roscoe (Ginger) belongs to the family Zingiberaceae, is one of the spices which is frequently used. It is extensively used in traditional medicine to treat various diseases including gastrointestinal and digestive problems. The components present in ginger are gingerols, zingerone, parasols and shogaols. Ginger shows a wide range of pharmacological properties like anti-inflammatory, anti-cancer, anti-allergic, anti-diabetic, analgesic, anti-hypertensive, antioxidant, immunomodulator activity, neuroprotective activity, memory enhancing activity and many other. Ginger may also be used to treat autism and antisocial behaviour of autistic children.

The gut microbiota in organisms are having a potential to change the brain and behaviour. It signs in autism and other neurological disorders. These gut microbiota produce propionic acid as a secondary product which is commonly used as food

preservatives. The infusion of propionic acid into veins induces repetitive dystonic behaviour, excessive movements, turning behaviour and retropulsion. Several social interaction studies were conducted in mice using ginger extracts and it was observed the activity of ginger against propionic acid induces social behaviour impairment. The neurodegeneration, change in neuronal cell integrity by the interference with propionic acid was resulted in antisocial behaviour and behavioural changes. This type of propionic acid induced social impairment can be treated using ginger as it is having protective effects against it. Thus ginger may be included in treatment strategy of autism spectrum disorders (Parashar and Udayabanu 2016; El-Ansary et al. 2018).

18.6.2 Flavonoids in Camellia sinensis *(Tea Plant)*

In ASD patients, higher levels of oxidative stress are seen. The autism patient's exposure to various environment pro-oxidant factors including pharmaceutical compounds such as valproic acid, heavy metals, air pollutants and toxins of bacteria or viruses are involved in triggering oxidative stress in them.

It is evident from different studies that green tea therapy using *Camellia sinensis* is effective in decreasing oxidative stress. This plant is a major dietary source of polyphenol- flavonoid. Catechins such as epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate and epicatechin are the flavonoids present in *Camellia sinensis*. It also contains gallic acid, chlorogenic acid, caffeic acid and flavanol derivatives such as kaempferol, myricetin, quercetin, etc.

*18.6.3 Pepper (*Piper nigrum*)*

The active phytochemicals in *Piper nigrum* have effect on behavioural alterations and oxidative stress in autistic patients. Piperine is the major alkaloid present in *Piper nigrum* which shows antioxidant, neuroprotective and cognition enhancing effects. The oxidative stress and behavioural impairments can be reversed by piperine in autistic patients. A study on amelioration effects of piperine in behavioural alterations reveals that piperine treatment restores the motor deficit and decreases the reorientation time due to its ability to cure cerebellar damage, which is a condition of autism spectrum disorder.

*18.6.4 Turmeric (*Curcuma longa*)*

Turmeric (*Curcuma longa*) is an Indian spice of ginger family Zingiberaceae. Turmeric is well known for its protective action against neurodegenerative diseases

and neuropsychiatric disorders. It is because of the presence of chemical compounds called curcuminoid. Curcumin (Diferuloyl methane) is the major curcuminoid present in turmeric which is a nontoxic molecule, able to cross blood–brain barrier (BBB). It is also reported to have positive effects on the treatment of autism as curcumin targets several cell signalling pathways. Curcumin is also having effects on increasing the intracellular level of glutathione, reducing inflammatory components, mitochondrial dysfunction, oxidative stress and protein aggregation, counteracting against tissue damages which are caused by heavy metals and it helps in liver detoxification.

Altered brain shape and structure is a sign of autism in children. It is due to the brain toxicity and delayed maturation of brain. These alterations can be reversed by curcumin. It also helps in improving abnormal brain weight and delayed maturation. Oral administration of curcumin restores the neurological, behavioural, biochemical and molecular changes happening in autism spectrum disorders. As such curcumin can be developed as a neuro-psychopharmacotherapeutical drug because of its characteristics and potential effects for ASD treatment (Lopresti 2017; Bhat et al. 2019).

*18.6.5 Bacosides in Brahmi (*Bacopa monnieri*)*

Bacopa monnieri, commonly called as brahmi is a medicinal plant widely used in improving cognition and memory formation. Bacosides, the medicinal substances are the main bioactive compounds extracted from brahmi plant, which is widely used by Indian tribes. It is evident that supplementation with bacosides has been shown to improve cognition, by reducing anxiety and also in improving memory formation. Neuron communication is promoted by bacosides as it is able to interact with neurotransmitter, dopamine. It does this by enhancing the Tate at which the nervous system can communicate by increasing the growth of nerve endings called dendrites. The major bioactive compounds found in *B. monnieri* are two triterpenoid glycosides denoted as bacoside A and bacoside B. Both the bacosides are able to improve cognition and memory formation. Pharmacological effects of this plant are attributed to the number of alkaloids, saponins and sterols present in it. It has been reported that bacosides modulate cholinergic densities along with acetylcholine levels, and also in presence of these compounds, the central nervous system shows beta-amyloid scavenging properties and anxiolytic relieving process. Although its biological molecular mechanism is not proven, it is known that these bacosides increase certain brain chemicals involved in thinking, learning, memory and also protect brain cells from toxic chemicals substances.

*18.6.6 Soybean (*Glycine max*)*

Individual with autism spectrum disorders consume inadequate levels of vitamins and minerals related to selective eating, decreased gut absorption, depletion of nutrients and increased needs of nutrients. The deficiency or low intake of vitamins and minerals is mainly caused by restrictive diets. Children with ASD are characterized with sensory processing disorder (SPD) which is a condition in which the brain is unable to receive, process and to respond to the information that comes in through various sensory organs. Eating is a very sensory rich activity which includes all the senses at once and this can be very overwhelming for autistic children with SPD. This nutrient deficiency causes additional cognitive and behavioural issues. To balance the nutrition, a diet rich of vitamins and minerals is needed. Soya bean (*Glycine max*) is a species of legume which is rich in vitamin B6, vitamin B12, etc. It is recommended that autistic patients use magnesium-rich food like soya bean, which is also rich in selenium (Woolf 2003).

18.6.7 Essential Fatty Acids (Vegetables, Seeds and Nuts)

Because of the restricted diets and selective eating, ASD patients have less intake of essential fatty acids such as omega-3 fatty acid resulting in many behavioural and cognitive issues. Omega-3 fatty acid is vital for cognition and brain health. A low level of this fatty acid may cause brain fog, lack of concentration, slow language development, delay in brain development and other cognitive impairment.

Supplementation with omega-3 fatty acid is helpful in improving cognition and brain development. Fish oil is rich in essential fatty acids including high amount of omega-3 fatty acid. A dose of double the dietary reference intake (DRI) is an adequate dosage for children with ASD (1200–1600 mg for children ages 9–14). Some plants are also excellent sources of omega-3 fatty acids. Autistic patients can consume vegetables, seeds and nuts which are rich in omega-3 fatty acids to meet the recommended quantity. ALA, DHA and EPA are the major 3 types of omega-3 fatty acids. Algae such as spirulina and chlorella are important sources of omega-3 fatty acids, they contain DHA and EPA. Chia seeds are very good source of ALA omega-3 fatty acids. Kidney beans, soybeans and walnuts are other best plant sources of ALA omega-3 fatty acids; they are also rich in riboflavin, folate, magnesium, potassium, etc.

*18.6.8 Ginkgo (*Ginkgo biloba*)*

Gingko (*Ginkgo biloba*) is the only living species in the Ginkgophyta division. It is an herb used to treat memory loss, cognitive disorders, glaucoma, dementia, and as a

Table 18.1 Medicinal herbs used for autism treatment and their effects

Common name of plant	Scientific name	Effects
Ginger	*Zingiber officinale*	It has effects like neuroprotective and immunomodular activities which improves neurological functions, cognition, memory and reduces antisocial behaviours
Tea plant	*Camellia sinensis*	Taking green tea therapy reduces oxidative stress as it is an antioxidant
Pepper	*Piper nigrum*	Antioxidant, neuroprotective, anxiolytic and cognition enhancing effects
Turmeric	*Curcuma longa*	Protecting from neurodegeneration and involved in cell signalling pathways
Brahmi	*Bacopa monnieri*	Improves memory, thinking, learning, communication and cognition
Soya bean	*Glycine max*	Rich in magnesium, selenium, vitamin B6 and B12. Supplement nutrients
Almond (badam)	*Prunus dulcis*	Provides recommend vitamins B12 and B6 for autism patients
Ginkgo	*Ginkgo biloba*	It affects neurotransmitter system and reduces the symptoms and aberrant behaviour in ASD
Algae—Spirulina Chlorella	*Arthrospira platensis Chlorella vulgaris*	Rich in omega-3 fatty acids, recommended for cognitive and behavioural impairments

vasodilator. As it is effective in reducing cognitive disorders and in improving memory, its extracts are being used in autistic patients. The components isolated from *Ginkgo biloba* extract contain terpenes, flavonoids, alkyl phenols, carboxylic acid, polyprenols, etc. Pharmacological studies say that Ginkgo flavonoid glycosides are predominantly responsible for its antioxidant activity. It reduces the oxidative stress induced by reactive oxygen species, which contributes to the neurodevelopmental disorders caused by membrane damage, change in DNA structure and damage, degradation of lipids, etc. Terpene trilactones present in Ginkgo are associated with the neuroprotective properties which aids in resolving the pathogenesis of autism (Table 18.1).

18.7 Conclusion

Autism spectrum disorders are recognized as neurological disorder with pervasive developmental disabilities in which no specific drug or treatment is available. As there is no medicine for treating autism, a treatment strategy including herbal medicines, education and behaviour therapy combined with balanced diet would be a great method of treating autism, which might be useful in reversing the behavioural patterns and improving cognition, social interaction and

communication. Numerous researches and studies are undergoing for treatment of autism in which herbal sources are resulting as a successful and prominent treatment method with less or no side effects.

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Chapter 19
Action of Herbal Products in Suppressing Parkinson's Disorder

Manickam Sudha Devi and Lakshmanan Krishnavignesh

Abstract The advancement of the modern health care sector enhanced longevity, resulting in age-associated chronic ailments. Parkinson's disease/disorder (PD) is the second most common neurodegenerative diseases (NDDs) of the central nervous system following Alzheimer's disease (AD) yet significantly differ in their clinical and pathological features. Biological aging is a complex process linked with aggregated cellular impairment believed to be caused by genetic and/or environmental factors causing noticeable alterations in the structure and function of the brain. Plants are having an inevitable role from time immemorial as food, spices, medicines and have been found to have many phytochemicals with various bioactivities. Current treatment regimes of PD marginally influence these diseases and are inadequate in treating the multifunctional pathological mechanisms and are treated with drugs that cause significant negative side effects, often relieve symptoms alone. Therefore, a need arises to develop novel therapeutic method devoiding serious side effects. Natural product-based agents can lower the potential side effects, offer promising treatment and prevention. Of late, plenty of ethnopharmacological studies have been reported to claim the role of herbal preparations and/or functional foods in treating/preventing of NDDs which are superior to synthetic drugs. Let's explore, elaborate, and elucidate the action of herbal products in suppressing PD.

Keywords Aging · Parkinson's disorder · Phytotherapeutics · Functional food · Nutraceuticals

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19.1 Introduction

PD is characterized by genetic defects, mitochondrial dysfunction, oxidative stress, cytotoxicity, calcium and iron overload, and neuro-inflammation, and is manifested as stiffness and bradykinesia (Thomas et al. 2019). PD is an ever-growing socio-economic challenge leading to a comprehensive reduction in the quality of life of the affected individual and also their beloveds. Though the etiology of PD has long been thought to involve both genetic and environmental factors, until recently, there has been no solid evidence to support these factors. In the recent past, six different genes have been identified to cause familial PD, namely α-synuclein, parkin, UCHL1, DJ1, PINK1, and LRRK2 following Mendelian pattern of inheritance (Schapira 2006). The established association of individual lifestyle and food habits with neurodegeneration proposes nutraceuticals for prophylactic treatment of PD. Still in the scientific world, ambiguity exists in defining the Parkinson's as disease or disorder or syndrome. Firstly, let's discuss the history, stages, rating scales, effects of PD, prevention, and probable phytotherapeutics to improve human health and lifespan.

19.2 History

In Ayurveda, one of the ancient Indian medical systems, PD was referred as Kampavata (in Sanskrit kampa refers to tremor). In Western medicine, it was termed as "shaking palsy" by the physician Galen in AD 175 (Verma et al. 2019). Ancient Chinese descriptions also provide PD. In 1960, results of the analysis done in the brains of Parkinson's patients revealed a chemical difference in lower dopamine levels and degeneration of neurons in the substantia nigra and striatum part of the brain suggesting dopamine agonist a possible candidate for effective treatment of PD (Goetz 2011).

In the year 1817, a detailed research work entitled "An Essay on the Shaking Palsy" was published by London doctor James Parkinson on this subject after whom it was coined as Parkinson's disease (PD) after six decades by a French neurologist, Jean Martin Charcot which established PD as a recognized medical condition. He studied and reported six cases in his own practice. Sylvius de la Boë described the symptoms of resting tremor, and Sauvages described festination—a form of gait/walk related to PD (Hurwitz 2014). Arvid Carlsson was awarded the Nobel Prize in Physiology and Medicine in 2000 (together with Eric Kandel and Paul Greengard) for his find a decrease in neurotransmitter dopamine levels in the brain led to PD-like symptoms (Carlsson et al. 1957).

William Gowers in 1886 in his "Manual of Diseases of the Nervous System" identified and reported that males were more susceptible to the disease than females

and also described the joint deformities which are typical of PD (Toodayan 2017). Frederick Lewy in 1912 identified and reported these Lewy bodies as a pathologic hallmark of PD. A person with PD is found to have clumps of protein in their brain known as intra-cytoplasmic inclusion bodies or Lewy bodies. Lewy body dementia is a different illness, yet has an association with PD (Engelhardt and Gomes 2017).

First injury in substantia nigra as a site of brain damage in PD was proposed by Brissaud, later in the year 1920, Trétiakoff and his coworkers further recognized the disease-related pathological studies of the midbrain (Impellizzeri et al. 2016). In the year 1953, Greenfield and Bosanquet studied brain changes and brain stem lesions delineating PD from other related illnesses. Hoehn and Yahr analyzed the staging and clinical progression of PD and developed a staging system which is recognized internationally (Rothstein and Olano 2008).

Parkinsonism defines the collection of symptoms and signs found in PD including tremor, stiffness, slowness, and postural imbalance. Mimicking Parkinson's there are conditions other than PD having one or more of these symptoms, typically more challenging to combat than PD, namely progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies, corticobasal syndrome, vascular Parkinsonism and drug-induced Parkinsonism. Idiopathic Parkinson's is one of the most common form of Parkinsonism. Fifteen percent of those with symptoms suggesting PD have one of several diseases termed, a typical Parkinsonism disorder (Greenland and Barker 2018).

19.3 Stages and Rating Scales of Parkinson's

19.3.1 Stages

Identifying the typical stages of PD can aid in the management and treatment strategies, whereas symptoms and disease progression vary person to person from less than a year to over decades making it complicate. All may neither experience all the symptoms nor in the same order and/or intensity. Typical patterns of progression in PD are defined by Krüger et al. (2017) in five stages as follows:

19.3.1.1 Stage One

Mild symptoms, namely changes in walking, posture, and facial expressions occur normally on only one side of the body, that generally do not have much impact on daily activities.

19.3.1.2 Stage Two

Symptoms start to get worse. Symptoms seen in stage one progress affecting both the sides of body. Though the individual may still be capable to be independent, the daily routine is often challenging and prolonged.

19.3.1.3 Stage Three

Considered mid-stage with impair activities like dressing, eating, hallmarking symptoms, namely loss of balance and sluggishness in movements leading often falls and yet fully independent.

19.3.1.4 Stage Four

Symptoms are severe, limiting the independence. Though standing without assistance may be possible, walker may only aid movement, making the individual dependent on someone else for the activities of daily living.

19.3.1.5 Stage Five

Standing alone itself becomes impossible due to the stiffness of legs leading to a life in a wheelchair/bedridden with 24 × 7 nursing care with many important motor symptoms and non-motor symptoms, living through hallucinations and delusions.

19.3.2 Rating Scales

Parkinson's stages related to both severity of movement symptoms and impact on the daily activities. The most frequently used rating scales focus on motor symptoms and/or non-motor symptoms. They are the:

1. **Hoehn and Yahr** introduced a scaling system for PD in the year 1967, following a simple rating scale from 1 to 5, aiding the clinicians in describing only the progress of motor symptoms without any information on non-motor problems in PD. In this, scale 1 and scale 2 are representing early, scale 3 is representing mid, and scale 4 and scale 5 are representing advanced stages of PD (Perlmutter 2009).
2. **Modified Hoehn and Yahr Scale**: The modification is made in the Hoehn and Yahr scaling by adding 0.5 increments as intermediate stages accounting for the

Table 19.1 Schwab and England activities of daily living scale

Rating scale (%)	Description of function or ADL capability or indications
100	Completely independent. Able to do all activities without slowness, difficulty, or impairment
90	Completely independent. Able to do all activities with some slowness, difficulty, or impairment. Activities may take twice as long to complete
80	Independent in most activities, but activities take twice as long. Conscious of difficulty and slowing
70	Not completely independent. More difficulty with activities, which may take three to four times as long. May take large part of day for chores
60	Some dependency. Can do most activities, but very slowly and with much effort, but some chores are impossible
50	More dependent. Help required with half of chores. Difficulty with everything
40	Very dependent. Can assist with all chores but can manage few alone
30	With effort, now and then does a few chores alone or begins alone. Much help needed
20	Cannot do anything alone. Can give some slight help with some chores. Severe invalid
10	Totally dependent, helpless
0	Vegetative functions such as swallowing

intermediate course of PD. This scaling system warrants clinimetric testing which is designed to be a descriptive staging scale to evaluate both disability and impairment related to clinical disease progression (Goetz et al. 2004).

3. **Schwab and England Activities of Daily Living Scale** grades functional status in patients with PD. The clinometric properties of rating scales used to assess motor impairment and disability in PD patients (Perlmutter 2009; Ramaker et al. 2002).
4. **Unified PD Rating Scale (UPDRS)** accounts for non-motor symptoms, like mood swing, sense of smell, cognitive difficulties, mental functioning, and social interaction introduced in 1987. Also accounts the ability in carrying out day-to-day activities and treatment complications. It is divided into three sections that assess essential aspects of disability and a fourth section that assesses any complications of treatment. It is often used with two other Parkinson's rating scales: the Hoehn and Yahr, and the Schwab and England Activities of Daily Living (ADL) Scale (Tibar et al. 2018).
5. **Trunk Impairment Scale** is a measurement which quantifies disability after stroke, also validated in PD by Verheyden et al. (2004).

"Schwab and England Activities of Daily Living Scale" is represented in Table 19.1. Though a number of scaling systems are available to assess the PD the "International Parkinson and Movement Disorder Society Task Force" recommended the selection of the most suitable instrument for a particular objective

requires consideration of the characteristics of each scale and assessment goal than development of a new scale (Shulman et al. 2016).

19.4 Different Hypothesis Proposed for PD

19.4.1 Braak's Hypothesis: Theory of PD Progression

Braak's hypothesis, which suggests that the very first signs of PD appear in the enteric nervous system, the medulla, and the olfactory bulb, which governs smell. According to this theory, PD progresses only to the substantia nigra and cortex over time, which is increasingly supported by evidence that non-motor symptoms such as a loss of sense of smell (hyposmia), insomnia, and constipation may occur several years before the motor symptoms of the disease. As a result, researchers are increasingly focusing on these non-motor symptoms in order to detect PD as early as possible and find ways to slow or stop its progression (Rietdijk et al. 2017).

This theory also suggests, sporadic PD is caused by a pathogen that enters the body through the nasal canal, is swallowed, and then enters the stomach, causing Lewy pathology (LP) in the nose and digestive tract. The same study group proposed a staging approach to describe the spread of LP from the periphery to the CNS. Braak's hypothesis has been challenged, in part because not all patients follow the recommended staging strategy (Visanji et al. 2013).

Obergasteiger et al. (2018) proposed **Spiral inflammatory Hypothesis** of PD. Compared to Braak's idea that the disease ascends from the PNS to the CNS, the **threshold theory** better accounts for the present neurobiology of PD symptom development (Engelender and Isacson 2017).

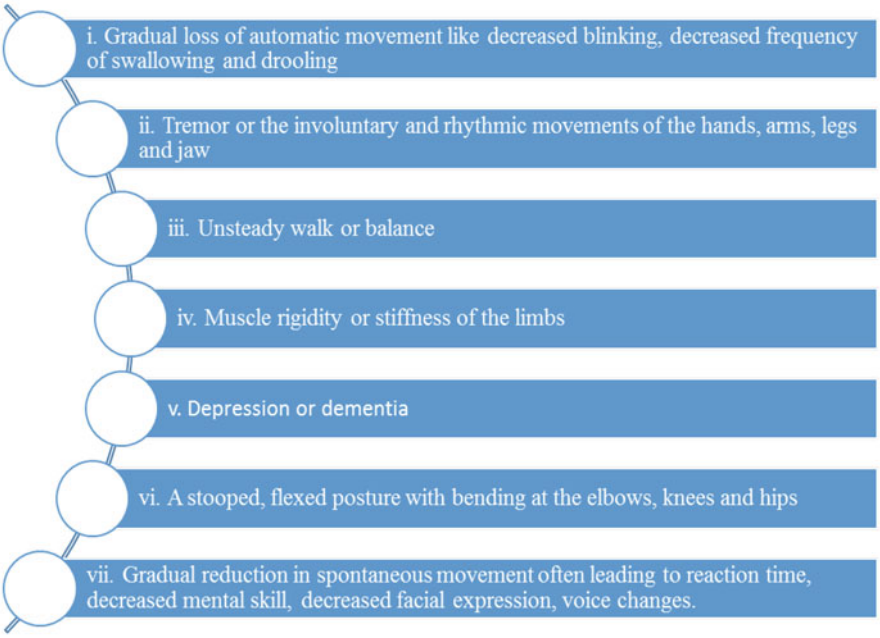
19.4.2 Brain-First Vs Gut-First Hypothesis

Pathological α-synuclein aggregates begin in the intestinal or peripheral nervous systems (PNS) and travel backwards through the vagus nerve to the central nervous system (CNS). It is thought that PD can be classified into two subtypes: PNS-first and CNS-first subtype (Per and Berge 2019).

19.5 Common Symptoms and Diagnosis

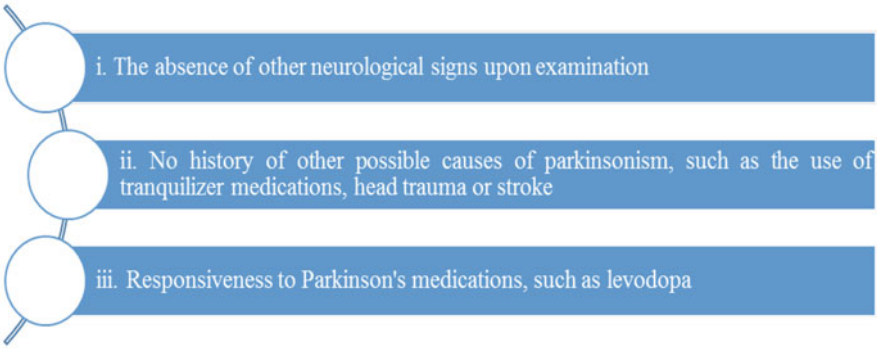
19.5.1 Symptoms

The following are the common symptoms or signs for PD.



19.5.2 Diagnosis

The diagnosis of PD is predominantly based on the common signs/symptoms delineated above. Invasive blood test or X-ray-like diagnostic procedure is lacking to authorize the PD. Non-invasive diagnostic imaging such as positron emission tomography (PET) can aid clinicians diagnosis. "National Collaborating Centre for Chronic Conditions" (UK) (2006) provided conventional methods for diagnosis which includes the presence of two of the three following primary symptoms.



19.6 Features, Causes, and Risk Factors

19.6.1 Neuropathological Features

Neuropathological features of PD include oxidative stress, imbalance in the intracellular calcium ion level, impairment of ubiquitin-proteasome system, endoplasmic reticulum stress, mitochondrial dysfunction, low levels of acetylcholine and dopamine (Chen et al. 2019).

19.6.2 Causes

The causes are unclear. Yet it is seen in the clinical examination of PD individuals when neurons die in the brain.

19.6.3 Low Dopamine

Falling levels of dopamine, a neurotransmitter, have been related to PD. This occurs when dopamine-producing cells in the brain die. Dopamine aids in the transmission of messages to the region of the brain that regulates movement and coordination. People with low dopamine levels may find it more difficult to control their movements (Juárez Olguín et al. 2016). When a person's dopamine levels fall, the symptoms of PD grow more severe.

19.6.4 Low Norepinephrine Levels

Another neurotransmitter, norepinephrine, is vital for controlling many automatic physiological functions, such as blood circulation. The nerve terminals that produce this neurotransmitter perish in PD. This could explain why persons with PD have not just movement problems but also tiredness, constipation, and orthostatic hypotension, when blood pressure changes on standing up, causing to light-headedness (NIH, Parkinson's disease, Hope Through Research).

19.6.5 Genetic Factors

PD may appear to be inherited in some cases; however, this is not always the case. Researchers are attempting to uncover particular genetic markers that may contribute to PD, but it appears that other factors are involved. As a result, they believe the illness is caused by a combination of hereditary and environmental factors. Toxic exposure, such as pesticides, solvents, metals, and other contaminants, could be a role in the environment (Billingsley et al. 2018; Klein and Westenberger 2012).

19.6.6 Autoimmune Factors

In 2017, scientists published a study in JAMA that revealed evidence of a probable genetic relationship between PD and autoimmune diseases including rheumatoid arthritis. Researchers looking into Taiwanese health data discovered that patients with autoimmune rheumatic disorders (ARD) had a 1.37 times higher likelihood of simultaneously having Parkinson's disease (PD) than people without ARD (Chang et al. 2018).

19.7 Phytotherapeutics for PD

Herbal medicines are increasingly being employed in therapy to help destroy tumor cells, as antimicrobial agents, anti-malarial, lowering of blood cholesterol and while also lowering the toxicity of combination chemotherapeutic drugs. A study reveals that traditional remedies are still used by more than 3/4th of the population in developing nations. During the early nineteenth century, a new trend involving the separation of active chemicals from plants emerged. As a result of this tendency, various active chemicals originating from plants have been discovered. Over the last few decades, an increasing number of novel plant-derived compounds have been approved and subscribed as medications (Fridlender et al. 2015).

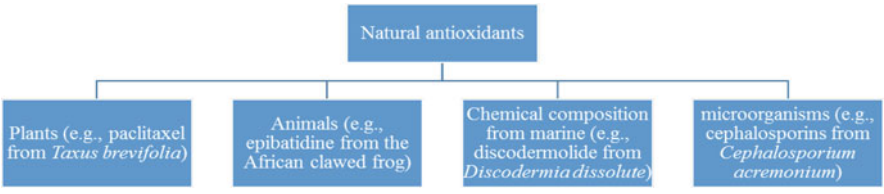
In recent years, the usage of and search for medications and dietary supplements produced from plants has increased. Ethnopharmacologists, microbiologists, botanists, and natural-product chemists are scouring the globe for phytochemicals and "leads" that could be used to treat infectious diseases and other ailments. While plants are utilized in half of today's medicines, none of them are employed as antimicrobials (Ngarivhume et al. 2015). Secondary metabolites found in plants, such as phenols, flavonoids, alkaloids, tannins, and terpenoids, have antibacterial effects in vitro. These formulations, which have no or low toxicity, may be more effective than synthetic medications (Deb et al. 2015).

Traditional therapy for PD in India and a few other parts of the world included herbal remedies containing anticholinergics, levodopa, and monoamine oxidase inhibitors (Manyam and Sánchez-Ramos 1999). Levodopa was found to be present in Mucuna pruriens and was used in the treatment of PD known as Kampavata in Sanskrit, reported by Manyam (1990).

The scientific basis of plant-derived natural products on the neuroprotective effect of 12 Chinese medicinal herbs/formulations, six Ayurvedic herbs/formulations, 33 other plants, and five plant-derived molecules has been thoroughly investigated, with a focus on behavioral, cellular, and biochemical aspects of neuroprotection observed in cellular and animal models of the disease. They increase cell viability while lowering the danger of cellular degeneration. It lends scientific support to the use of plant-derived natural compounds for the treatment of PD (Sengupta et al. 2016).

Panchkarma procedures, namely "Abhyanaga (Dashmool Tail), Svedana (Dashmoola Kwatha), Shirobasti (Ksheerbala Taila), Nasya (Ksheerbala Taila), Shiropicchu (Ksheerbala Taila), Mustadi Yapana Bast" were studied by Verma et al. (2018) and reported that the PD treated with a multimodal approach, with Panchkarma and oral medications showing considerable improvement.

Unknown author source (1995) with PMID: 9395621 reported plant-based natural antiparkinsonian medications to include anticholinergics in Datura stramonium, dopamine agonist activity in Claviceps purpura, levodopa in Vicia faba and Mucuna pruriens, and monoamine oxidase (MAO) inhibitor activity in Banisteriopsis caapi. The efficacy and tolerability of HP-200, a Mucuna pruriens-derived supplement, were investigated in this study which is a drug derived from Ayurveda, has been found to be an effective treatment for PD patients. Natural antioxidants protect neurons against PD. These natural products can be broadly classified into four categories based on sources which are given below (Mignani et al. 2018).



Zhao (2009) reported that a few natural antioxidants, namely green tea polyphenols, flavonoids, isoflavone, and nicotine protect neurons against PD. Drastic depletion of dopamine level in the brain, oxidative stress, depletion of antioxidants, and damage to mitochondria lead to neurodegeneration resulting in PD (Mythri et al. 2015). Passiflora incarnata L. is one of the important plants used in alternative systems of medicine, namely Ayurveda, one among the plants having a rich source of flavonoids. It was reported that the flowers may be used in managing dementia and Parkinsonism (Elsasa et al. 2010).

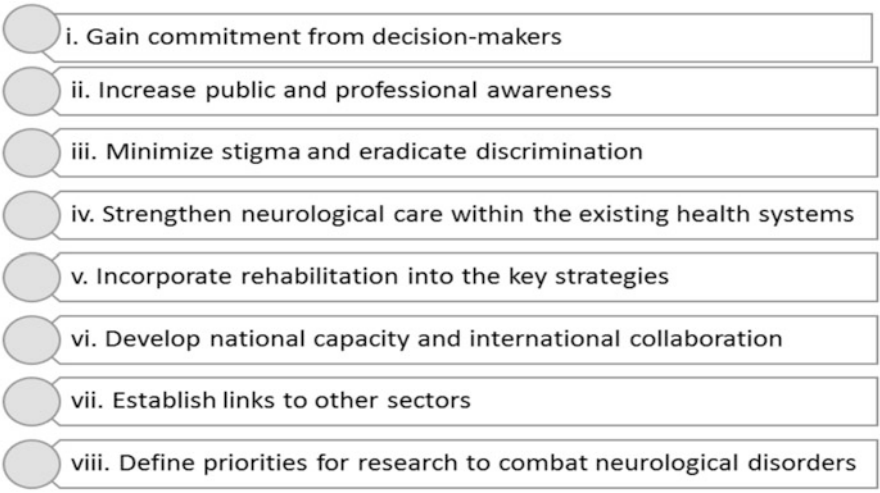
Though there are a significant number of scientific study reports available, there is an emerging need for a systematic study involving a large population to scientifically validate these natural preparations.

19.8 Prevention/Reducing the Risk

PD has been characterized with certain motor disorders like muscle stiffness, resting tremor, and sluggish movement due to slow and steady loss of dopaminergic nerves in the substantia nigra and striatum in the midbrain. At present, it may not be possible to prevent PD, but research revealed that few lifelong habits might aid in reducing the risk. These prevention factors include natural ingredients like turmeric, flavonoids and avoiding toxins and reheating certain vegetable/cooking oils like refined sunflower or corn oil which are shown to release a higher concentration of aldehydes, increases trans fatty acids and 4-hydroxy-trans-2-nominal (HNE) toxin which affects the functioning of major biomolecules, namely DNA, RNA, and proteins (Willett et al. 2006). Scientific evidence on the role of Cinnamomum species in neuroprotection in in vitro and in vivo models of different neurodegenerative disorders has been summerized by Kaur and Shri (2018). The natural products may represent a great promise for the treatment of many NDs (Paolo et al. 2019).

19.9 World Health Organization (WHO) Recommendations for Action for Neurological Disorders

WHO suggested that countries work with international agencies, NGOs, or other partners to put their plans into practice under eight subthemes.



19.10 Conclusion

There is no life deprived of mother nature. Neither the plants nor the animal. It is so vital for every life on earth! Though medical advancements extended human life to a greater extent, the majority of the aging diseases/disorders are incurable by synthetic drugs. Nature has answers for these disorders which can be used in the form of nutraceuticals. The ancient system of medicine emphasizes food as medicine. Hence, it is high time to initiate steps for research and validation of these natural products to aid one of the global challenges caused by aging called PD.

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Chapter 20
Impact of Diet on Neurotransmitters

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Abstract Practicing healthy and balanced diet is essential to ensure the body development. To date in spite of calories, focusing on food quality is much important as it plays a vital role in regulating the weight gain and loss. Foods that we intake has a vital impact on regulation of the brain parts. These have a strong relationship in either boosting or reducing the activity of central nervous system and peripheral nervous system. Nervous systems function and coordinate the body's function with the help of electrical signals generated by neurons. Major constituent (proteins, carbohydrates, and fats) and minor constituent (minerals and vitamins) serve either as an energy source or precursor for neuroactive substances. Chemical signals are known as "neurotransmitters" that control the brain for any kind of responses. Neurotransmitters such as GABA (Gamma-aminobutyric acid), dopamine, serotonin, norepinephrine, and acetylcholine have a crucial effect in the brain's functional activity. Dietary substance and supplements regulate such kind of neurotransmitters. Too high consumption of processed, packed food and other artificial additions led to physical and mental illness. This chapter discusses precisely on how different nutrients and types of diet are crucial in activating and deactivating the neural chemical signal.

Keywords Neurotransmitters · Neuromodulators · Chemical signal · Excitatory · Inhibitory

20.1 Introduction

"It is healthy that is real wealth and not pieces of gold and silver"
—Mahatma Gandhi

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A diet is one of the best things that prevents and controls health of the living system. Healthy diet plays an important role in shaping the lifestyle of humans. The biological functions of the human body depend on the dietary components in the food systems. Developing countries particularly in India, traditional foods mostly are considered as ayurvedic healthy diets since they contain functional components such as body-healing chemicals, antioxidants, dietary fibers, and probiotics. Consumption of high calorie foods has led to the ailments like obesity, food poisoning, dehydration, cardiac problems, diabetes mellitus, arthritis, and other serious complications (Shridhar et al. 2015). The human brain can function better when balanced and nutritious diet is provided. Brain works round the clock (even at sleep) by regulating the actions of movements, breathing, heartbeat, and senses. In addition to regular exercise and good sleep, eating nourishes food makes the brain function in appropriate way. Foods have a property to initiate the chemical signals called neurotransmitters in the brain. These neurotransmitters are responsible for the mood and well-being of mankind. Mental illness such as anxiety and depression is due to these chemical signals. Although supplements are available in markets to initiates these signals, neurotransmitter-rich foods can boost up these ill effects most significantly (Millstine et al. 2017).

Specifically the food that boosts the mental health has been a special consideration in the current years. In this chapter, we attempt to discuss in detail on the dietary components that directly or indirectly influence the neurotransmitters.

20.1.1 Major Brain Boosting Foods

Healthy and balanced diet practice is essential to ensure the development of the body. Foods that we consume are so vital in developing and regulation of the brain parts. These have a strong relationship in either boosting or reducing the activity of central nervous system and peripheral nervous system. A few examples of foods that are ubiquitous which aid in the functioning of brain are discussed below.

20.1.1.1 Whole Grains

Whole grain provides the brain with simple carbohydrate specifically glucose which is responsible for growth and development process (Vega-Gálvez et al. 2010). In contrast to carbohydrates, whole grain foods contain fiber that mediates the level of released glucose into the blood stream and inhibit the extreme spikes in blood sugar levels because increased sugar level causes children to lose focus and concentration.

20.1.1.2 Eggs

High content of protein is found in eggs and this protein is used in the formation and regeneration of body cells. Eggs also boost up the memory stem cells of the brain helping the infants to boost their memory retention (Miranda et al. 2015).

20.1.1.3 Vegetables

Vegetables have most abundant of vitamins that helps in development of body process. Deep colored vegetables such as carrots, kale, tomatoes, and spinach have a high content of antioxidants which promote a health of the brain. Vegetables that are rich in antioxidants help to counter the neurodegenerative effects caused by free radicals in the body (Spencer et al. 2017).

20.1.1.4 Sea Foods

Sea foods are rich source of omega 3 fatty acids, which are responsible for the growth of the brain and the cognitive function. Several reports and research done on omega 3 fatty acids have shown that they aid to boost the mental skills and increase concentration. Fishes like Salmon, tuna, sardines, and oysters are some of the few examples that contain high omega 3 fatty acids (Hosomi et al. 2012).

20.1.1.5 Lean Meat

Lean meat is one of the iron-rich source foods that promotes the production of red blood cells and helps in formation of cells. In concern with infants, iron makes them to be energized throughout their daily activities and in addition it increases their attention. Vitamin B12, which is also present in lean meat, promotes normal brain function and zinc promotes the brain neurotransmitters (Wade et al. 2019) (Table 20.1).

20.1.1.6 Dairy Foods

Dairy foods such as milk and its product are highly rich in proteins and vitamins. They are essential for the tissue growth, particularly in functioning of neurotransmitters as well as enzyme activity in the brain (Lee et al. 2018).

Table. 20.1 Dietary source that critically impacts the brain neurotransmitters

Neurotransmitters	Fruits	Vegetable/ plant source	Animal source	Pulses	Dairy foods	Sea food	Solid foods	Liquid foods	References
Acetyl choline	Aubergine, bitter orange, wild strawberry	Bean, radish, spinach, squash, fox-glove, mistle-toe, nettle broccoli	Lean chicken breast, beef, pork, eggs	Mung bean, pea, navy bean	Low fat milk	Fish (salmon) and shrimp	–	Human milk	Hartmann and Kilbinger (1974), Fryer et al. (2012), Ilcol et al. (2005)
Glutamate	Grapes	Tomato, sauce, mush-rooms, spinach	Meats, salami	Fermented beans, miso, soy sauces	Cheese, parmesan cheese	Fish sauces, sea-weeds, oyster sauce	Gravies, noodle dishes, ready-to-eat meals, savory snacks, stews	Instant cof-fee powder, soups	Jinap and Hajeb (2010), Rangan and Barceloux (2009)
GABA	Pokeroot	Fava beans, broccoli, kale, maypop, mouse-ear hawkweed, Rice shiitake, spinach St John's wort, sweet potato, tomato, vale-rian, wheat, wild celery	Chicken, beef	Adzuki bean, bar-ley, chest-nut, buck-wheat, com-mon bean, lupin, oat, pea, soya bean	Cheese	Fish (*Pleuronectes flesus*)	Rice pasta	Supplements	Li et al. (2011), Park and Oh (2007)

Dopamine	Aubergine, apple, orange, banana	Avocado, Banana, plantain, spinach, tomato, velvet bean	Unprocessed chicken and turkey	Common bean, pea	Milk, cheese and yogurt	Salmon and mackerel	Dark chocolate	Supplements	Geldwert et al. (2006), Briguglio et al. (2018)
Serotonin	Bananas, green coffee bean, kiwi, nettle, passion fruit, paw-paw, pineapple, plantain, plum, pomegranate, strawberry, tomato	Chicory, Chinese cabbage, coffee powders, green onion, hazelnut, lettuce, Griffonia Simplicifolia, pepper, potato, spinach, velvet bean, wild rice	Eggs, turkey	Nuts	Cheese milk	Salmon	Paprika, chocolate	Soya milk	Jenkins et al. (2016), Briguglio et al. (2018)
Histamine	Citrus fruits, papaya, pineapples, plums, kiwi, and bananas	Dandelion, fermented sausages, sauerkraut, soybean food products, soy, tempeh	Cured dry meat products, ham, ketchup, nettle	Doenjang, doufuru, doenjang	Aged cheeses, sour cream, fresh milk, yogurt	Anchovy, billfish, sardine, Scomberesocidae	Pickles or pickled veggies	Beer, champagne. Sherry, red, white dessert wines	Shukla et al. (2011), Briguglio et al. (2018)

20.1.1.7 Peanuts

Peanuts has abundant source of Vitamin E that provides a shield to the nervous membranes. Peanuts in addition consist of vitamin B that is necessary for brain development in children and old age women (O'Brien et al. 2014).

20.1.1.8 Fruits

Fruits are important part of healthy eating pattern and obviously rich in many vita nutrients. They are the important sources of vitamins and antioxidants. Fruits for example apples and plum are enriched with quercetin, an antioxidant that helps to boost mental skills. Other fruits such as berries contain seeds that are high in omega-3, which helps to boost brain function.

These fruits nourish the nerve cells, reduce inflammation, and protect against neural degeneration (Miller et al. 2017).

20.2 Neurotransmitters

Neurotransmission is a signaling process that transmits the information from one nerve cell to another. The information transmitted is passed as tiny electrical signal by the neuron. The cell information are not passed directly from one to another target cell (muscle, glands, and nerve cells); however, significantly chemical messengers play a key role in transmitting these information. These chemical messengers are called as neurotransmitters. They stimulate the brain cells for a variety of functions which are integral in shaping everyday life and functions (Sheffler and Pillarisetty 2020). The overall chemical process is termed as synaptic transmissions. During this process, the release of neurotransmitters from presynaptic neural cells to postsynaptic receptors occurs. Changes in the level of specific neurotransmitters lead to several neurological disorders predominantly such as Parkinson disease, schizophrenia, depression, and Alzheimer disease.

20.2.1 Types of Neurotransmitters

Based on the actions, neurotransmitters are classified into three types (Fig. 20.1).

(a) **Excitatory neurotransmitters**: These types of neurotransmitters generate a signal called action potential in the receiving neuron that is, encourages the target cells to take action.
(b) **Inhibitory neurotransmitters**: These types of neurotransmitters have inhibitory effect on the receiving neuron, that is, discourages the target cell to take action.

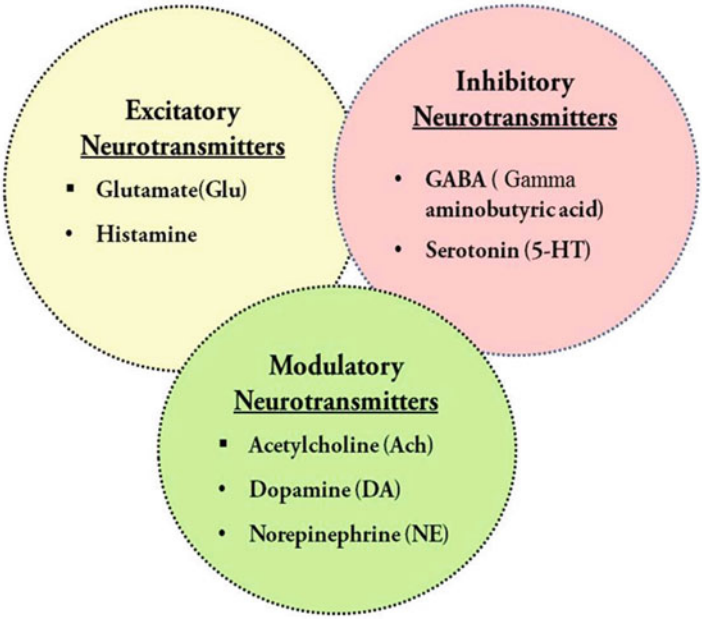

Fig. 20.1 Major types of neurotransmitters

(c) **Modulatory neurotransmitters:** These type of neurotransmitters affect the number of neurons at the same time influence the effects of other chemical messengers, that is, at the same time they can send message to different neurons.

20.3 Acetylcholine (Ach)

Acetylcholine (Ach) is a neurotransmitter that performs its functions in both the central and peripheral nervous systems. Like other neurotransmitters (for example, serotonin and dopamine) it does not contain amino group attached to aromatic ring by carbon chains. But it contains a unique group, choline and acetyl coenzyme A (Ac-CoA). Acetylcholine is found in both vertebrates and invertebrates (Picciotto et al. 2012). Acetylcholine (Ach) is one of the neurotransmitter that is present in ample amount in the animals and human body. The body parts that mimic the influence of acetylcholine termed as cholinergic effect. In plants Ach is present in most of the plant species that are categorized in the major systemic groups (plant families: *Gramineae*, *Leguminosae*, and *Solanaceae*) (Odjakova and Hadjiivanova 1997).

20.3.1 Significance of Acetylcholine (Ach)

The critical body functions are vitally mediated by Ach neurotransmitters. Significant functions of Ach are observed both in central nervous system (CNS) and peripheral nervous system (PNS). In central nervous system, it is responsible for the network dynamics and thereby resulting of behavioral transitions, for instance, distraction to attention, learning, sleep to wakefulness and recall (Lee and Dan 2012). In addition, it influences highly the cognitive functions of the target areas. In peripheral nervous system particularly it is involved in the contraction of muscles. These neurotransmitters are present in all motor neurons and involve most predominantly in all primary body movement functions such as stomach, heart movements and movement of eyelash.

Insufficient amount of acetylcholine leads to brain disorder such as dementia and Alzheimer's disease (Haam and Yakel 2017).

20.3.2 Dietary Influence on Acetylcholine (Ach)

Direct intake of acetylcholine cannot be possible; however, the dietary supplements regulate the release of Ach neurotransmitters (Fig. 20.2). Certain foods are responsible for the increase of acetylcholine and some inhibits its release. Increasing the acetylcholine levels can be achieved by consuming foods that are highly rich in essential nutrient, choline, which is a precursor to acetylcholine (Purves et al. 2001). Choline is an essential nutrient for both human and animal, which is naturally present in variety of foods and in addition it is obtained as dietary supplements.

Fig. 20.2 Diets that escalate acetylcholine (Ach) neurotransmitters, Top (left to right)—human milk, lean chicken, mung bean; Bottom (left to right)—aubergine, broccoli, foxglove

Although choline is secreted endogenously in liver (synthesized in the form of phosphatidylcholine), the amount produced is not adequate for the human needs (Zeisel et al. 2003). Common foods that contain this essential nutrient (choline) are: water-soluble compounds (free choline, phosphocholine, and glycerophosphocholine) and fat-soluble compounds (phosphatidylcholine and sphingomyelin) (Zeisel et al. 1986). The body system after absorbing directs the water-soluble forms of choline to reach the liver through portal circulation and as well the lipid-soluble forms are packed into chylomicrons, then they are absorbed and transported through lymphatic circulation.

The dietary recommended intakes are developed by Food and Nutrition Board (FNB) of the Institute of Medicine (IOM). According to the board, the nutrient intakes are classified based on the age and sex. The intake level per day of choline is also the most important to consider as excess consumption leads to lowering the blood pressure, sweating, fishy body odor, and gastrointestinal side effects.

20.3.3 Rich Sources of Choline

20.3.3.1 Human Milk

Human milk contains choline ranging from 125 to 166 mg/L (1198–1600μmol/L). The human milk contains predominantly water-soluble forms of choline (approximately 84%) and very small fraction of lipid-soluble forms. In particular for the infants at the first 6 months the only source of choline is from their mother's milk as this requires the large amounts of choline to support a rapid growth rate and optimal development of the infants (Fischer et al. 2010). Two important pathways that circulates the milk choline in the blood system are PEMT pathway (de novo synthesis) and by maternal circulation. Commercial substitutes (choline chloride and soy lecithin) for human milk are also available in the markets when breastfeed is not possible (World Health Organization 2009).

20.3.3.2 Animal Sources

Foods such as whole eggs and meats are highly rich in choline. According to recent research, an adult which consumes one egg per day is more likely to meet their gender and life-stage AI as compared to non-consumers and as well the risk of increase in heart problem considerably found to be reduced since by the increased level of choline (Wallace and Fulgoni 2017). In general, choline maintains the structure of cell membrane and acts as a key element in producing neurotransmitters for brain cell communication.

20.3.3.3 Plant Sources

In more than 50 plant species that grouped under major systemic group, the presence of acetylcholine has been reported. Plant species of *Solanum melongena* L., (aubergine) *Spinacia oleracea* L. (spinach), *Pisum sativum* L.(Pea), *Phaseolus radiatus* L (mung beans), and *Phaseolus vulgaris* L. (common bean) have observed to contain considerable amount of acetylcholine. The highest concentration in fruits also have been noticed considerably for example the fruits that contain substance that influences Ach neurotransmitters are *Citrus aurantium* L. (bitter orange), *Fragaria vesca* L. (strawberry), *Malus domestica* (Apple), and Musa (banana). The sulfur containing secondary compounds, glucosinolates(GLs), which are present in cruciferous vegetables like Broccoli (Vitamin k source) has been noticed to boost the brain cognitive power (Briguglio et al. 2018). These glucosinolates main function is to slow the breakdown of the neurotransmitter acetylcholine (Jaafaru et al. 2018).

20.4 Glutamate (Glu)

The most plentiful amino acid in the brain is glutamate which is significant brain neurotransmitters that perform excitatory action. Glutamate has excitatory effects on the nerve cell where it can excite cells to their death which is termed as "excitotoxicity." These effects are due to the presence of glutamate receptors on the brain cells (Zhou and Danbolt 2014). In vertebrates, glia cells (non-neuronal cells present in central nervous system and pheripheral nervous system which do not produce electrical pulse) uses glutamate receptors and transporters for sensing the synaptic activity (Martínez-Lozada and Ortega 2015). Although glutamate is synthesized by the human body, it is used for the construction of proteins and brain chemicals. Out of scientific term glutamate is commonly known as monosodium glutamate or "MSG" where it is widely used as a taste enhancer.

20.4.1 Mechanism of Glutamate Neurotransmitters

The signaling effect of glutamate not depends on its chemical nature as like other signaling substances instead it is activated by extracellular fluid with the receptors that occurs in the surface of the cell. The signaling effect is thereby due to the cellular receptors that perform uptake cellular mechanism which is catalyzed by the family of transporter proteins (Vandenberg and Ryan 2013). This glutamate in the brain should be at the optimum level and exhibit the activity at the right time (Danbolt 2001). In this recombinant era, several families of glutamate receptors are identified. These receptors are classified into four types: (1) *N*-methyl-D-aspartate (NMDA) receptors (Gonda 2012), (2) AMPA receptors (a-amino-3-hydroxy-5-methyl-4-

isoxazole propionic acid) (Rogawski 2013), (3) Kainate receptors (Lerma and Marques 2013), and (4) Metabotropic receptors (Gregory et al. 2013). Due to these receptors, glutamate is one such a neurotransmitter for brain development and cognitive performance.

20.4.2 Dietary Influence on Glutamate (Glu)

In general, glutamate and glutamic acid that are present in the diet impact the excitatory action of the brain. Plant based foods (Seaweeds, soy sauces, fermented beans, coffee powder mushroom and Spinach) (Skypala et al. 2015) and non-plant based foods (meats, seafood, stews, Dried Cods cracklings, salami soups, fish sauces cheeses and sauces) (Rangan, C and Barceloux, 2009) consist significant amount of glutamate. Ubiquitously monosodium glutamate is considered as a flavor enhancer that can be added to variety of foods and sauces (Zhang et al. 2017). Upon consumption of these "MSG" and other salt of glutamate, they are being dissociated and released in the form of free glutamate. These types of food enhancers are mostly used in fish, oyster, and tomato sauces and also their usage has been reported in miso, gravies, noodle dishes, ready to eat, savory snacks and chips (Fig. 20.3). In concern with the food glutamate is available in two forms. Among them one is "bound glutamate"—that means glutamate is bound to other amino acid to form a protein and secondly is a "free glutamate" which exists as a single amino acid. Former one is the protein source that the body requires, whereas the latter results in problems ranging from headaches to neurodevelopmental disorders. Bound glutamate is incredibly important as it contributes for crucial purpose learning and

Fig. 20.3 Diets that escalate Glutamate (Glu) neurotransmitters. Top (left to right)—mushroom, dried cods, fermented beans; Bottom (left to right)—Seafoods, sauces, stews

memory. In contrast, free glutamate causes overexcitement to the digestive and nervous system.

20.4.2.1 Impact of Excess Glutamate

In the case too much availability of glutamate in the brain, a pathological process called excitotoxicity occurs, that means the brain cells become overstimulated and due to these symptoms such as anxiety or sensory overload are possible. Moreover in addition to effects in the brain, glutamate can have effects elsewhere in the body. Also it has a systemic response to blood glucose regulation. With excess glutamate an effect on the intestinal barrier occurs and thereby results in gut inflammation. Consuming foods rich in glutamate, particularly free glutamate, for instance processed and packed spicy food, multiple times a day results in the formation of toxic compounds. Excess glutamate in the diet is associated with the panic attack, impulsivity, obsessive-compulsive disorder, and depression.

20.4.2.2 Diets That Increase Excitotoxicity

Diets such as prepared foods (e.g., soups) that contain 70% MSG, diet drinks, non-sugared foods, all soy-based foods, peanuts particularly cashews, pistachios, and less-so almonds, seeds of pumpkin, sunflower, cow's product, wheat, and barley are high in glutamate concentration. Thereby increased intake of these foods will increase the excitotoxicity level.

20.4.2.3 Diets That Reduce Excitotoxicity

Diets like high fiber vegetables [carrot, beet, broccoli, etc.]; whole proteins [fish, milk, egg, pork, chia seed, buckwheat, quinoa, hempseed whole algal protein, wheat gluten]; dietary fiber resistance starch [raw potato starch, Hi maize flour, cooked starchy crabs, legume oats]; whole fruits [apricots, apples, pineapple, bananas, cherries, figs, dates, cranberries, blueberries, prunes (dried plums), and raisins (dried grapes)]; healthy fats (peanut butter, olives, avocados, nuts, flaxseed, walnuts, tofu).

Low glutamate level in the body leads to the various problems such as anxiety, posttraumatic stress disorder (PTSD), agitation, memory loss, sleeplessness, low energy level, and depression. So to keep the brain active glutamate neurotransmitters should be maintained at appropriate level which means increase or decrease of Glu leads to many disorders. So to have a balanced level of glutamate in the body, appropriate diet consumption need to be carefully considered.

20.5 Gamma-Aminobutyric Acid (GABA)

GABA is an inhibitory neurotransmitter that contributes to motor control, vision, and many other cortical functions and in addition it also regulates anxiety. GABA inhibits certain brain signals and decreases activity in the nervous system. Like glutamate, GABA is also one such an important neurotransmitter in the brain. A balance interaction between glutamatergic (caused by excitatory glutamate) and GABAergic (caused by inhibitory GABA) is most essential in maintaining the physiological homeostasis (Hampe et al. 2018). The imbalance in these interaction leads to autism spectrum disorders and anxiety disorders. In the human brain, attachment of GABA occurs in GABA receptors where they produce a calming effect. High stress leads to poor sleep, a weaker immune system, and a higher risk of depression, among other things GABA reduces the feelings of anxiety stress, and fear and the supplements are currently available in the market. These supplements reduce anxiety, high blood pressure, insomnia, stress, and fatigue.

20.5.1 GABA and BBB

GABA, neurotransmitter, in the brain is responsible for alleviating the painful sensations and manages mood disorders. BBB (Blood–Brain Barrier) protects the brain from toxic substances. Any substances that reach the brain need to pass through these barriers. Such substances need to be transported in, which needs energy and special molecules, or a substance which transports them through diffusion (from higher concentration to lower concentration). GABA rich foods consumed either through food or as a supplement travel through the BBB and influences the brain functions (Boonstra et al. 2015). Many researches were carried out in concern with GABA transport through BBB and among them some were contradictory and some scientist states only minimal level of GABA crosses the BBB. However, in rats, few research states GABA has potential to increase the brain GABA at 33% and GABA foods administered with arginine drastically increases the brain GABA more than 300% (Shyamaladevi et al. 2002).

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20.5.2 Impact of Diets on GABA

The increase or decrease of GABA depends on the biotic and abiotic factors. Plant-based diets that boost up GABA neurotransmitters are lupin, adzuki bean, soya bean, common bean, and pea (Kuo et al. 2004). Grains such as wheat, barley, and rice varieties (white, black, brown, and red rice) accumulate a considerable amount of GABA. The substantial amount of GABA can be obtained from the source of sprouts

Fig. 20.4 Diets that escalate GABA (Gamma-aminobutyric acid) neurotransmitters, Top (left to right)—grains, lupin, tomato; Bottom (left to right)—sweet potato, pokeroot, spinach

(buck wheat) and fruits (tomatoes) (Gan et al. 2017). Some cruciferous vegetables such as spinach also stimulate GABA. It has also been reported high content of GABA was noticed in Chinese white tea (Zhao et al. 2011). Many fermented foods are shown to increase GABA such as fermented pickles, sauerkraut, kimchi, plain kefir, and coconut water kefir. Interestingly microbes particularly bacteria, *Lactobacillus rhamnosus* have the potential improving the level of GABA. In addition to these foods, other supplements also boost GABA in the body. They are a) green tea (contains relaxing amino acid L theanine); inositol (vitamin like substance); an essential mineral magnesium (Miracle mineral); taurine—a GABA receptor activator; herbs and roots.

GABA supplementation will promote a healthy sleep cycle and calming neurotransmitter production. These supplements are often used to treat high blood pressure, stress, and anxiety as well as to trigger the body's natural growth hormone, often by athletes. These supplements help people to (Boonstra et al. 2015) alleviate anxiety and/or improve sleep quality, in addition to other beneficial effects (Fig. 20.4).

20.5.3 GABA Reduction Effects

Reduction or low level of GABA activity in the body causes: anxiety, chronic stress, depression, difficulty concentrating and memory problems, muscle pain and headaches, insomnia and other sleep problems alleviate anxiety and/or improve sleep quality, in addition to other beneficial effects.

20.5.4 GABA Deficient Associated Syndromes

Insufficient GABA availability causes serious problems and some of the commonly known problems are anxiety, depression and schizophrenia. The symptoms of this syndrome includes uneasy feelings, unable to sit in long period of times, Insomnia, mood disorder, excessive stress, hypertension motion sickness, Attention deficit hyperactivity disorder (ADHD), epileptic seizures, bronchitis and panic disorders.

20.6 Dopamine

Dopamine (3, 4-Dihydroxytyramine) neurotransmitters present both in humans and animals plays an important role in controlling the movements of a person as well as their emotional responses. It is responsible in influencing the brain's vital function such as mood, sleep, memory, learning, concentration, and motor control. In recent research, dopamine was reported to help with unlearning fearful associations (Luo et al. 2018). Dopamine acts as type of hormone called a catecholamine which is made in the adrenal glands. Low level of dopamine causes reduced alertness, difficulty concentrating, less motivation and enthusiasm, poor coordination, and movement difficulties. Diseases such as Parkinson's disease, depression, and dopamine transporter deficiency syndrome are associated with low dopamine level. High amount of dopamine leads to obesity, addiction, and schizophrenia.

20.6.1 Mechanisms

A dopamine signal in brain cell when approaches a nearby neuron, it attaches to that neuron's receptor. Dopamine receptors are proteins found in the brain and nerves throughout the body. The receptor as well as neurotransmitter work together as a lock and key. The dopamine attaches to the dopamine receptor, delivering its chemical message by causing changes in the receiving nerve cell. These receptors play an important role in many neurological processes, including movement coordination and fine motor control, pleasure, cognition, memory, and learning.

20.6.2 Impact of Diets on Dopamine

In many types of foods, dopamine is present; however, dopamine in its own form cannot cross into the brain from the bloodstream (Fig. 20.5). Interestingly the precursor of dopamine, tyrosine, an amino acid, could be able to cross the barrier and influence the function of the brain (Jongkees et al. 2015). So consuming

Fig. 20.5 Diets that escalate dopamine neurotransmitters, Top (left to right)—avocado apple/orange/banana, cheese and nuts; Bottom (left to right)—Peas, velvet bean, broccoli and cauliflower

tyrosine-rich food (cheese, nuts, and meat) would certainly increase the dopamine level. Fruits such as bananas, plantains, apple, avocado, and orange vitally influence the dopamine. A plant such as spinach, tomato, and common bean spikes the dopamine level. These substances exert a protective role and are involved in reproductive organogenesis, ion permeability, antioxidant activity (Kanazawa and Sakakibara 2000), and in the formation of alkaloids.

20.7 Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) also sometimes called as happy chemical transmits the message between the nerve cell and thereby activates the smooth muscles for well-being and happiness. Serotonin plays a role in appetite, the emotions, and motor, cognitive, and autonomic functions. Also it aids in sleep, sexual function, bone health, and blood clotting. Serotonin neurotransmitter although, some consider it to be a hormone where it is produced in the intestines and the brain. In addition, serotonin is present in the blood platelets and the central nervous system (CNS). In general, serotonin is considered as a natural mood stabilizer (Lv and Liu 2017). Tryptophan is the precursor for serotonin and foods that are rich in amino acid tryptophan increases the level of serotonin neurotransmitter. Low level of serotonin leads to depression, stress, unexplained irritability, and panic attacks.

20.7.1 Impact of Diet on Serotonin

20.7.1.1 Sea Food

Intake of sea foods particularly fish varieties (cold-water fish, mackerel, herring, tuna, halibut, salmon, cod liver, whale blubber, or seal blubber) are universally known to have omega-3 fatty acids that aid to fight inflammation throughout the body specifically in the brain (Jenkins et al. 2016) (Fig. 20.6). These fatty acids increase eicosapentaenoic acid (EPA) and docosahexaenoic acid (DPA) and thereby stimulate the neurotransmitters serotonin which drastically reduces the risk of Alzheimer's disease.

20.8 Epinephrine and Norepinephrine

Epinephrine and norepinephrine is a neurotransmitter also known as adrenaline or noradrenaline, respectively. Both of them are considered as a hormone. Epinephrine is a stress hormone which is released from the adrenal gland (Tank and Lee Wong 2011). Norepinephrine is a naturally occurring chemical which plays an important role in alertness, that is involved in the body's "fight or flight response." This neurotransmitter regulates the body and brain to take action in times of danger or stress. Levels of norepinephrine are typically lowest during sleep and highest during times of stress.

Fig. 20.6 Diets that escalate serotonin (5-HT) neurotransmitters. Top (left to right)—hazelnuts herring, passion fruits; Bottom (left to right)—green onion, Chinese cabbage, salmon

20.8.1 Functions

Epinephrine is responsible for increasing the blood sugar level, maintaining the heart rate, and improving the breathing capacity. Norepinephrine is responsible for maintaining the blood vessels.

20.8.2 Deficiency

The deficiency of these neurotransmitters results in anxiety, depression, fibromyalgia, hypoglycemia, migraine headaches, and restless leg syndrome and sleep disorders. The deficiency results in the intake of poor nutrients, chronic stress, and taking of certain medicines such as methylphenidate (Ritalin).

In the same way too much of epinephrine and norepinephrine results in various problems such as high blood pressure, anxiety, excessive sweating, heart palpitations, and headaches.

20.8.3 Impact of Diet on Epinephrine and Norepinephrine

Foods that are high in vitamin C, vitamins B (especially B-5 and B-6), and magnesium are important in maintaining the health of adrenal glands (Fig. 20.7). In specific, lean meats, fish, eggs, legumes, nuts, leafy greens, vegetables, whole grains, dairy foods, low-sugar fruits, sea foods, healthy fats such as olive oil, coconut oil,

Fig. 20.7 Diets that escalate norepinephrine neurotransmitters. Top (left to right)—fish/egg grapeseed oil, legumes; Bottom (left to right)— vegetables, meat, dairy foods

and grape seed oil improves the body health. Reducing white sugar processed food and artificial sweeteners in the diet will improve the level of this neurotransmitters in the body.

20.9 Conclusion

Brain neurons use different substance as a chemical link to communicate in central nervous system and peripheral nervous system. Specific type of diet actually acts as a synthesizer for neurotransmitter and improves the mood and well-being. Certain neurotransmitters exhibit excitatory effect and some has inhibitory effect. Acetylcholine, GABA, dopamine, norepinephrine, and serotonin are important neurotransmitters that are vital for memory, learning, alertness, and sleep. The design of this chapter has framed in a way to understand the dietary patterns and to have a balanced uptake of nutrients to stimulate the brain neurotransmitters in an appropriate level as high and low level synthesis of neurotransmitter leads to complications which has been discussed respectively.

Diet such as whole fibers, proteins, carbohydrates, and fats most significantly supports the function of brain apart from other physical and mental exercise. Specific diet has an effective impact on these brain neurotransmitters, for instance, Kimchi and Pu-Erh Tea for GABA (sense of calmness); fish, egg, and spirulina for dopamine (for movement/memory); Kiwis, banana, and walnuts for serotonin (learning/ memory process); egg yolk, sprouts for acetyl choline (muscle coordinator); avocados, pumpkin seeds, and lima beans for norepinephrine (fight or flight response). Certain foods will have influence directly on the neurotransmitters while in others the precursors play an important role. Thereby choosing a food wisely is much more important to have good consequences.

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