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Neurological Disorders: Causes and Treatments Strategies

Paper subtitle: Neurological Disorders

Maha Z. Rizk,Ghadha I. Fouad and*Hanan F. Aly

Therapeutic Chemistry Department

National Research Centre

Dokki, Giza, PO 12622, Egypt

*Corresponding author details:hanan_abduallah@yahoo.com

Abstract: **Due to increased life expectancy, ageing population was significantly increased. Ageing is one of the main risk factors for neurodegenerative disorders such as Alzheimer's disease, Parkinson disease, stroke, and other disorders. Neurological diseases represent a great social and economic burden that threatens public health. Neurodegeneration is associated with several transitions in brain including synaptic dysfunction and neuro cognition decline. There are several factors contributing to neurological disease incidence and progression, including oxidative stress, inflammation, metal disturbance, microbiota, as well as, genetic and dietary factors. This review demonstrated the increasing global public health importance of several neurodegenerative disorders, through introducing trials to reduce their incidence and risk, such as gene therapy.**

Keywords: **Neurological diseases, gene therapy, neurodegeneration, AD, PD, CNS, therapy, brain, dementia, brain infection, mental disorders**

The nervous system (NS) is a complex system that is responsible for establishing the body's basic functions, alsoregulating and coordinating its activities; consisting of two important systems, the first is the central nervous system (CNS) comprise brain and spinal cord and is considered as the central processing station.The second is the peripheral nervous system (PNS) which includes all other neural elements and these transmit sensory information between the muscles, tissues and nerves in the rest of the body to the brain **[1]**.Neurological disorder is a term used to describe a disease of CNS; as a result of physical injury to the brain, spinal cord, or nerves, in other words; it affects the central or peripheral nervous system. Other causes may be due to changes in certain biochemical aspects or even the cause may be unknown but the effects on CNS are observed.

Neurological disorders include dementia such as Alzheimer's disease (AD), Parkinson disease (PD), Huntington's disease and other contributed diseases, Cerebrovascular diseases such as stroke or migraine and other headache disorders, Degenerative conditions such as multiple sclerosis (MS), Neuroinfections (viral, bacterial or fungal), Malignant or benign brain tumors, brain trauma and other traumatic disorders of the nervous system and Mental disorders referred to as psychiatric diseases which are expressed mainly as abnormalities of thought, feeling or behavior, and cause either distress .

These diseases are widely distributed, affecting mainly the elderly causing serious effects. Inherited genetic mutations result in abnormal NS development, neurodegenerative disorders or neuronal dysfunction leading to aprogressive loss of structure and/or function of neurons. Moreover, environmental factors could provoke genetic and epigenetic mutations, as well as, disease-related inflammatory events such as Alzheimer's disease (AD) **[1-3].**

Neurodegenerative diseases such as; AD, PD, and HD reveal different intracellular and extracellular variations. Neurodegenerative disorders vary although they have numerous features in common at both cellular and sub-cellular levels where the cytosol and endoplasmic reticulum (ER) are responsible for biological events such as synthesis of new structural and functional protein molecules. Mechanisms of translational as well as posttranslational modifications are highly complex and sophisticated; any polypeptide that fails to fold properly is directed to its degradation processes, known as autophagy or ubiquitin proteosome system **[4, 5]**.

Neurodegenerative disorders induce changes in many biological and biochemical mechanisms in the central nervous system (CNS). These are manifested in increase in free radical production leading to oxidative injury, or abnormal protein aggregates and finally to inflammation. Moreover, neurotransmitters may be depleted, degraded or insufficiently synthesized in the synaptic cleft due to the higher activity of enzymes. Other disorders include dysfunction of mitochondria, and excite toxicity of neurons as well as damage in the blood brain barrier (BBB)**[6]**.

Statistical reports on Neurological Disorders

Prevalence of neurological and other chronic disorders is representing huge economic and social burden, especially in low income and developing regions, where there is increased life expectancy and elevated ageing populations, as well as, neurological services and resources were rare and limited.

Nowadays, there is a great effort to eradicate or decrease diseases such aspoliomyelitis and AIDS, through health initiatives and vaccination programs. Notably, the rate of communicable diseases decreased in developed regions, thus there is more interest to decrease chronic diseases including cancer, cardiovascular and neurological disorders.

Estimates of deaths

Neurological chronic disorders represent 12% of total deaths in the whole world, 85% of the deaths are due to cerebrovascular diseases. Over 80% of these occur in low- and middle-income countries with about 6.8 million dying each year (report of United Nations, 2007).Furthermore, globally, there are over 35.6 million people suffering from dementia-related diseases. AD contributing to 60–70% of cases AD prevalence was 67 among the elderly, and 9.5of Parkinson disease, 183for stroke , 101 for injury of traumatic brain, 4.5 for injury of spinal cord, and 1.6 for ALS **[7].**

Factors contributing to neurodegenerative disorders:

Iron homoeostasis

In the CNS, iron being a constituent in a number of proteins is involved in many biochemical processes including oxidative phosphorylation, myelin production, oxygen transportation, synthesis and metabolism of the neurotransmitters. In cases of abnormal iron homoeostasis, either due to altered cellular iron distribution or accumulation, such as in case of AD and PD, excess hydroxyl radicals are produced causing cellular damage which can induce the oxidation and structural dysfunction of macromolecules (lipids, proteins, carbohydrates, and DNA). Magnetic resonance imaging (MRI) is considered as a potential diagnostic biomarker for neurodegenerative diseases that could often identify these modifications. Iron chelators are neuro protecting mechanism through their ability to chelae iron and to cross the blood brain barrier (BBB), and finally reducing excessive iron accumulation**[8]**.

Diet

Fast foods and highly refined and processed foods all constitute the Western Diet, or the Standard American Diet. Consequently, many health risk problems arise, namely, obesity, cardiovascular disease (CVD), diabetes, and numerous other health conditions. However, this western diet not only causes these metabolic disorders but also greatly affect the brain function.

Ketogenic diet is regarded as an effective treatment for pharmaco-resistant epilepsy, ALS, AD, PD, and some mitochondrio-pathies which may be considered a protective diet for neurological disorders. The mechanisms underlying their use for the treatment of certain types of neurodegenerative diseases is being an effective source of energy, reducing the generation of free radicals or oxidative damage, increasing the mitochondrial biogenesis pathways and making use of the ability of ketones to bypass the defect in complex I activity found in certain neural disorders**[9].**

Gut Microbiota

There is a common shared relation between functions of gastrointestinal tract (GIT) and central nervous system (CNS) that is considered as "gut-brain axis", providing immunological, hormonal, and neuronal signals two-way communication. Some diseases, both within or outside GIT, are strongly associated with dysfunction of "gut-brain axis" and showed increased incidence over the last decades. It was suggested that many factors participated in this relation; including microbiota. GIT could be considered vulnerable area, where neuroinflammation could be induced, as there is a relationship between intestinal microbiota and CNS .

The role of the GIT-microbiota in human brain development and function attracts more interest and research **[11]**. Therefore, modulation of the gut microbiota could represent an innovative treatment approach in complex disorders. It was demonstrated that the dialogue of the potential microbiota-gut-brain is involved in the diseases of neurodegenaration **[10]**.

Microbiome is a term used to describe microorganisms genomes, it is defined by host factors such as genetics and nutrients, and at the same time, it is able to affect host immunity and disease development. Niche-specific microbiome, prominently the gut microbiome, can affect both local and distal sites within the host. The gut microbiome possesses a critical role in the bidirectional gut-brain axis, therefore; the concept of microbiome-gut-brain axis is emerging. It was evidenced that the disorders of different neuro-immune and neuro-psychiatric are attenuated by microbiome, microbiota-derived products and exogenous antibiotics and probiotics. Moreover, neural, endocrine and metabolic mechanisms are also critical mediators of the microbiome-CNS signaling. Research on the role of microbiome in CNS disorders brings promising future for developing novel prognostic and therapeutic approaches, either dietary or pharmaceutical, for different CNS disorders, as well as, to improve brain function and healthy brain ageing **[12]**.The UCLA researchers **[13]** interested in defining certain gut bacteria-derived chemical products that may be triggering the signals to the brain.

Age

In developing countries, the exposure to deleterious conditions early in life related to poverty such as infections, malnutrition, and prenatal stress, might have a great impact on the ageing and may reduce the life span**[5]**.Despite this, increasing age is considered the highest risk factor for dementia with prevalence of 2–11%, in those aged less than 65 years **[14, 15]**.

Oxidative stress initiates macro-biomolecules oxidation which leading to damage for cells. It is implicated in different processes of neurodegenerative involving cognitive deficits that occur either during normal brain ageing, or during neural disease development **[16]**.

Examples of neurological diseases

Dementia

Dementia is a syndrome of a chronic or progressive nature that is caused by disease of the brain, and is accompanied by disturbance of multiple higher cortical functions, including memory, learningandjudgment, thus it represents a social burden.

Alzheimer's disease (AD)

The pathological state of CNS particularly related to AD is characterized by neurofibrillary tangles, derangement of neurotransmitters in the neurons and synaptic cleft, andβ-amyloids plaques all of which are related inflammatory mechanisms **[17, 6].**

It was demonstrated that elevated oxidative stress in brains and peripheral tissues in AD subjects. AD is characterized by accumulation of senile amyloid beta peptide (Aβ) plaques, formation of neurofibrillary tangles, and a reduction of cholinergic neurons in brain. Aβ peptide (39-43 amino acids) is neurotoxic and able to induce oxidative stress (production of hydrogen peroxide and lipid peroxide) and inflammation in AD brain **[18]**.

Epilepsy

Epilepsy is a neurological disorder applied to "provoked or acute epileptic symptomatic seizures", which may represent a brain injury. Epilepsy is a neurological disorder occurs after stroke **[19]** affecting more than 50 million people worldwide **[20]**. It is a temporary disruption of normal brain function and is revealed as recurrent unprovoked seizures which occur when cortical neurons fire excessively, hyper-synchronously, or both. A seizure can be focal or generalized. Epilepsy might affect the muscles, the senses, or a combination and may lead to complete loss of consciousness. Epilepsy has been divided into epileptic syndromes, which occurs early during childhood. Approximately 60% of patients attain control of their epilepsy with the first drug they use, whereas about 30% fail to attain control with drugs. The disease is considered refractory when two or three anticonvulsant drugs have failed to control it **[19]**.

Disorders of headache

Headache is considered one of the most historical neural disorders, causing substantial disability in populations, and represent painful characteristic of a small number of main headache disturbance. It also produces as a characteristic symptom of many other situations; these are termed secondary headache disorders.

Multiple sclerosis

Multiple sclerosis is a neurological disease cause disability of different age, affecting about 2.5 million people worldwide. Recently, the disease is increasingly diagnosed because ofthe availability of more neurologists and magnetic resonance imaging. However, some people exhibit little disability during their lifetime;20 years post the onset of disease, more than 60% are no longer fully ambulatory, with a marked social and financial burden to society.

Parkinson's disease (PD)

One of the most neurodegenerative disease is Parkinson's disease which is described by the existence of motor and non-motor symptomatology (such as instability of postural and falls, gait freezing, difficulties in speech and swallowing), are presently one of the most difficult challenges to treat PD patients.

Neurological disorders associated with malnutrition

In low income countries, malnutrition and inadequate diversity of food continues to be priority health problems and elevate the risk of disease and early death, in different age groups among poor people. Most of the malnutrition-related neurological disorders are preventable.

Pain associated with neurological disorders

Neurological disorder as a consequence can lead a director an indirect to pain, with the effects of physical and psychological. Pain either acute or chronic is considered as a major health problem that represents noticeable challenges to its diagnosis and treatment.

Neurological Infections

Infectious diseases that include the nervous system affect considerable people worldwide, and represent the sixth reasons of consultation of neurology . Neuroinfections, even with the availability of effective antibiotics and vaccines, represent a major challenge in developing countries. Neurological infections occur when these microorganisms (viruses, bacteria, parasites or fungi) invade the nervous system through bloodstream or peripheral neurons. Some viral infections such as Rabies viruses, reach the brain and cause confusion and convulsions. Some neurological infections are bacterial, such as tuberculosis, syphilis and brain abscess. They are many neuroinfections, including Encephalitis (bacterial or viral brain inflammation), Meningitis (bacterial or viral inflammation of CNS-covering membranes). Viral Neuroinfections are either acute and quick, or chronic slow. Acute viral infections include encephalitis aseptic meningitis and encephalomyelitis, while chronic viral infections include pan encephalitis and retrovirus disease.

Brain tumors

Glioblastomamultiforme, grade IV, is an offensive brain tumor. The progress in surgical methods, radio and chemotherapies have increased the patients survival months **[21]**. Fatal tumors are considered to produce from glioma cells and/or glioma-originating cells post therapy. Viral vector development, together with the concept that injection of vectors into the brain might act tumor cells not killed by other treatments, led to the progress of gene therapy for brain tumors **[22]**.

Stroke

Stroke is one of the major non-communicable disorders. Stroke is the major cause of death in developed countries post coronary heart disease (CVD) and cancer. Stroke is considering an expected neurological deficiency due to the presence of ischemia and /or hemorrhage in brain. They are mainly related to ischemic stroke defined as focal occlusion of the cerebral blood vessel and the remainders are attributed to hemorrhagic stroke resulting from blood vessel rupture.

Autism spectrum disorder (ASD)

Autism represents a group of complex neuro-developmental disorders featured by repetitive and characteristic patterns of behavioral attitude and difficulties with social interaction. The symptoms begin at early childhood and affect daily functioning. ASD patients also have a higher risk of having epilepsy. Researchers hope that understanding the formation and function of neuronal synapses, the sites of communication between neurons, which may malfunction in ASD and neurodevelopmental disorders, can help identify new opportunities for therapeutic interventions.

the neurological causes of autism might include excess of axons that leads to over-connection in certain brain area **[23]**, lack of coordination and synchronization among different brain regions **[25]**, therefore affecting brain function and represented in ASD by difficulty in organizing different cognitive functions and mal processing of data **[24]**.

Recent approaches in the study of neurological disorders

Most neurodegenerative diseases, such as PD and AD represent an augmenting demographic as they are affecting the ageing population and **[26, 27]**, and they occur more commonly in idiopathic form, thus there is concentration on neuroprotection and repair **[1]**. On the other hand, some neural disorders, such as Huntington disease (HD), are genetic **[28, 29]**; therefore, there is a focus on evaluating the defect of gene and the consequent neurodegradation **[1]**.

Finding clinically relevant biomarkers of human neurological disorder attracts a lot of interest. Moreover, most neurological disorders are recognized too late, leading to late therapy and poor prognosis. Additionally, most current clinical chemistry tests are neither sensitive nor specific. Therefore; emerging metabolomics is a powerful approach that enables assessment of metabolic profiles of biofluids, to discover novel biomarkers and biochemical pathways and finally to distinguish between different disease status and to improve early diagnosis, metabolomics gives accurate information about the biochemical status of CNS tissue at a given time point and thus; it is capable of produce disease-specific metabolite signatures unique to individuals. Recent, and more accurate, advances in metabolomics enabled identifying novel biomarkers for neurological disorders. Cerebrospinal fluid (CSF), is a rich source of neurological markers and could potentially be used for neural disease diagnosis followed by effective therapy **[30, 31]**, it was shown that the metabolic profile in CSF is particularly disturbed in patients with AD have high inositol concentration **[33]**. Furthermore, Signal-processing algorithms were developed to detect metabolites - at very low concentration- in *in vivo* human brain to indicate possible pathways impaired in neural diseases **[31]**.Analysis of metabolomics profile, can be determined to permit the identification of disease specific biomarkers, and finally to aid in early diagnosis, estimation of disease status and to give aguide therapeutic decisions **[32]**. **Bogdanov *et al.* [34]**discriminate between 25 neurogically normal and 66PD patients established on their blood metabolite profile, characterized by marked reduction in uric acid and elevation in glutathione.

Genetic influences on brain structure

Huge number of genetic studies and neuroimaging are beginning to uncover normal and disease-specific patterns of gene and function of brain worldwide **[35, 36]**. Many mental skills are inherited, with vigorous genetic effectiveness on IQ (intelligence quotient) **[37, 38]**, as well as, verbal and spatial abilities **[39]** and emotional reactions to stress **[40]**.Studies of structure of brain in twins showed that large volume of the brain **[41]**and *corpus callosum* brain structures **[42, 43]** and ventricles are genetically influenced, whereas gyral patterns **[44]** are much less heritable **[45]**.

The progresses technology in brain mapping enabled the structural of the human cortex that varies with age, gender, handedness, hemispheric dominance, and cognitive performance in normal and disease **[46]**; this helps to determine whether heredity and non- genetic factors are involved in determining specific aspects of brain structure. Gray matter distribution across the cortex is one of the genetically structural features regulated for cortical function. Hence strong connection between genes, structure of brain and behavior is determined by maps of genetic brain **[47]**.

Treatment strategies

Neurodegenerative disorders are of great social and economic burden and cause significant load on both patients and healthcare costs. Treatment options for patients are still limited, and provide modest symptomatic relief. Monoamine oxidase B (MAO B) and Monoamine oxidase A (MAO A) are two flavin-dependent isozymes that function in the oxidative deamination of neurotransmitters and exogenous aryl alkyl amines, resulting in accumulation of H_2O_2, regarding that the enzyme level is highly elevated in aged human neuronal tissue.. These oxidases attract a lot of interest as inhibitors of MAO A and B are used clinically in the treatment of neurological diseases. Deprenyl (MAO B inhibitor) is used in the treatment of PD to potentiate l-dopa therapy and to provide protective effects in patients have pre-Parkinson's Syndrome. Recently, it was demonstrated that elevated MAO B levels induce apoptosis in neuronal and kidney cellsand has been demonstrated in plaque-associated astrocytes of AD-brains; MAO B inhibitors are used currently in AD treatment clinical trials **[48]**.

Pre-treatment serum samples were obtained from 125 patients with newly diagnosed epilepsy who were taking part in a randomized immunotherapy trial. Serum samples were investigated by both nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). There was no clear distinction in the metabolic profile, acquired by either NMR or MS, of responders and non-responders to treatment, suggesting that pre-treatment serum samples do not contain any prominent biomarkers of responsiveness to initial treatment in new-onset epilepsy. Finally, this will enable prediction drug responsiveness using pharmaco-metabonomics and demonstrated the need toallow discrimination of smaller molecules in complex biofluids such as blood using more advanced signal acquisition techniques **[49]**.

Genetic therapy for neurological disorders

As surgical interventions are not effective in treatment of neurodegenerative diseases and the current drugs are unable to prevent or halt disease progression as well as they have side effects, thus gene therapy could be regarded as an emerging powerful and possible treatment approach for some common neurological diseases through understanding the underlying mechanisms and amelioration of design of gene vector, curative selection of gene and delivery methods, transfer of the normal gene into diseased cells can normalize the biochemical disturbance , realizing on the disease, nature of other gene techniques transfer as well as direct replacement of gene may be needed **[1]**.

Another approaches may be used as small interfering RNA to inhibit the main -negative genes **[50]**.Vector delivering of the treated gene to the brain entirely represents a big challenge in patients , however it is promising in animal models **[51-53]**, including multiple tracks injection of the vector **[54]**,reach the vector to the distal regions of the brain *via* neural pathways **[55]**, transfer of vector through BBB by intravenous injection **[56]**,and vector injection into the spaces of CSF **[57]**.

Other approaches of gene therapy have included adenovirus mediate dexpression of tumor suppressor gene p53 and augmentation of the localized immune response through adenoviral delivery of IFN-β, however, possibly owing to limited transduction of tumor cells with p53 or toxicity from the adenovirus–IFN-β construct, they were not developed **[58.- 60]**.

The replication-competent utilization on colytic viruses to enhance diffusion of intra-tumoral vector and tumor killing was suggested due to the safety of viral vectors demonstrated in clinical trials. Replication-competent HSV-1, adenovirus, reovirus and Newcastle disease virus are presently being examined as vectors in clinical trials **[61-63]**. Protocols involve vector construction to express the reporter gene of ferritin that is detectable by MRI, and viral vector covalent binding to nano-particles of iron oxide for detection by MRI to guide viral vector and delivery of transgene, as well as to track distribution of vector **[64, 65]**. Using MRI Focused ultrasound connected with MRI to focally interrupt the BBB is suggested to elevate noninvasive viral vectors delivery to certain regions of brain, allowing controlled and focused therapeutic delivery to brain tumors **[66]**.

Another approach to gene therapy is normalization at the chromosomal level of the primary genetic lesion, but it showed limited efficiency. Transgene-carrying vector delivery is the technique employ to medicate ocular neovascularization. This strategy includes Flt1 transgene expression, which encodes a tyrosine kinase that links vascular endothelial growth factor **[67]**.Vectors delivery to express genes encoding proteins with the function of anti-neovascular or antiapoptotic. For instance, transport of the pigment epithelium-derived factor-encoding gene, which has anti-angiogenic characters, is in development for treatment of choroidal neovascularization. High genes encoding growth factors expression has been employ to increase nerve regeneration **[68, 69]**. Such strategy has also been employ to develop auditory cells in the animal models **[70, 71]**. Lastly, molecular prosthetics is used to return visual function by insert light-sensitive ions channel or pump proteins into the retina **[72]**.

Strategies of gene therapy are now in phase I–II clinical trials involve oncolytic wild-type viruses containing molecular therapeutics (retroviruses encoding cytosine deaminase), and adenoviral vectors that provide a combination of genes encoding cytotoxic factors and immune-stimulatory cytokines **[73, 74]**. Early phase I–II trials of gene therapy are introducing safety and more susceptibility to success in randomized phase III trials **[1]**. Augmentation of gene and/or gene knockdown is purposed to normalize expression of gene by introducing wild-type cDNA **[75- 77]**.

Clinical trials demonstrated RPE65 gene augmentation efficacy in patients with Leber congenital amaurosis **[78, 79]**. This protocol was helped in identification of the disease-connected genes. More than 25 genes connected with blindness have been known post detection of the first two genes of choroideraemia and rhodopsin in 1990 **[80-82]**. Gene therapy concept is realize on various inherited conditions resulting in deafness **[83, 71]**. Development in the genetics field has led to progress of animal models of blindness **[1]**.

In another study, a gene encoding the missing vesicular glutamate transporter-3 was delivered to the cochlea in mice lacking this enzyme; gene augmentation therapy at least partially restored hearing in these mice **[83]**. A third pivotal

proof-of-concept study showed correction of a splicing defect in one form of Usher syndrome through administration of antisense oligonucleotides to a mouse model of the disease. Finally, although target organs such as the nose and tongue are more accessible than the retina and cochlea, very few studies have addressed disorders of smell and taste, probably owing to the complex aetiologies of these disorders and risk–benefit ratios for these indications **[84]**.

Different trails therapy for neurological disorders

Silica loaded nanoparticles: Citrus (SOAE), naringenin and hesperetin administered to acrylamide intoxicated rats induced neurological disorders for one month and half, showed beneficial effects on different brain neurotransmitters and biochemical parameters . These may be illustrated on the basis of , flavonoids which are a group of naturally occurring substances, including flavones, flavanones, and isoflavones, having several useful biological activities of flavonoids, including antioxidant, antitumor, and anti-inflammation properties **[85].** Some of these flavonoids (SOAE, hesperetin and naringenin), due to their phenolic structures, have antioxidant effect and inhibit free radical-mediated processes **[85].** Naringenin was found to possess antitumor, anti-inflammatory and hepato protective effects **[85].** In addition hesperetin has been shown to be a potential anti-oxidant, anti-inflammatory, neuroprotective agent **[85].** Accordingly, nano-components (SOAE, hesperetin and naringenin) which possess antioxidant properties are possibly to be defensive against ACR-induced neurotoxic effects **[85].** In summary brain damage which might be related to oxidative stress. Administration of the three nano-components lessened the negative effects of acrylamide on the brain by inhibiting free radical mediated process; an effect that could be attributed to the antioxidant property of three nano-components.

Aly et al. **[86]**, demonstrated that dehydroepiandrosterone (DHEA) has a potent role in modulating the neurodegeneration characterizing AD through its antioxidant, antiapoptotic, neurotrophic characteristics andantiamyloidogenic effect as well as its cholinesterase - inhibiting activity. On the other hand,El- Baz and Aly**[87]** found that *Dunaliellasalina* methanol extract improved the cerebral cortex , suppressed oxidative destruction and architecture alterations as well as normalizing neuronal protein and lipid contents which might be attributed to its high contents of 9-cis b-carotene protecting the brain cells from the oxidative stress in AD rats. Hence *Dunaliellasalina* extract considers a prospect formularization for ameliorating neurotoxic diseases. Further , El –Baz et al. **[88]** illustrated that, red berry (*Morusrubra*) and white berry (*Morus alba*) ethanolic extracts have the ability to inhibit reactive oxgen species (ROS) production and apoptotic related enzymes that may lead to their neuro-ameliorative effect in Alzheimer's disease.

Conclusion

Several presented approaches are useful for helping in identifying the fatal and the nonfatal outcomes for neurological disorders and determination of developmental stages and progression of the disease. They demonstrated that neurological disorders cause a huge burden because of non-communicable conditions such as Alzheimer dementia, as well as, communicable conditions such as meningitis.

Chemical drugs that are used for the management of AD, PD, HD, and other chronic illnesses are with side effects. Phytochemicals are promising therapeutic agents for neurodegenerative disorders, due to their anti-inflammatory and antioxidative as well as anticholinesterase activities, in addition to their minimal side effects. These agents may be applied in the future for treatment of brain disorders using nanotechnological approach to facilitate their crossing the blood brain barrier (BBB) and reaching the target organ with maximum efficacy**.**

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