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REVIEW ARTICLE

# Natural products in neuroprotective therapies: Experimental and cheminformatics approaches to manage neurological disorders

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## ABSTRACT

Neurological disorders (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, despondency, and dementia have been evidenced as a rising concern among diverse geographical regions. Brain-related diseases are currently the main concern because they increase mortality and morbidity in the elderly. Regardless of the continual efforts by modern scientists to develop a promising pharmacological or surgical management, the outcome has not been satisfactory. Also, due to synthetic drugs' associated side effects, scientists have taken the initiative to consider using natural compounds as an alternative. Hence, they obtain pretty effective results by using natural compounds. Natural ingredients are synthesized from a variety of plant and animal sources. These natural ingredients cure brain diseases through a variety of mechanisms. For effective medication advancement, the molecules must go through preliminary clinical systems that require some investment and significant speculation. In this situation, cheminformatics is fundamental in diminishing time and venture. Cheminformatics methods play a significant role in these issues, including 3-dimensional quantitative structure-activity relationship 3D-(QSAR), virtual screening, docking, molecular dynamic studies, and quantum chemical studies. The vital purpose of this study is to disclose different types of NDs and the neuroprotective effect of several natural products for experimental and cheminformatics-based therapy. Natural products like green tea, flavonoids, and ginseng are discussed as effective neuroprotective products. However, more investigation is expected to comprehend the better utilization of regular items in future exploratory and cheminformatics-based treatment for NDs.

***Keywords:*** neurological disorders; docking; molecular dynamic studies; cheminformatics; mortality; drug discovery

## 1. Introduction

Plants have been fundamental to human existence, serving as primary sources of medicinal agents throughout history[1]. An estimated 3.3 million people in the least developed countries (LDCs) have traditionally relied on herbal remedies for various ailments[2–4]. Today's neuropsychiatric ailments are often a result of intricate genetic predispositions, prenatal neuro-developmental challenges, or adverse environmental factors[5–7]. Further studies and technological advancements have illuminated the connections between systemic dysfunctions like inflammation, immune response, and oxidative stress with neuropsychiatric afflictions[8]. Chronic inflammation has been consistently linked to the pathogenesis of several neuropsychiatric conditions, including depression, schizophrenia, and bipolar disorder[8].

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Furthermore, the activation of microglia, the primary immune cells in the brain, has been documented in post-mortem brain samples of individuals diagnosed with schizophrenia[9]. Elevated oxidative stress markers, such as malondialdehyde (MDA), have been detected in the plasma of patients with bipolar disorder and schizophrenia[10]. It can also be said that the dysfunction of the human body's normal processes, such as inflammation, immune system, and oxidative stress (OS), is strongly linked with neuropsychiatric diseases[11]. Moreover, the central nervous system (CNS) remains highly susceptible to age-related degenerative processes[12–14]. While there have been remarkable advancements in neuropsychiatric therapeutics, many current treatments have significant limitations, including undesirable side effects[15]. In light of these challenges, there is a pressing need for alternative therapeutic strategies. Notably, the rich polypharmacological potential of natural plants offers a promising pathway, primarily because these plants can act on multiple neural targets[16]. Many drugs owe their origin to these plants, emphasizing their importance across pharmacology, organic chemistry, and medicinal chemistry[17–21]. The traditional drug discovery process, spanning disease selection to pharmacogenomic optimization, is a sequential and often cumbersome endeavor, with disruptions potentially halting the entire process[22]. This approach, coupled with the challenges in new drug design, highlights the necessity for innovative strategies in medicinal chemistry[17,23]. Notably, some natural compounds are characterized by a reduced molecular weight, a factor beneficial in drug design. However, it is essential to recognize the structural diversity and complexity inherent in many natural products. This diversity presents an opportunity. Given their multitarget potential, understanding these compounds requires a comprehensive approach. Here, cheminformatics, integrating organic and computational chemistry, becomes pivotal. It offers tools to discern the pharmacological features and intricate structures of natural products, paving the way for the next generation of drugs[24,25].

This review highlights our focus on the synergy between natural products and cheminformatics in addressing neurodegeneration. We aim to bridge the realms of neurological disorders (NDs) and cheminformatics, shedding light on computational strategies vital for early-stage lead discovery from nature's abundance.

## 2. Summary of cheminformatics tools applied to natural products

Cheminformatics Toolkits provide a versatile range of functions, including saving and reading chemical structures in various formats, substructure, and exact structure matching, identifying common substructures, disassembling molecules, accumulating molecules from elements or sub-molecules, applying reactions, and generating

molecular fingerprints. These toolkits are pivotal in efficient chemical data management, structural analysis, and reaction exploration[26].

Quantitative structure-activity affinity is a convenient apparatus in medical chemistry when looking into the interlinkage in the middle of herbal products as well as belonging to other macromolecular targets taken away within the body, particularly when the rapid prognosis of unspecified herbal products of biological activities is needed[27–29]. QSAR methods consider a variety of probe atoms, force fields, and methods for measuring electronic interactions. Alignment-based 3D-QSAR-CoMFA is a method that examines the interaction between molecules and macromolecular targets by analyzing their steric and electrodynamic properties in a three-dimensional space. On the other hand, 3D-QSAR-CoMSIA uses a broader range of properties, including steric, electrodynamic, hydrophobic, and atom hydrogen contributor/acceptor electric area, to understand the similarity between molecules and their targets[29,30]. The application of statistical and machine learning techniques to vast and complex data sets has advanced QSAR modeling from the survey of the little sequence of congeners working simple regression. Ligand-based theoretical methods are commonly used to model the physical, biological, and pharmacological characteristics of compounds in today's QSAR, and they are a significant first step in drug development. In several leading drug discovery companies, statistically-based QSAR approaches and structure-based methods are critical tools in lead optimization. The Hansch group published the first QSAR approach in 1962, and disclosing an arrangement of congeners trailed it. The stearic accomplishment of substituents was propitiously identified. In a series of overlaying 3-D configurations of analogs, CoMFA, and other 3D-QSAR methods contained electrostatic interaction energies[31]. Partial least squares (PLS) are used to calculate the steric and electrodynamics bimolecular areas of bonding, which are then linked to the bioactivities in CoMFA. The steric, electrodynamics, hydrogen-bonding, and hydrophobic accomplished of bonding are all covered by the COMSIA process, which was formulated based on the CoMFA approach.

Virtual screening (VS) is a procedure utilized in drug advancement to limit enormous items to a sensible number for more production, just as in natural *in vivo* research. Because of computational innovation, medicinal scientists can foster new medications in a period and cost-proficient mode[32]. The construction-based vs. strategy then utilizes an assortment of demonstrating methods, including docking, to reenact the limiting communication of ligands to a bimolecular target. Ligand-based VS scans immense compound data sets for perceived dynamic particles in a few measurements. Subatomic comparability is typically evaluated by contrasting geography-based descriptors of perceived dynamic mixtures and conceivable bioactive hits. Virtual screening utilizes two primary approaches: ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS). LBVS relies on the resemblance between established ligands and the target binding site. At the same time, SBVS encompasses the placement of small molecules within the binding site of a target protein to anticipate binding modes and strengths[33]. In virtual screening, scoring functions are crucial in evaluating the binding affinity between target proteins and ligands. These functions compute energy values by considering van der Waals interactions, hydrogen bonding, electrostatics, and solvation effects[34].

Docking is a statistical method for predicting one molecule's desired orientation towards another. Ligand-protein docking is a process that investigates the different shapes of small molecules, called ligands, within the binding sites of proteins. This is achieved using scoring functions to assess which ligand shape more accurately matches the protein's binding site[16]. Advances in high-performance computing and machine learning have enhanced molecular docking's accuracy and efficiency. Combining docking with techniques like virtual screening and fragment-based approaches holds promise for future drug discovery endeavors[35]. Molecular docking has facilitated numerous successful drug discovery efforts. For instance, identifying potential inhibitors for the Zika virus NS2B-NS3 protease involved molecular docking, leading to the discovery of promising candidates for antiviral drug development. In another study, molecular docking aided in designing

new non-nucleoside reverse transcriptase inhibitors for HIV-1, contributing to developing effective anti-HIV drugs. These examples underscore the pivotal role of molecular docking in identifying potential drug candidates[36,37].

## 3. Cheminformatics toolkits

Cheminformatics toolkits are frequently used to test new methodologies. The most important functions they perform are manipulating chemical structures and comparing structures. The properties of individual bonds and atoms can be accessed programmatically. There are several tools and methods available in cheminformatics to represent chemical structure, store chemical data in a database, perform search processes, and predict physical, chemical, and biological properties of molecules, including QSAR (Quantitative Structure-Activity Relationship) and QSPR (Quantitative Structure-Property Relationship). Cheminformatics is crucial in managing and accessing large amounts of chemical data chemists generate through an appropriate database[38,39]. In studying the effects of chemicals on genes and developing new medications, having this knowledge is crucial to developing small-molecule probes that effectively study the functions of proteins and cellular networks[40]. Similar informatics tools are also necessary to determine the structural and physicochemical relationships between compounds found in metabolic or signaling pathways[41-43]. 3-D QSAR studies, virtual screening, docking, and *in silico* studies are helpful toolkits for preventing neurological diseases[22].

### 3.1. 3-D QSAR study of multi-aim compounds

QSAR is generally utilized for displaying the natural physical and pharmacological elements of mixtures and strategies, which are a primary innovative phase in drug discovery **(Table 1)**. It works with structure-founded systems and makes an essential cheminformatics toolkit for developing new drugs[31,32]. 3D-QSAR studies make numerous successful reports of CNS drug discovery.

**Table 1.** Testified 3D-QSAR studies utilized in CNS drug discovery[16].

| Drug target | CNS disease | 3D-QSAR method | Software package | References |
|---|---|---|---|---|
| Acetylcholinesterase Enzyme (AChE) | AD | Molecular field-based 3D-QSAR modeling | CoMFA, (http://strcomp.unimore.it/comfa/), PHASE (www.schrodinger.com) | [39,40,44] |
| AChE, Butyrylcholinesterase (BuChE) | AD | CoMFA-based 3D-QSAR modeling | Tripos Sybyl (www.tripos.com) | [45,46] |
| AChE | AD | 3D multitarget QSAR | MT-QSAR (http://mtqsar.unipg.it/), DRAGON (http://www.talete.mi.it/) MARCH-INSIDE | [47–49] |
| Histamine 3-Receptor (H3-R), Histone methyltransferase (HMT), AChE, BuChE | AD, PD, Depression, Schizophrenia | Molecular field and GRID-based 3D-QSAR modeling | PHASE (www.schrodinger.com) Pentacle (www.moldiscovery.com), MOE (https://www.chemcomp.com/molecular-operating-environment/) | [49–51] |
| MAO-A, (Monoamine oxidase) MAO-B, AChE, BuChE | AD | GRID-based 3D-QSAR modeling | Pentacle www.moldiscovery.com | [51,52] |

### 3.2. The method of finding drugs that target many locations for the treatment of CNS diseases utilizing virtual screening

Virtual screening is a method that enables the reduction of extensive collections of compounds for

synthesis and biological testing, making it a valuable technique in drug discovery **(Table 2)**[45]. This approach provides pharmacists with new opportunities to discover novel drugs. There are two main techniques used in virtual screening: ligand-based virtual screening (LB-VS) and structure-based virtual screening (SB-VS)[47]. Numerous successful reports of CNS drug discovery have been achieved through virtual screening studies.

**Table 2.** Testified VS studies utilized in CNS drug discovery[16].

| Compounds | CNS diseases | Virtual screening methods | Software package | References |
|---|---|---|---|---|
| Human DOPA decarboxylase inhibitors | PD | Structure-based (SB) approach based on pharmacophore model and molecular docking | MOE; Dovis 2.0AutoDock Vina (http://vina.scripps.edu/), MolSoft LLC's (https://www.molsoft.com/) | [53,54] |
| Neurokinin-3 receptor (NK3 receptor) antagonists | Schizophrenia; depression; anxiety | Sequential similarity analysis followed by CoMFA | ROCS 2.4.1. and 3.0 www.eyesopen.com | [55] |
| BuChE inhibitors | AD | Ligand-based (LB) virtual screening based on two- and three-dimensional similarities | LiSiCA (https://biosig-portal.uni-jena.de/LiSiCA/), OpenBabel (http://openbabel.org/) | [56,57] |
| Histamine (HT)-H3 receptor ligands | PD; AD; epilepsy; sleeping disorders | LB and structure-based virtual fragment screening | FLAP (www.moldiscovery.com), Schrödinger Suite (https://www.schrodinger.com/) | [58,59] |
| Serotonin 5-HT6 antagonists | AD; Schizophrenia; Obesity | LB virtual approach based on two-dimensional similarities and pharmacophore model | InstJChem; JChemForExcel; (www.chemaxon.com), Phase-program www.schrodinger.com | [60] |

## 3.3. Docking studies for multiple-target chemical molecules for the treatment of NDs

The lock-and-key model, which entails achieving the highest affinity for a target while avoiding side effects, is the fundamental principle of drug action. In recent years, there has been a growing interest in studying polypharmacological compounds that can act on multiple targets to tackle complex diseases like cancer, NDs, and infections. Molecular docking is a computational tool commonly used in researching multifunctional drugs[61]. It is a strategy where the direction of one compound close to the next happens, and the absolute cycle is constrained by a computer[62]. Molecular docking is a commonly used method in designing drugs based on the structure of the target protein, as it can accurately predict how small molecules will bind to the protein's active site. Understanding binding behavior is critical in developing new drugs and gaining insights into important biochemical processes[63,64]. It is used for identification and as the primary optimizing device for known target structures before compound synthesis[65]. The most commonly used docking software is given below **(Table 3)**.

**Table 3.** Testified Docking studies used in CNS drug discovery[16].

| Compounds | CNS diseases | Software package | References |
|---|---|---|---|
| Metallothionine-III inhibitors | AD | Discovery Studio 2.5.5 www.accelrys.com | [66] |
| MAO-A, MAO-B, AChE, BuChE inhibitors | AD | GLIDE http://www.schrodinger.com/Glide | [67] |
| MAO-B inhibitors | PD, AD | AutoDock, GOLD, LibDock | [68] |
| MAO-A inhibitors | Depression | AutoDock http://autodock.scripps.edu/ | [69] |
| AMP (Adenosine monophosphate)-activated protein kinase (AMPK2) inhibitors | Stroke | AutoDock, FlexX http://autodock.scripps.edu/ https://www.biosolveit.de/FlexX/ | [70] |

There are two commonly used and popular approaches in molecular docking. One of these approaches involves a technique that matches the protein and the ligand by describing them as surfaces that complement each other[71–73]. The second method imitates the docking process by pairwise computing the interaction

energies between the protein and the ligand[74]. Both approaches have advantages and limitations, which are discussed in further detail below.

## 4. Natural products and their role in neurodegenerative disease (ND) treatment

Although there are significant advances in our understanding of NDs, there has been minimal success in developing effective treatment[75]. Furthermore, the available therapies for NDs are inadequate because they only reduce the symptoms but cannot prevent the progress of the disease[76]. Due to some factors, the preference for natural products in treating ND is increasing **(Figure 1)**[77].

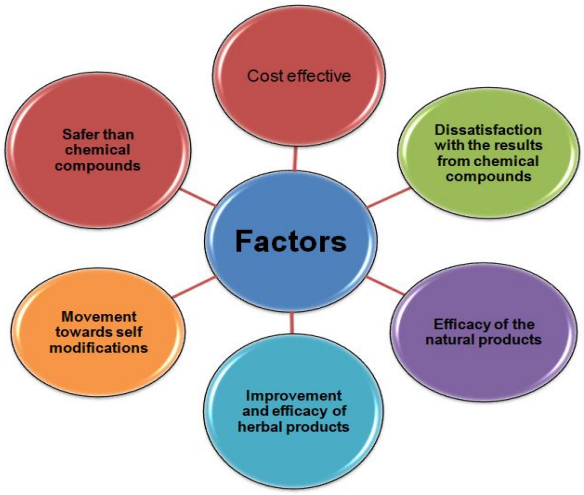


**Figure 1.** Factors increasing the preference for using natural products to treat NDs[78].

Natural products offer significant potential in treating NDs, and researchers have already begun exploring their therapeutic properties[78–80]. Although NDs differ in their specific manifestations, common characteristics include abnormalities in protein deposition, cellular transport, excitotoxicity, inflammation, and intracellular calcium ion excess[81]. Various therapies such as receptor agonists/antagonists, neurotransmitter modulators, stem cell-based therapies, second messenger modulators, and hormone replacement have been implemented over the years[82]. They primarily alleviate symptoms rather than cure disease progression and may exhibit severe side effects or lose efficacy over time[83]. Natural products such as herbal remedies and phytochemicals have been proposed to complement conventional medications and therapies as potential therapeutic candidates, as they exhibit neuroprotective activities against targets such as mitochondrial dysfunction, protein misfolding, OS, and inflammation[84–88]. Animal-derived products like omega-3 fatty acids have also demonstrated anti-inflammatory and cell toxicity-reducing effects in AD[89]. Specific natural products such as Lunasin, polyphenols, alkaloids, and tannins have been identified as possible therapeutic candidates for AD[21,88,90,91]. Lunasin represses the expression of genes related to tumor suppression and demonstrates anti-inflammatory effects by inhibiting cytokines like tumor necrosis factor α and interleukin-6, as well as reducing nitric oxide release. These findings suggest that Lunasin could be a potential therapeutic option for inflammation conditions[92]. In the Drosophila eye model system, Lunasin's effects were investigated using transgenic flies expressing high levels of human Aβ42 in differentiating retinal neurons. The study also revealed that Lunasin downregulates the Jun-N terminal kinase signaling pathway implicated in AD. Since AD involves neuro-inflammation due to ROS production, Lunasin could be a potential therapeutic target for AD[93].

The application of curcumin (a polyphenol) in animal models of AD halted neuro-inflammation, excessive tau phosphorylation, and the Akt/glycogen synthase kinase 3 signaling pathway. Additionally, it aided in reducing ROS levels through the modulation of neurodegeneration-related pathways[94,95] Around 128

flavonoids have been documented, showcasing potential as a prospective treatment for AD due to their ability to inhibit acetylcholinesterase[96]. Derived from *Huperzia serrata*, Huperzine A was traditionally utilized in ancient Chinese medicine to enhance memory. This targeted and specific acetylcholinesterase inhibitor elevated acetylcholine levels within the rat brain[97].

Research using rat PC12 cell lines derived from rat adrenal medulla cells has highlighted that the root extract of *Platycodon grandiflorus* containing Platycodin D can enhance synaptogenesis in the hippocampus by activating the mitogen-activated protein kinase/extracellular regulated protein kinase pathway. Further exploration of *Platycodon grandiflorus* root extract's potential effectiveness in AD models is warranted to evaluate its therapeutic prospects[98].

Natural products may offer a promising avenue for treating NDs. However, challenges such as ensuring durability and neuro-availability and addressing standardization, regulation, and quality control issues must be overcome[99,100]. Recent studies have shown that natural products like curcumin from turmeric, *Ginkgo biloba*, and cannabidiol from cannabis exhibit neuroprotective effects against specific NDs[101–103].

### 4.1. Natural nonpeptide compounds: Potential in brain disorder management

Recent research has investigated the polytherapeutic effects of natural products, such as Mentha and Eucalyptus species, in managing NDs. These compounds have been highly recommended, along with antibiotics and anti-inflammatory medicines, for their potential in treating various NDs, including bacterial meningitis caused by *Neisseria meningitidis* and *Streptococcus pneumonia*, glioma, neuropsychiatric disorders, and other NDs[104,105]. Resveratrol, a natural compound found in grapes and red wine, has been recognized for its health benefits in preventing various diseases, including brain issues such as inflammation, viral and bacterial infections, and type-2 diabetes. Resveratrol has been shown to protect astrocytes and microglia from inflammation and defend against pathological α-synuclein accumulation in PD[106]. Recent studies have also revealed the therapeutic effects of resveratrol on hippocampal neurons of mice infected with bacterial meningitis[107]. Another natural compound, 1,8-cineole (eucalyptol), has polytherapeutic effects in NDs. Studies have shown that eucalyptol has the potential to treat AD and epilepsy due to its ability to modulate neurotransmitters and reduce neuroinflammation. Limonene, another natural compound found in citrus fruits, has shown promise in treating *Listeria meningitis* in infants, increasing the survival rate without any side effects[108].

### 4.2. Exploring the therapeutic potential of natural products in neurodegenerative diseases (NDs)

#### 4.2.1. The neuroprotective properties of bee and wasp venom

Recent research has further explored the potential of natural products in treating NDs. Bee and wasp venoms have been found to contain cocktails of peptides and proteins, enzymes, biogenic amines, and nitrogen-containing compounds that have been used successfully for centuries to treat inflammatory diseases, including NDs[109]. The neuroprotective effects of bee venom have been investigated in treating conditions such as PD and multiple sclerosis (MS), with results showing the potential to prevent the loss of dopaminergic neurons, reduce neuroinflammation, and inhibit apoptosis[110–112]. Furthermore, bee venom has been found to prevent neuronal death in rotenone-induced cell toxicity in NSC34 motor neuron cells, indicating its potential to prevent neuronal damage[113].

#### 4.2.2. Apamin, Melittin, and Mastoparan: Venoms in ND treatment

Apamin is an 18 amino acid peptide from the venom of bees that is an inhibitor of $Ca^{2+}$-activated $K^{+}$ transport channels. The medicinal qualities of bee venom have also been attributed to apamin. Apamin turned around the drawn-out potentiation inadequacy, especially with septic encephalopathy, due to its inhibitory

effect on $Ca^{2+}$-activated $K^+$ channels (SK channels). The most well-known difficulty of sepsis and the primary source of death is septic encephalopathy. The problem is portrayed by a critical disintegration in intellectual capacity that prompts vulnerability, changes in character, psychological deficiencies, and deficiency of consideration[114]. Epilepsy is a disorder in which rapid and coordinated firing of neurons produces frequent convulsions. The calcium-binding protein S100B was overexpressed in the development of epilepsy, even though the epileptogenesis mechanisms are poorly understood. Melittin is a product collected from 40%–60% of the dry venom of the bee. It can effectively interact with S100B and can be a very potent medicine against epilepsy[115]. The compound Mastoparan is a component of wasp venom. It can activate G-alpha proteins of hippocampal neurons and increase $Ca^{2+}$ in dendrites. Thus, it can be an effective medicine for NDs[116].

# 5. Application of ND treatment based on cheminformatics

Cheminformatics, or chemical informatics, merges computer and informational techniques to aid in understanding and manipulating chemical data, playing an integral role in drug discovery and therapeutics[117].

## 5.1. Introduction to the Parzen-Rosenblatt window approach

The Parzen-Rosenblatt window approach, often termed kernel density estimation, is a non-parametric method used to determine the probability density function of a random variable[118]. Within cheminformatics, it predicts a compound's primary pharmaceutical target and possible off-targets by examining its molecular structure. It functions by overlaying a window, or kernel, on each data point in the set and aggregating the results to formulate a continuous function[118]. This offers insights into how closely a compound might associate with potential targets.

## 5.2. Cheminformatics to characterize multitarget compounds for ND

In the pharmaceutical sector, cheminformatics is becoming increasingly important for developing multi-target medications, particularly for complicated illnesses and disorders linked to drug resistance. This computational method for drug development simplifies research time and provides cost-effective solutions, making it a desirable choice[119].

### 5.2.1. Rise of multitarget drugs

Due to their potential benefits in treating illnesses with various manifestations, multitarget medicines are gaining more and more attention. These medications can help with drug resistance issues, which can be a big problem when treating some conditions[119].

### 5.2.2. Cheminformatics and drug development

The integration of cheminformatics has accelerated the development of new drugs. This computational approach is advantageous because it is cost-efficient and can optimize research duration[119].

### 5.2.3. Multitarget directed ligands (MTDLs)

MTDLs are an emerging drug development method. The capacity of MTDLs to improve the efficacy of multidrug therapies is driving the increase in interest in them. MTDLs can interact with several targets concurrently, unlike conventional medicines focusing on a single biochemical route[119].

#### Benefits of multitarget therapy

Maximum selectivity for a single target is stressed in conventional pharmacological treatments. However, multitarget therapy may be more efficient. This is because complex illnesses frequently include several molecular pathways, and simultaneous targeting of these pathways might result in superior treatment outcomes. Multitarget medications are viewed as a viable approach to treating Alzheimer's disease, a study revealed. Recent research has highlighted the promise of multitarget medications in treating this crippling illness,

focusing on developing various target combinations for AD treatment[119].

### 5.2.4. Role of computer-aided drug design (CADD)

Designing multitarget chemicals to fight illnesses like AD is made possible using CADD. By utilizing computational tools, CADD streamlines the drug development process by facilitating drug candidate prediction, validation, and optimization[119].

Cheminformatics is transforming the identification and development of multitarget pharmaceuticals through tools like CADD and approaches like MTDLs. Such developments show much potential, particularly for difficult-to-treat conditions like Alzheimer's, where conventional single-target medicines might not be as efficient[119].

## 5.3. Advantages of cheminformatics-based therapy

- **Streamlined Drug Discovery:** Chemoinformatics accelerates the typical drug discovery process by enabling researchers to study the relationship between chemical structure, properties, and molecular activity using *in silico* techniques, eliminating some manual steps in traditional research[120].
- **Efficient screening process:** With virtual screening, researchers can filter out non-compatible compounds early on, saving resources by not physically testing unsuitable candidates. The software-driven process rapidly determines a molecule's solubility, cross-reactivity, and potential toxic groups, leading to more targeted testing[120].
- **Cost and time savings:** Chemoinformatics can significantly reduce costs associated with drug discovery. Virtual screening and simulations minimize the need for physical screenings, thus speeding up the discovery process[120].
- **Enhanced throughput:** High throughput screening (HTS), already a fast and efficient method, is further enhanced by chemoinformatics. Combining virtual screens with HTS leads to more precise results by sifting through vast molecular databases pinpointing compounds with therapeutic potential[120].
- **Predictive analysis of drug behavior:** With *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies, chemoinformatics allows for an early understanding of a drug's physical and chemical characteristics. This early-stage prediction means that researchers can gauge how a drug might behave in the body even before it reaches advanced testing stages[120].
- **Improved efficiency:** By integrating chemoinformatics with HTS, the drug screening process becomes more sequentially refined. This integration ensures that only the most promising compounds undergo the resource-intensive HTS process, ensuring better results and fewer resources wasted on non-viable compounds[120].
- **Future-ready drug discovery:** Chemoinformatics continually refines its databases and prediction models with the latest findings. As the system "learns" from past screenings and current discoveries, it becomes even more efficient at identifying potential therapeutic agents, setting the stage for an ever-evolving, adaptive approach to drug discovery[120].

## 5.4. Overview of AD

AD is the most common type of dementia, which involves a gradual deterioration in cognitive abilities, including memory loss, difficulty with language, and reduced ability to interact with the surroundings. The decline in cognitive function can range from mild to severe[121]. AD mainly impacts the parts of the brain that control thinking, language, and memory. A significant characteristic of this disease is the lack of acetylcholine, a neurotransmitter essential for learning and memory. Furthermore, the development of beta-amyloid protein plaques and tau protein tangles in the brain results in a decline in synaptic connections[122].

AD results from genetic, environmental, and lifestyle factors that affect the brain over time (**Table 4**).

However, less than 1% of cases involve specific genetic alterations that increase the risk of developing the condition[123]. Genetic tests can help identify individuals at higher risk of developing AD, and family members of AD patients may also share genetic factors that increase their risk. Although there have been significant research endeavors, no successful medications or treatments are available to halt or reverse the advancement of AD. However, bioscience research is advancing, and clinical evidence on AD is rapidly accumulating, providing hope for future treatments[124].

**Table 4.** Epidemiological Data and Worldwide Burden of AD.

| Fact | Data | References |
|---|---|---|
| Number of people with dementia | 55 million (2023) | [125] |
| Percentage of people with dementia living in low- and middle-income countries | 60% | |
| Number of new cases of dementia each year | Nearly 10 million | |
| Most common form of dementia | Alzheimer's disease (60%–70% of cases) | |
| Seventh leading cause of death | Yes | |
| Major cause of disability and dependency among older people | Yes | |
| Cost of Dementia in 2019 | $1.3 trillion | |
| Percentage of dementia care costs attributable to informal carers | 50% | |
| Gender disparity in dementia | Women experience higher disability-adjusted life years and mortality due to dementia and provide 70% of care hours for people with dementia. | |

### 5.4.1. Neuroprotective effects of various natural compounds on AD

#### Strawberry

Strawberry is a shrub-like tree, pervasive in most of Europe. The cells support polyphenols, for instance, anthocyanins, tannins, supplements C and E, and carotenoids, which are accessible in strawberries to make them an enormous piece of the conventional eating plant. The counter-oxidative impact of strawberries has been evaluated utilizing Pheochromocytoma (PC12) cells. In addition, the strawberry extract has demonstrated its ability to lessen the bothersome conduct changes brought about by the iron-56 (56Fe) isotope. Above all, the strawberry diet improved hippocampal-subordinate practices[126]. Recently, a study found that strawberry extract has potent antioxidant properties and can improve hippocampal-dependent behaviors in rodents[127].

#### Grape seed

Anthocyanidins and phenolic antioxidants are in great abundance in grape seeds. According to the amyloid-beta (A) hypothesis, a key contributing element to the onset of AD is the buildup of A. It has been established that the polyphenols in grape seed extract (GSE) are effective inhibitors of substances that cause amyloid to form. In an experiment, female Tg2576 mice were given 200 mg/kg/day of GSE for around five months. Another important cause of AD is inflammation brought on by microglial activation[128]. Grape seed extract (GSE) has also been identified as a potent anti-amyloidogenic agent due to the presence of polyphenols in it[129].

#### Papaya

A significant portion of the pathophysiology of AD is attributed to the production of free radicals and other oxidative stressors. Metals, like copper and iron, are the typical culprits with the mistrust and anticipation of a supportive reformist creation. Application and A have copper-restricting areas, while AD patients have a

high degree of copper centralization in their amyloid storage[130]. A study found that papaya can reduce free radical formation and OS, which play a significant role in AD pathogenesis[131].

### Green tea

Green tea is a standard beverage used by many people. Research demonstrates that the polyphenols in green tea have iron-chelating and reformer-seeking activities and can significantly influence cell good judgment and signaling pathways. The o-di-phenolic packing in the B ring and the keto structure in the C ring of the flavonol result in the metal chelating activity. In this analysis, cells treated with epigallocatechin-3-gallate (EGCG) showed improved cell reasonableness, decreased free radicals, and reduced caspase-3 events[132]. Besides, green tea, which contains polyphenols such as Epigallocatechin-3-Gallate (EGCG), has been found to have metal-chelating properties and can improve cell viability while reducing free radicals and caspase-3 levels[133].

## 5.4.2. Cheminformatics in investigating the ligand space of GPCRs

With the rising number of accessible constructions, natural data sets, and *in silico* procedures for cheminformatics and current medication revelation, it is not astounding that ligand and structure-based methodologies are utilized in the blend to exploit the bountiful GPCR ligand data while utilizing as of late explained critical protein underlying data to help in expanding achievement in GPCR drug disclosure research. An astounding instance of ligand- and design-based coordination in GPCR drug disclosure has appeared in examinations, including A2A Adenosine Receptor (A2AAR), an appealing medication focus for treating PD[134].

## 5.5. Parkinson's disease (PD) overview

Parkinson's Disease (PD) is characterized by the neurodegeneration of the midbrain's nigral dopaminergic neurons, leading to a progressive functional impairment. The exact cause of PD remains to be fully understood, but several pathological processes and central factors are evident. These encompass protein aggregation, mitochondrial dysfunction, iron accumulation, neuroinflammation, and oxidative stress (**Table 5**) [135].

**Table 5.** Key Features and mechanisms involved in Parkinson's Disease (PD) progression.

| Feature | Description | Reference |
|---|---|---|
| **Protein aggregation** | Accumulation of alpha-synuclein leads to Lewy body formation in neurons, disrupting cellular activities and potentially causing neuronal death. | [136] |
| **Mitochondrial dysfunction** | Mitochondria exhibit signs of malfunction in PD. Dysfunction may decrease ATP production and increase oxidative stress, contributing to neuronal damage. | [137] |
| **Iron accumulation** | Elevated iron levels in the brain, particularly in the substantia nigra, can heighten oxidative stress. | [138] |
| **Neuroinflammation** | Persistent inflammation within the brain can result in neuronal destruction. Elevated inflammatory markers have been observed in PD patients. | [139] |
| **Oxidative stress** | An imbalance between free radical production and antioxidative defenses causes oxidative damage to proteins, lipids, and DNA, contributing to neurodegeneration. | [140] |

## 5.5.1. Natural compounds and their neuroprotective effects on PD

The majority of PD therapies now available target symptoms. These medicines, sadly, have drawbacks and cost concerns. Natural products have demonstrated potential as effective anti-Parkinsonian treatments[141]. Notably, a 2021 study highlighted the neuroprotective effects of harmane, found in various plants. Other compounds like curcumin, resveratrol, and EGCG also show potential benefits for PD[142].

### 5.5.2. NPs and cheminformatics in PD treatment

#### Natural products

Aside from their antioxidative properties, the possible system of activity of flavonoids is their association with neuronal flagging falls like (Phosphoinositide 3-Kinase) PI3K, protein kinase C, and mitogen-activated protein kinase (MAPK), which prompts diminished apoptosis and upgraded neuronal endurance. One investigation has shown that withanolide is an intense silencer of NF-κB enactment interceded by various incendiary specialists[143,144].

#### Characteristics and requirements of COMT inhibitors

Several COMT substrates, like dopamine and norepinephrine, incline to methylation of meta-hydroxyl, in importance para hydroxyl **(Figure 2)**[145]. Computations of binding free energy and quantum methods/Molecular (QM/MM) improvement showed that quercetin favors vivaciously at the incredible site of human Catechol-O-Methyltransferase (COMT) meta-O-methylation restricting; nonetheless, the Para-O-methylation is best for luteolin[146]. Both motor and thermodynamic cutoff points are solids for meta-O-methylation for quercetin, and for luteolin, the energy factors do not maintain the district selectivity, instead of administered thermodynamics[147].

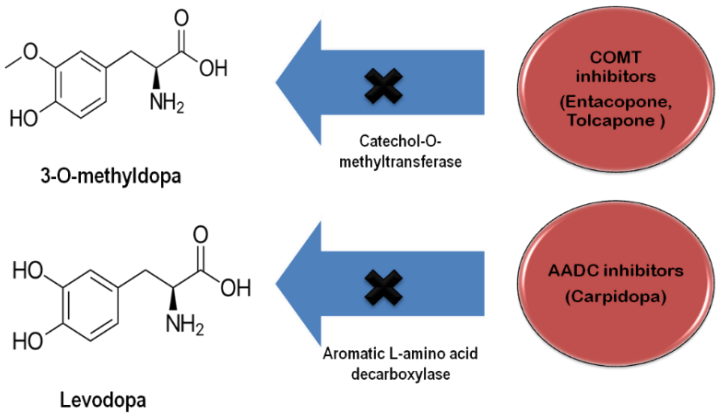


**Figure 2.** Catechol-O-methyl transferase (COMT) and aromatic L-amino acid decarboxylase catabolize levodopa (AADC). COMT inhibitors block levodopa from being converted to 3-O-methyldopa[148].

## 5.6. Overview of HD

Huntington's Disease (HD) is a neurodegenerative condition that is hereditary and is characterized by motor impairment, cognitive decline, and mental symptoms. The illness is caused by an increase in the CAG trinucleotide repeat in the huntingtin gene, which results in the creation of an abnormal huntingtin protein[149].

### 5.6.1. Molecular and genetic aspects

Recent discoveries of HD's molecular and genetic origins have given insight into the underlying pathogenic pathways. DNA methylation pattern alterations have been discovered in the brains of HD patients, which may impact disease development[150]. Furthermore, changes in the levels and activity of histone-modifying enzymes have been identified in HD, indicating possible therapeutic intervention paths[151]. Because of developments in sequencing technology, the discovery of novel genetic modifiers provides insights into variables that may impact the start age and severity of the illness[152].

### 5.6.2. Animal model research

Animal models have helped researchers understand the pathogenesis of HD and evaluate potential treatment options. These models, which range from worms and flies to mice, mimic various elements of the illness and have aided in identifying molecular pathways disrupted in HD.

Rodent models, particularly, have proved helpful in studying prospective HD therapies. In these models, gene silencing techniques that try to limit the production of the mutant huntingtin protein have shown potential. Furthermore, animal studies have shown that stem cell treatments can restore function and delay disease progression in HD[153].

Furthermore, animal models have played an essential role in explaining the significance of epigenetic alterations in HD. For example, investigations utilizing HD rodent models have revealed changes in histone-modifying enzymes, correlating with human HD research[151].

### 5.6.3. Treatment and support

With our expanding knowledge, new therapeutic avenues are emerging. Promising treatments currently in clinical trials include gene-silencing techniques and targeted neuroprotective agents[154]. Recognizing the burden HD places on caregivers and families is essential on the psychosocial front. Addressing their challenges, from financial hardships to social isolation, is becoming a focal point in providing comprehensive care[155].

## 5.7. Protective effects of natural ingredients on HD

### 5.7.1. *Bacopa monnieri*

*Bacopa monnieri*, a plant that has long been utilized in Ayurvedic medicine, has lately drawn interest in the literature of contemporary science because of its putative neuroprotective properties. This plant has become the subject of study to comprehend its underlying processes, focusing on improving memory and cognitive function.

A notable investigation exploring the impact of a *Bacopa monnieri* extract on cognitive performance and brain activity in healthy older people took place in 2021. BME administration (7 days, 50 mg/kg/day) improved spatial working memory in adolescent mice. The memory enhancement persisted through day 28 in the adolescent group[156]. This study produced significant results: the extract improved working memory function and affected neuronal activity in particular brain areas inherently linked to memory processing[157]. This suggests a profound influence on the neural pathways that modulate memory retention and recall.

A further investigation on the effects of *Bacopa monnieri* supplements on younger people was conducted that same year. The outcomes were fascinating and encouraging. After receiving the supplement, young people showed increases in working memory, an increase in attention span, and an improvement in cognitive flexibility. Additionally, there was a noticeable rise in neural activity in brain regions crucial for cognitive control[158].

This suggests a broader range of possible advantages, extending to younger people in addition to merely the old.

Such consistent results across several investigations suggest that *Bacopa monnieri* may have therapeutic value and potential as a cognitive enhancer. Any substance with neuroprotective qualities might open up new paths for treatment or prevention, especially in light of the catastrophic effects of neurodegenerative disorders (NDs) like Huntington's Disease (HD).

#### Historical, phytochemical, and therapeutic dimensions

Although the studies above provide helpful information, a thorough investigation of *Bacopa monnieri*'s historical use, phytochemical makeup, and other current studies is necessary to grasp the plant's potential fully.

Bacopa monnieri, also known as "Brahmi" in Ayurvedic medicine, has been used historically to improve memory, lessen anxiety, and cure various illnesses. Its neuroprotective properties are thought to be caused by the high concentration of bacosides, the main active ingredients[159,160].

Numerous research studies have also examined its anti-inflammatory and antioxidant benefits, which may

be extremely important to its neuroprotective qualities. Understanding how Bacopa monnieri interacts with these processes is essential since oxidative stress and inflammation are crucial factors in advancing NDs[161].

Animal model studies have also suggested that *Bacopa monnieri* (BM), a commonly used herb, has shown neuroprotective effects in animal and *in vitro* studies[8].

So, *Bacopa monnieri* has a wide range of possible uses and consequences. However, there is strong evidence from recent studies that it also benefits cognitive function[8].

### 5.7.2. Ginsenoside

Ginseng is a traditional medicinal root whose therapeutic potential has been investigated for several conditions. Its usage has been chiefly supported for restoring metabolic homeostasis and energizing fragile physiologies[162].

Ginseng's multifaceted effects span a range of conditions, including hepatotoxicity, infections, immune system deficits, and diseases of the central nervous system (CNS). Ginsenoside is a crucial element that gives ginseng its medicinal properties.

Researchers have recently focused on how ginsenosides can protect the brain against Huntington's disease (HD). For instance, in research using animal models resembling HD symptoms, ginsenoside Rg1 was protective against neuronal cell death. The formation of reactive oxygen species (ROS) and brain inflammation were two significant reasons for their effectiveness, respectively[163]. Another study focused on the advantages of ginsenoside Rb1 in HD-affected rats, extending our understanding of ginsenoside's potential. This substance enhanced motor performance and significantly reduced striatal neuronal damage[164].

It is crucial to acknowledge the rising importance of incorporating cheminformatics in figuring out the medicinal potential of ginsenoside. Cheminformatics has significantly improved our understanding of bioactive substances using computational and informational tools to speed up drug development and molecular design[165]. The possible binding locations, molecular interactions, and even the predictive effectiveness of ginsenosides have been highlighted in recent research using cheminformatics approaches.

One such study analyzed using cheminformatics methods to measure the effectiveness of different ginsenosides in binding to brain receptors, providing insightful information about their potential therapeutic uses[166].

### 5.7.3. Flavonoid

A wide range of polyphenolic chemicals known as flavonoids demonstrate various advantageous physiological effects, such as anti-inflammatory, anti-hepatotoxic, anti-ulcer, anti-allergic, and antiviral activity[167]. Research on the neuroprotective properties of flavonoids against neurodegenerative diseases (NDs), such as Huntington's disease (HD), has increased. Quercetin and epigallocatechin gallate (EGCG) are notable flavonoids that have drawn attention for their possible therapeutic advantages in treating NDs. These substances are thought to give neuroprotection through several mechanisms, including their anti-inflammatory, antioxidant, and anti-apoptotic qualities[168].

A recent study employed cheminformatics tools to analyze the molecular properties of flavonoids from *Andrographis paniculata*, explicitly examining their potential as inhibitors of acetylcholinesterase, butyrylcholinesterase, and monoamine oxidase in the context of neurodegenerative diseases. Their findings revealed that rutin exhibited the highest binding affinity (−12.6 kcal/mol), surpassing the standard references. However, regarding ADMET properties, only tangeritin demonstrated potential for blood-brain barrier permeation, which is crucial for therapeutic efficacy in neurodegenerative conditions. These insights suggest that with strategic structural modifications, these flavonoids could further enhance their binding to neuroreceptors and possibly bolster their neuroprotective effects, potentially offering more effective

alternatives to treatments like donepezil[169].

In conclusion, the integration of cheminformatics in flavonoid research elucidates a broader spectrum of their potential applications, particularly in neurodegenerative disorders. The amalgamation of computational insights with traditional pharmacological research can pave the way for more targeted and efficient therapeutic interventions in the future.

### 5.7.4. Celastrol

Celastrol, a naturally occurring triterpenoid, is primarily extracted from the roots of the Thunder God Vine (*Tripterygium wilfordii*). Historically, this compound has been utilized in traditional medicine for its anti-inflammatory and anti-cancer properties. Recent research has also suggested its potential as a neuroprotective agent[170].

One especially noteworthy study examined the effects of Celastrol, a triterpene with anti-inflammatory and antioxidant characteristics. There had never been any research demonstrating that celastrol might lessen PD motor symptoms prior to that study. So, their research used PD cell and mice models to evaluate celastrol's therapeutic effectiveness and mechanism of action. Compared to healthy people, sporadic PD patients have lower levels of autophagic activity in the substantia nigra. Increased levels of Beclin 1, Ambra1, Vps34, Atg7, Atg12, and LC3-II in neurons suggest that celastrol enhances autophagy and autophagosome formation. Furthermore, it promotes mitophagy, as seen by increased PINK1 and DJ-1 levels and decreased LRRK2. MPAK signaling pathways may be connected to these modifications[171].

Celastrol is shown to lessen the harmful effects of MPP+-induced dopaminergic neuronal mortality, mitochondrial membrane depolarization, and ATP depletion in the PD cell model. Celastrol reduced motor symptoms and slowed neurodegeneration in the substantia nigra and striatum in the PD animal model. Additionally, the striatum's mitophagy was exacerbated by a rise in PINK1 and DJ-1. We found that celastrol protects mitochondrial quality by guiding damaged mitochondria towards autophagosomes for later destruction when MPP+ was employed to cause mitochondrial damage in neurons.

The study is the first to show that celastrol enhances PD patients' neuroprotection by promoting mitophagy, which destroys damaged mitochondria and further delays the death of dopaminergic neurons. These results imply that celastrol has the potential as a preventative medicine[171]. Celastrol substantially reduced the MPTP-induced loss of dopaminergic neurons in the substantia nigra. This suggests that Celastrol can exert a protective effect on these neurons by inhibiting apoptotic pathways or neutralizing the oxidative stress induced by MPTP[172].

## 5.8. Overview of MS

Multiple sclerosis (MS) is a condition that affects the central tangible framework (the brain and spinal cord). In the disease known as MS, the immune system assaults the myelin that covers nerve fibers, obstructing the flow of information between the brain and the rest of the body. Chronic nerve damage or paralysis can develop over time due to the illness. Depending on the severity of nerve damage and which nerves are impacted, MS symptoms can vary substantially. Some people with severe MS may entirely or partially lose their ability to walk, while others may go for extended stretches without developing new symptoms. However, some medicines may be used to control symptoms, change the course of the condition, and hasten the recovery from episodes[173]. New research suggests that the gut microbiota may be involved in the development of MS and that utilizing cannabidiol (CBD) may alleviate specific symptoms of MS and enhance the quality of life for patients[174]. Furthermore, a clinical trial demonstrated that a novel medication named inebilizumab successfully decreased the likelihood of relapse in patients who suffer from NMOSD, a rare illness similar to MS[175].

### 5.8.1. Anti-ALS medications from natural products

Amyotrophic lateral sclerosis (ALS) is a neurological condition that can affect anybody, regardless of race, ethnicity, or income. There has been much interest in natural goods and herbal therapies because of the adverse effects of riluzole on muscular degeneration and wasting, weakness, muscle stiffness, dysarthria, dysphasia, and general quality of life[176].

#### Polyphenols and ALS

**1) *Ginkgo biloba.*** The terpene trilactones, known as ginkgolides, differ in the number and positioning of their hydroxyl gatherings, and the sesquiterpene trilactone bilobalide are both excreted by the *Ginkgo biloba* leaves. Additionally, several flavonol glycosides are found in *Ginkgo biloba* on their own. The most widely used and widely accepted native plant on the earth is *Ginkgo biloba*[177]. Recent studies have investigated the potential role of *Ginkgo biloba* in treating ALS. One study suggested that the extract of *Ginkgo biloba* may have neuroprotective effects and may help improve motor function in ALS patients[178]. Another study found that combining *Ginkgo biloba* extract and donepezil, a medication commonly used to treat AD, may help improve cognitive function in ALS patients[179].

**2) Ginseng.** A perennial plant of the Araliaceae family, ginseng has been utilized in traditional medicine for more than 2000 years as a healing herb. The Panax variety of ginseng is the most commonly used and is grown in countries such as Japan, China, Korea, Russia, and Germany. The two most widely used types of *Panax ginseng* are *Panax ginseng* C.A. Meyer and *Panax quinquefolius*, found in Southern Canada and the United States. Ginseng contains over 20 types of Ginsenoside[162,180].

**3) Effects of ginsenosides.** Ginsenosides, the primary active components of ginseng, are believed to possess various therapeutic properties. Their effects can be categorized as follows:

a) **Neuroprotective effects:** Ginsenosides have been observed to protect against neurodegenerative diseases and are used in treating ischemic stroke[181].
b) **Anti-inflammatory properties:** They have been shown to inhibit inflammatory processes in the body, which can help in conditions like arthritis and asthma[182].
c) **Antioxidant properties:** These compounds exhibit antioxida nt activities, reducing oxidative stress in the body and thereby preventing cellular damage[183].

**4) Genistein.** A heterocyclic di-phenolic structure of genistein (4', 5, 7-trihydroxyisoflavone), a dietary phytoestrogen categorized as an isoflavone, enabling it to bind to estrogen receptor beta in cells. Various physiological and pharmacological effects of genistein include illness prognosis, specialist, anticancer, antitumor, antiviral, and anti-angiogenic activities[184]. Recent studies have investigated the potential therapeutic effects of genistein in ALS. For example, one study found that genistein treatment improved motor function and reduced muscle atrophy in a mouse model of ALS[185].

## 6. For the treatment of NDs, natural product testing

Traditional remedies can be used to treat neurodegenerative disorders as an alternative to conventional allopathic medication. Indian ayurvedic drugs can offer plant-derived compounds with neuroprotective, anti-inflammatory, and immunomodulating properties, enhancing cognitive functions, memory, and overall quality of life while reducing amyloid deposits. Additionally, practicing a balanced lifestyle, receiving socio-psychological support, adopting healthy dietary habits, using Rasayanas, and undergoing psychotherapies can effectively prevent and treat AD[186]. Plants, animals, and microbes are significant sources of natural products, secondary metabolites, and bioactive molecules used to develop medical treatments for numerous conditions[187]. The Earth provides abundant resources, including natural products found on land and underwater. These resources are essential for enhancing the well-being of both humans and animals and

controlling various diseases[188]. Through *in vitro* and *in vivo* research, natural compounds that have been utilized in various preclinical models of NDs have been further validated. Plants, fruits, nuts, and vegetables, along with marine and freshwater flora, contain phytoconstituents such as polyphenolic antioxidants that can assist in preventing neurodegeneration and improving cognitive function. These plant-derived compounds are thought to be essential in preventing and treating NDs like epilepsy, AD and PD[189].

# 7. Limitations and challenges

Using natural products as therapeutic agents for various illnesses, including neurological problems, has long been considered a possibility. They continue to be a focus of study and serve as the foundation for many modern medications. Natural products may provide a variety of substances with potential therapeutic benefits when considering neuroprotective therapy in particular. However, using them comes with difficulties and restrictions. An overview of some of these drawbacks and difficulties, which include both experimental and cheminformatics methods, is given below:

## 7.1. Complexity and variability of natural products

Many natural products are complex mixtures of compounds, which can lead to variability in their composition depending on factors like harvesting conditions, geographical sources, and preparation methods[190].

## 7.2. Toxicity and side effects

Natural does not always mean safe. Some natural products can be toxic or cause adverse effects, especially in high doses or when combined with other drugs[191].

## 7.3. Experimental challenges

Standardized protocols for evaluating neuroprotective effects may not exist, leading to inconsistent results across studies[192].

## 7.4. Cheminformatics challenges

While computational tools can predict potential neuroprotective compounds from natural products, they can also generate false positives and negatives[193]. Cheminformatics models often require vast datasets, and there may be limited data available on lesser-known natural products.

# 8. Conclusion and future perspectives

Numerous research studies have provided evidence for the therapeutic potential of natural products and bioactive compounds in protecting the nervous system. These substances are necessary to avoid harm while preventing and treating various NDs. As neurodegenerative pathologies involve various functional pathways, utilizing multiple modes of action is preferred to exhibit the neuroprotective effects of natural products and bioactive substances in ND prevention and treatment approaches. For natural products and their bioactive components to provide neuroprotective benefits, they must be able to penetrate the blood-brain barrier (BBB). Therefore, exploring new approaches and technologies, such as nanotechnology, is crucial for delivering natural substances and medications. These efforts can enhance the effectiveness of natural products and bioactive compounds in preventing and treating NDs and facilitating access to the brain for neuroprotective products. Advancements in medical science have led to longer life expectancies, resulting in a higher prevalence of NDs in the aging population. Factors such as lifestyle changes, altered eating habits, and increased stress from work or the environment have contributed to the growing frequency of NDs, including AD. To effectively manage or cure these diseases, it is necessary to address multiple causative agents. Conducting *in vivo* animal model studies can provide insight into the molecular mechanisms underlying NDs

and help identify potential therapeutic targets, including phytochemicals. Natural products have demonstrated promising bioavailability as therapeutic targets for AD.

As a result, adhering to a strict diet regimen emphasizing natural products with medicinal properties may hold promise for finding cures for AD. Because of their medicinal properties, scientists have turned to natural products for drug development for NDs such as AD. NDs such as AD, PD, epilepsy, wretchedness, and dementia are critical diseases and issues influencing individuals. At present, cheminformatics is essential in diminishing time and adventure. Using cheminformatics in drug design enables the verification and optimization of potential leads by analyzing the structural activity relationships. This approach aims to use natural sources to screen for potential leads to manage neurological conditions, opening up a broad area for future research. However, despite the expansion of these innovative methods in the pharmaceutical industry, the increased complexity of the drug-designing process cannot be overlooked.

## Conflict of interest

The authors declare no conflict of interest.

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