

Review

# Neuroprotective and Mental Health Benefits of Salt-Tolerant Plants: A Comprehensive Review of Traditional Uses and Biological Properties

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**Abstract:** This study undertakes a thorough review of the ethnomedicinal properties of salt-tolerant plants and their potential to treat neurological disorders and enhance mental health. Aimed at bridging the gap between historical knowledge and contemporary scientific validation, our research meticulously evaluates both the traditional uses and the existing scientific evidence supporting the neuroprotective effects of these plants, leveraging in vitro and in vivo experimental findings. Through a comprehensive search of articles from 2001 to December 2023 across scientific databases, we identified sixteen species across nine plant families with demonstrated in vitro neuroprotective properties. Among these, the Chenopodiaceae and Juncaceae families emerged as the most represented, including plants such as *Salicornia* sp., *Juncus* sp., and *Limonium* sp., primarily recognized for their cholinesterase inhibitory activity. However, a notable disparity exists between traditional applications and scientific examination, with only six species undergoing in vivo testing. This discrepancy underscores the imperative for future research to delve deeper into validating traditional uses and elucidating the mechanisms underlying neuroprotection. Our findings highlight the need for research on salt-tolerant plants traditionally used for neurological benefits. Key steps include systematic screening, identification of active compounds through bioassay-guided fractionation, and in vivo testing. Integrating traditional knowledge with modern pharmacology, while emphasizing sustainable and ethical approaches, is essential for advancing neuroprotective drug discovery.

**Keywords:** ethnobotany; halophytes; cognitive enhancement; secondary metabolites; therapeutic potential



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## 1. Introduction

The global prevalence of mental health and neurological disorders poses a challenge to public health systems worldwide. Recent research indicates a notable increase in the burden of these conditions, exacerbated by factors such as rapid urbanization, industrialization, and the COVID-19 pandemic. For instance, in China, rapid socio-economic transformations have led to a significant rise in mental health issues, with urbanization and ageing populations contributing to an increased prevalence of depression and dementia [1]. The COVID-19 pandemic has further amplified mental health problems globally, with a surge in depression, anxiety, and stress levels across various populations [2]. Neurological diseases like Alzheimer's and Parkinson's have seen an increase in Europe, underscoring the growing concern for these disorders [3]. The pandemic has highlighted the urgent need for scalable mental health interventions to mitigate the crisis, with calls for government support to enhance research and develop effective prevention and treatment strategies [4]. Moreover, the increase in the global burden of depression from 1990 to 2017 signals that depression continues to be a major public health issue that requires immediate action [5]. These findings collectively underscore the critical need for enhanced prevention, care,

and treatment strategies to address the growing impact of mental health and neurological disorders globally.

### *1.1. Biochemical Targets in Mental Health Disorders*

Key biochemical targets for mental diseases involve complex interactions within the nervous system, impacting neurotransmitter function, neuroplasticity, and neuroinflammation. For instance, recent research has illuminated the crucial roles of acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), and amyloid beta ( $A\beta_{42}$ ) across Alzheimer's disease (AD), Parkinson's disease (PD), and psychiatric disorders, suggesting these biomolecules as pivotal therapeutic targets. In AD, both AChE and BuChE are associated with disease pathology, indicating their potential as targets for diagnostic and therapeutic interventions [6]. The development of multi-target-directed ligands, such as 4-methylthiocoumarin derivatives, highlights the advancement in AD treatment by inhibiting these enzymes alongside  $\beta$ -amyloid aggregation and oxidative stress [7]. The exploration of novel cholinesterase inhibitors with multi-faceted therapeutic approaches, as reviewed by Saxena [8], emphasizes the need for a comprehensive strategy to address the multifactorial nature of AD [8]. Furthermore, the identification of BuChE as a pharmacological target for neurological disorders accentuates its role in amyloid-beta regulation, offering a new perspective on therapeutic targets [9]. These insights suggest a complex but promising frontier in developing effective treatments for neurodegenerative and psychiatric disorders by targeting AChE, BuChE, and  $A\beta_{42}$ .

While direct research on the role of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) in Parkinson's disease (PD) remains limited, the utilization of AChE and BuChE inhibitors—traditionally employed in Alzheimer's disease (AD)—for treating PD dementia indicates a shared therapeutic approach among neurodegenerative disorders. Rivastigmine, an FDA-approved dual inhibitor of AChE and BuChE, exemplifies this convergence in therapeutic strategies between AD and PD dementia. Recent investigations into novel carbamates have demonstrated superior inhibitory potency compared to rivastigmine, suggesting their potential as efficacious treatments for both conditions [10,11]. This line of research unveils a promising trajectory for the development of innovative drugs targeting AChE and BuChE in the management of various neurodegenerative diseases.

Moreover, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) also play crucial roles in psychiatric disorders, impacting mood and cognitive functions through the cholinergic system. Research indicates their involvement in substance abuse and related neurochemical imbalances, highlighting their significance in conditions such as depression, attention deficit hyperactivity disorder (ADHD), and schizophrenia. For instance, studies on substance abuse underscore the complex interplay between cholinergic neurons and psychiatric conditions, pointing towards the therapeutic potential of targeting AChE and BuChE in these disorders [12]. Additionally, research focused on schizophrenia patients provides further evidence of the critical role these enzymes play in the pathology of psychiatric diseases, advocating for their exploration as therapeutic targets [13]. This body of work suggests that AChE and BuChE inhibitors may offer novel approaches for treating psychiatric conditions by modulating cholinergic neurotransmission.

### *1.2. Role of Natural Remedies in Promoting Mental Wellness*

The global trend towards embracing natural remedies is evident in the adoption of herbal practices for treating health issues and promoting environmental well-being. Studies highlight a pivot to traditional and herbal methodologies for managing mental wellness, underscoring a preference for safer and natural options [14]. Recent research underscores the therapeutic potential of medicinal plants and traditional medicine in addressing mental health and neurological disorders. Studies conducted in various regions, including Ghana, Lesotho, and Namibia, have identified numerous plant species with analgesic, anxiolytic, and anticonvulsant properties, indicating their importance in traditional healthcare practices [15,16]. The integration of herbal medicine into modern drug discovery processes,

especially for neuropathic pain and neurodegenerative diseases, has shown promising outcomes, with several herbal drugs demonstrating preventive effects on neurological disorders [17]. Furthermore, the concept of plant-based functional foods for neurological health aligns with the advancing field of nutritional neuroscience, advocating for the use of bioactive phytochemicals in preventing and treating mental and neurological disorders [18]. Ayurvedic and traditional remedies offer a complementary approach to synthetic medications for various mental problems, emphasizing the cultural acceptance and cost-effectiveness of plant products in treating neurological conditions [19]. Notably, the neuroprotective potency of spice herbs, such as *Crocus sativus* and *Nigella sativa*, in traditional medicine systems highlights their potential to enhance neural functions and treat neurodegenerative diseases, offering new avenues for research and therapeutic applications [20].

### 1.3. Importance of Salt-Tolerant Plants

Research has traditionally focused on glycophytes for neuroprotective and mental health benefits. However, salt-tolerant plants, which thrive in high salinity environments, are now gaining interest for their medicinal properties, including unique secondary metabolites that could offer new neuroprotection and mental health treatment strategies.

Salt-tolerant plants, or halophytes, can thrive in highly saline ( $\geq 200$  mM sodium chloride) environments, such as salt marshes and coastal dunes. Salinity stress triggers the development of specialised adaptations, including the synthesis of osmolytes (proline, sugars), antioxidative enzymes (superoxide dismutases, catalases, peroxidases), or the synthesis of non-enzymatic antioxidants, crucial for the plant's defence mechanisms and survival [21]. Besides their role in plant welfare, these metabolites also have significant pharmacological potential, including various flavonoids, phenolic acids, and alkaloid derivatives, which are well-documented for their potent antioxidant, anti-inflammatory, and neuroprotective properties [22]. Moreover, with the progression of climate change leading to increased soil and water salinisation, these plants offer a sustainable agricultural alternative well-adapted to these changing conditions. As rising temperatures and altered precipitation patterns exacerbate soil salinity, salt-tolerant plants can be cultivated on lands that would otherwise be unsuitable for agriculture, thus helping to maintain food security and agricultural productivity in salt-affected regions [23].

Despite the growing interest in these plants, information on their neuroprotective properties remains scattered across various studies. Therefore, this review will provide a detailed analysis of the ethnomedicinal uses, alongside their *in vitro* and *in vivo* protective effects for neurodegenerative diseases and mental disorders, and the bioactive metabolites of salt-tolerant plants. It aims to highlight their potential in traditional and herbal medicine for improving mental wellness and neurological health. By merging traditional knowledge with modern research, we can explore novel treatments leveraging the neuroprotective qualities of salt-tolerant plants, advancing therapeutic options for mental and neurological disorders.

## 2. Methodology

This review concentrates on the potential applications of salt-tolerant plants for deriving bioactive compounds and natural products aimed at treating mental health conditions. A literature search was conducted, covering English-language articles with full texts available from 2001 through December 2023. Databases consulted included PubMed, Web of Science, Embase, and Google Scholar. Keywords used in the searches included "ethnomedicinal", "traditional use", "halophyte", and "salt-tolerant plant", combined with terms such as "neuroprotective", "antidepressant", and "mental health". The classification of plants as salt-tolerant was verified using the eHALOPH database and/or descriptions of their presence in coastal regions. Following the search, 40 relevant papers were reviewed and analysed.

### 3. Traditional Uses of Salt-Tolerant Plants as Neuroprotective and Mental Health Commodities

The exploration of salt-tolerant plants in traditional medicine, particularly for addressing mental health disorders highlights the rich diversity and proven effectiveness of natural therapeutics. Table 1 provides an overview of plant species, countries, medicinal uses, and methods of administration.

**Table 1.** Examples of salt-tolerant plants used in traditional medicine to treat mental health problems.

Plant Species	Medicinal Use	Plant Organs/Administration	Country	References
<i>Centaurium spicatum</i> (L.) Fritsch.	Mental-nervous issues	–	Egypt	[24]
<i>Helichrysum italicum</i> (Roth) G.Don	To treat sleeplessness	Fumes of leaves and flowers	Italy	[25]
<i>Peganum harmala</i> L.	Mental-nervous issues	–	Algeria	[24]
	Soporific	Fruits and seeds, external application	Iran	[26]
<i>Plantago major</i> L.	Mental-nervous issues	–	Spain	[24]
<i>Polygonum aviculare</i> L.	Sedative	Whole plant, fresh juice	Portugal	[27]
<i>Portulaca oleracea</i> L.	Mental-nervous disorders	–	Cyprus	[24]

The spread of these medicinal plants encompasses several countries along the Mediterranean region from Italy and Spain to Portugal, Algeria, Egypt, and Iran, highlighting their use in various cultural medicinal traditions. This broad distribution underscores not only the recognition of their therapeutic value but also the ubiquity of their use in traditional medicine. However, the application methods are not described in detail, while others are not mentioned at all. Moreover, the utilization of diverse plant parts, ranging from leaves and flowers in *H. italicum* [25] to fruits and seeds in *P. harmala* [24], reveals the understanding of the unique active components each part holds, indicates a deep knowledge and skills in harnessing the specific therapeutic benefits of various plant sections.

These plants are employed for their mental and nervous system-alleviating properties. For instance, *C. spicatum*, *P. major*, *P. harmala* and *P. oleracea* are renowned for their general mental therapeutic effects [24], while *H. italicum*, *P. harmala* and *P. aviculare* are specifically used for their soporific/sedative qualities [25–27]. The diversity in the medicinal applications of these plants highlights their substantial pharmacological potential, demonstrating a deep traditional medicinal knowledge in identifying and using the various benefits of these plants, as well as the understanding of their phytochemical diversity. Overall, ethnomedicinal knowledge opens avenues for further research into their pharmacological properties.

### 4. Salt-Tolerant Plants as Sources of Neuroprotective and Mental Health Commodities

In line with their historical applications in traditional medicine, numerous salt-tolerant plants have been identified as potential sources of bioactive compounds for the treatment of mental disorders and neurodegenerative diseases. These conditions, encompassing a wide spectrum of cognitive and behavioural abnormalities, pose significant challenges to global health. Mental disorders, such as depression, anxiety, and schizophrenia, affect hundreds of millions of individuals worldwide, severely impacting quality of life and societal productivity. Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, are characterized by progressive neuronal loss and dysfunction, leading to cognitive decline and motor impairment [1–5]. The complexity of these disorders, coupled with the limitations of current pharmacotherapies, underscores the urgency in exploring novel therapeutic options.

## 4.1. In Vitro Assays

Table 2 provides a comprehensive overview of the in vitro neuroprotective activities of various salt-tolerant plants, highlighting their significance in modern scientific research, particularly for neurodegenerative diseases.

**Table 2.** In vitro neuroprotective activity of salt-tolerant plants.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<b>Aizoaceae</b>						
<i>Mesembryanthemum crystallinum</i> L.	Edible parts	Ethanol/ultrapure water mixture (1/1 v/v) acidified to pH 2 with 0.1 M HCl, using a T-25 Ultra-Turrax homogenizer, followed by an ice bath and sonicated with a Q700 sonicator (Qsonica, Newton, CT, USA), using 16 min cycles at 90% amplitude, with 60-s intervals every minute.	Flavones, apigenin, diosmin, luteolin, 4-hydroxybenzoic acid, p-coumaric acid, and a hydroxycinnamic acid derivative (2-O-(p-cumaroyl)-l-malic acid)	Prolyl Endopeptidase (PEP) inhibition	Extract: 98.6%, at 1 mg/mL Fraction 2: 90.6%, at 200 µg/mL	[28]
<i>Carpobrotus edulis</i> (L.) N. E. Br.	Leaves	Sequentially extracted with hexane, dichloromethane, ethyl acetate, and methanol in extracted in a Soxhlet apparatus	Phenolics, flavonoids, and condensed tannins contents Ethyl acetate: gallic and salicylic acids and quercetin	AChE and BuChE inhibition Protective effect on H <sub>2</sub> O <sub>2</sub> -induced cytotoxicity on Neuroblastoma cells (SH-SY5Y) In vitro anti-neuroinflammatory activity on LPS-stimulated microglia cells	Ethyl acetate (10 mg/mL): 75.6% (AChE); 78.8% (BuChE) Methanol: (10 mg/mL): 86.1% (AChE); 59.4% (BuChE) Dichloromethane (50 µg/mL): 105% of cell viability Methanol (50 µg/mL): 143% of cell viability Methanol (100 µg/mL): 77% of decrease	[29]
<i>Carpobrotus edulis</i> (L.) N. E. Br.	Leaves	Magnetic stirring with methanol for 16 h	phenolic compounds, flavonoids, and tannins, linoleic acid (32.5%)	AChE and BuChE enzyme inhibition	AChE (10 mg/mL): 41% BuChE (10 mg/mL): 35%	[30]
<b>Amaranthaceae</b>						
<i>Arthrocnemum macrostachyum</i> L.	Leaves	Magnetic stirring with methanol for 16 h	Alkaloids, phenolics, flavonoids, and tannins linolenic (25.6%) and linoleic acids (20.9%)	AChE and BuChE enzyme inhibition	AChE (10 mg/mL): 81% BuChE (10 mg/mL): 77%	[30]
<i>Atriplex laciniata</i> L.	Whole plant	Soaked in Methanol 85% for 15 days, was dissolved water and fractionated with n-hexane, chloroform, ethyl acetate, and residual water fraction Saponins: double extraction with 20% ethanol at 55 °C for 4 h Flavonoids: 80% aqueous methanol at room temperature.	Phenolic and flavonoid, carotenoids	AChE and BuchE enzyme inhibition	Methanol Fraction: IC <sub>50</sub> (AChE) = 280 µg/mL; IC <sub>50</sub> (BuChE) = 220 µg/mL Hexane Fraction: IC <sub>50</sub> (AChE) = 310 µg/mL; IC <sub>50</sub> (BuChE) = 400 µg/mL Chloroform Fraction: IC <sub>50</sub> (AChE) = 390 µg/mL; IC <sub>50</sub> (BuChE) = 160 µg/mL Ethyl Acetate Fraction: IC <sub>50</sub> (AChE) = 270 µg/mL; IC <sub>50</sub> (BuChE) = 260 µg/mL Water Fraction: IC <sub>50</sub> (AChE) = 263 µg/mL; IC <sub>50</sub> (BuChE) = 210 µg/mL Saponins Fraction: IC <sub>50</sub> (AChE) = 90 µg/mL; IC <sub>50</sub> (BuChE) = 120 µg/mL Flavonoids Fraction: IC <sub>50</sub> (AChE) = 70 µg/mL; IC <sub>50</sub> (BuChE) = 100 µg/mL	[31]
<i>Salicornia europaea</i> L.	Stem and Leaves	Enzyme-digested PhytoMeal ethanol extract (PM-EE)	Caffeic acid, trans-ferulic acid, acanthoside B, isorhamnetin, irilin B carbohydrates (58.3%), uronic acids (12.8%), proteins (10.9%)	AChE enzyme inhibition; Neuroinflammation on BV-2 microglial cells	AChE: IC <sub>50</sub> = 0.92 mg/mL NO production: 50% reduction at 200 µg/mL	[32]

Table 2. Cont.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<i>Salicornia ramosissima</i> L.	By-product	Water extraction with time ranging from 10 to 60 min and temperature varying between 40 and 80 °C	caffeoylquinic acid derivatives, hydroxy methoxyisoflavone derivatives and isorhamnetin-3-O β-D glucopyranoside, asparagine, arginine, betaine, and propionylalanine, methyl digalloyl glucopyranoside and methoxy chromone	AChE enzyme inhibition	23.84% (at 250 µg/mL) and 32.34% (at 1000 µg/mL)	[33]
<b>Apocynaceae</b>						
<i>Apocynum venetum</i> L.	Leaves	Refluxed for 1 h in aqueous ethanol (70% v/v, 60 mL) twice	Not mentioned	Corticosterone-induced neurotoxicity in PC12 cells for 48 h	Cell viability was significantly increased in a dose-dependent manner (41.2–78% of the control) at 25, 50, and 100 µg/mL. Reduction in cell cycle arrest at G0/G1 and G2/M phases, and decreased number of cells in S phase	[34]
<b>Asteraceae</b>						
<i>Calendula arvensis</i> L.	Stems, leaves, flowers	Maceration with cyclohexane, dichloromethane, ethyl acetate, acetone, and acetonitrile for 24 h	Phenolics and flavonoids	AChE enzyme inhibition	Cyclohexane: Stems (41.3%) and leaves (20.2%) at 100 µg/mL; Dichloromethane: lowers (47.8%) at 100 µg/mL	[35]
<b>Chenopodiaceae</b>						
<i>Chenopodium murale</i> L.	Stems, leaves, flowers	Maceration with cyclohexane, dichloromethane, ethyl acetate, acetone, and acetonitrile for 24 h	Phenolics and flavonoids	AChE enzyme inhibition	Cyclohexane: Flowers (53.08%) at 100 µg/mL; Dichloromethane: Stems (100%) and flowers (46.27%) at 100 µg/mL; Ethyl Acetate: Leaves (100%) at 100 µg/mL IC <sub>50</sub> (dichloromethane, stems) = 40.9 µg/mL; IC <sub>50</sub> (ethyl acetate, leaves) = 31.7 µg/mL;	[35]
<i>Salsola tetragona</i> Delile	Aerial parts	Maceration at ambient temperature with MeOH: H <sub>2</sub> O (70:30, v/v) followed by liquid-liquid extraction with n-hexane, dichloromethane, ethyl acetate, and n-butanol	Phenolics and flavonoids	AChE enzyme inhibition	IC <sub>50</sub> (Hexane) = 63 µg/mL; IC <sub>50</sub> (dichloromethane) = 60 µg/mL; IC <sub>50</sub> (Ethyl acetate) = 30 µg/mL; IC <sub>50</sub> (Butanol) = 32 µg/mL	[36]
<b>Cynomoriaceae</b>						
<i>Cynomorium coccineum</i> subsp. <i>songaricum</i> (Rupr.) J. Leonard	Stem	50% ethanol followed by eluted in a macroporus resin column by H <sub>2</sub> O, 50% EtOH, and 95% EtOH. The 50% EtOH elution was then subjected to CC over an MCI CHP20P resin and eluted stepwise by H <sub>2</sub> O, 30% EtOH, 50% EtOH, and 95% EtOH. The 95% EtOH MCI elution (162 g) was loaded onto a silica gel column and eluted by CHCl <sub>3</sub> -MeOH (100:1–1:100) to give 12 fractions	Triterpenes, steroids, lignans, flavonoids, and other phenolics	Glutamate (Glu) and oxygen glucose deprivation (OGD) induced SK-N-SH cell death	Compounds 7, 8, 12, 13, 15, 16, 18, 19, and 21–24 could significantly reduce Glu-induced SK-N-SH cell death with viability rates of 20.3–42.9% at 10 µM. Compounds 1, 7, 8, 10, 15–21, and 24 showed significant neuroprotective activities against OGD-induced SK-N-SH cell death with viability rates from 18.9% to 90.7% at 10 µM.	[37]

Table 2. Cont.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<b>Cyperaceae</b>						
<i>Cladium mariscus</i> L. (Pohl.)	Seeds	Water, acetone, 80% aqueous acetone, ethanol, 80% aqueous ethanol	Flavonoids, phenolic acids, fatty acids, stilbenes	AChE and BuChE enzyme inhibition	Water (AChE: 3.73 GALAE/g; BuChE 5.13 GALAE/g); Acetone (AChE: 3.89 GALAE/g; BuChE: 5.05 GALAE/g); 80% aqueous acetone (AChE: 3.92 GALAE/g; BuChE: 3.47 GALAE/g); Ethanol (AChE: 4.21 GALAE/g); 80% aqueous ethanol (AChE: 3.83 GALAE/g; BuChE: 6.02 GALAE/g).	[38]
<b>Fabaceae</b>						
<i>Glycyrrhiza inflata</i> Bat.	Roots	Not applicable—purchased	Licochalcone B	Amyloid beta (Ab42) self-aggregation, metal-chelation, and H <sub>2</sub> O <sub>2</sub> -induced cell death in SH-SY5Y cells.	Amyloid beta (Ab42) self-aggregation: IC <sub>50</sub> = 2.16 µM	[39]
<b>Frankeniaceae</b>						
<i>Frankenia thymifolia</i> Desf.	Aerial parts and roots	Magnetic stirring with methanol 80% for 2 h. The obtained filtrate is 1st extracted with hexane followed by dichloromethane, ethyl acetate, and finally butanol	Hydroxytyrosol and p-hydroxybenzoic acid	Aβ-induced toxicity in PC12 cell line	Ethyl Acetate: Aerial parts (~70 and 100%) and Roots (~100 and 90%) at 25 and 50 µg/mL, respectively.	[40]
<i>Frankenia pulverulenta</i> L.	Aerial parts and roots	Magnetic stirring with methanol 80% for 2 h. The obtained filtrate is 1st extracted with hexane followed by dichloromethane, ethyl acetate, and finally butanol	Gallic acid, catechin, procyanidin, trigalloyl hexoside, quercetin galloyl glucoside, flavonoid sulphate. quercetin	Aβ-induced toxicity in PC12 cell line	Ethyl Acetate: Aerial parts (~80%) and Roots (~80–90%) at 200 and 300 µg/mL.	[41]
<b>Juncaceae</b>						
<i>Juncus acutus</i> , <i>J. maritimus</i> , and <i>J. inflexus</i>	Seeds, leaves and roots	Methanol and dichloromethane, overnight stirring followed by a bio-guided fractionation	Juncunol ( <i>J. acutus</i> leaves, dichloromethane)	AChE and BuChE enzyme inhibition, and AChE inhibition on human neuroblastoma SH-SY5Y and murine microglia N9 cells	<i>J. acutus</i> dichloromethane: leaves (IC <sub>50</sub> = 665 µg/mL) and roots (IC <sub>50</sub> = 951 µg/mL) Juncunol: AChE (IC <sub>50</sub> = 940 µg/mL); BuChE (IC <sub>50</sub> = 758 µg/mL); AChE-SH-SY5Y (IC <sub>50</sub> = 158 µg/mL); AChE-N9 (IC <sub>50</sub> = 117 µg/mL).	[42]
<i>Nitraria retusa</i> (Forssk.) Asch.	Shoots	Maceration with 10% ethanol for 2 weeks	Isorhamnetin	Amyloid β-induced cytotoxicity and amyloid β aggregation in human neuroblastoma SH-SY5Y cells	Amyloid β-induced cytotoxicity (increased cell viability above 100%); Amyloid β aggregation in human neuroblastoma SH-SY5Y cells (~40% of adhered area—similar to control)	[43]
<b>Orobanchaceae</b>						
<i>Cistanche phelypaea</i> (L.) Cout	Flowers, stems and roots	Ethyl acetate, acetone, ethanol and water, overnight stirring	Flowers: tubuloside, glucoside and bartsioside Stems: tubuloside Roots: echinacoside	AChE and BuChE enzyme inhibition	Flowers: AChE (0.58 mg GALAE/g), BuChE (1.72 mg GALAE/g). Stems: AChE (0.30 mg GALAE/g), BuChE (1.47 mg GALAE/g). Roots: AChE (0.58 mg GALAE/g).	[44]

Table 2. Cont.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<b>Plumbaginaceae</b>						
<i>Armeria pungens</i> (Link) Hoffmanns. and Link)	Flowers, peduncles and leaves	Ethyl acetate, acetone, ethanol and water overnight under stirring, at room temperature	Catechin	AChE and BuChE enzyme inhibition	AChE: Ethanol, Flowers (IC <sub>50</sub> = 276 µg/mL); Ethanol, Peduncles (IC <sub>50</sub> = 221 µg/mL); Ethanol, Leaves (IC <sub>50</sub> = 90.3 µg/mL); Water, Leaves (IC <sub>50</sub> = 87.6 µg/mL)	[45]
<i>Limoniastrum guyonianum</i> Boiss	Aerial parts	Aqueous acetone (6:4, v/v) extraction followed by partitioning with petroleum ether and ethyl acetate	Fraction 3: p-coumaric acid, catechin and epigallocatechin-3-O gallate Fraction 4: gallo-catechin, sinapic acid, N-E-caffeoyl tyramine and Limoniastramide	Thioflavin T fluorescence spectroscopy (anti-amyloidogenic activity)	Fractions 3 and 4: inhibition percentage of 57 and 54%, respectively (at 10 mg/mL)	[46]
<i>Limonium spathulatum</i> (Desf.) Kuntze	Leaves	Ethanol (100% and 50%) and water, overnight stirring	Hydroxybenzoic acids (gallic and syringic acid), hydroxycinnamic acids (caffeic, coumaric, and ferulic acids), and flavonoids (catechin and epigallocatechin)	AChE and BuChE enzyme inhibition	AChE: Ethanol (IC <sub>50</sub> = 1.75 mg/mL); Water (IC <sub>50</sub> = 0.23 mg/mL); Hydroethanolic (IC <sub>50</sub> = 0.31 mg/mL) BuChE: Ethanol (IC <sub>50</sub> = 0.27 mg/mL); Water (IC <sub>50</sub> = 0.06 mg/mL); Hydroethanolic (IC <sub>50</sub> = 0.03 mg/mL);	[47]
<i>Limonium spathulatum</i> (Desf.) Kuntze	Aerial parts	Delipidation with petroleum ether and successive extraction with chloroform, methanol, methanol: water (5:1) for 72 h.	Fatty acids and phenolic compounds including flavonoids, tannins, hydroxycinnamic acids, anthocyanins, flavones, and flavonols	AChE and BuChE enzyme inhibition	AChE: Methanol (IC <sub>50</sub> = 31.14 µg/mL); Methanol:Water (IC <sub>50</sub> = 3.28 µg/mL) BuChE: Methanol (IC <sub>50</sub> = 36.65 µg/mL); Methanol:Water (IC <sub>50</sub> = 26.64 µg/mL)	[48]
<i>Limonium algarvense</i> Erben	Flowers	Infusions and decoctions	Salicylic and gentisic acids	AChE and BuChE enzyme inhibition	AChE: Infusion (IC <sub>50</sub> = 0.22 mg/mL); Decoction (IC <sub>50</sub> = 0.39 mg/mL) BuChE: Infusion (IC <sub>50</sub> = 0.84 mg/mL); Decoction (IC <sub>50</sub> = 0.96 mg/mL)	[49]
<i>Limonium delicatulum</i> (Girard) Kuntze	Leaves	methanol for 24 h	salvianolic acid B, and polydatin	AChE and BuChE enzyme inhibition	AChE: EC <sub>50</sub> = 5.94 µg/mL BuChE: EC <sub>50</sub> = 11.68 µg/mL	[50]
<b>Rhizophoraceae</b>						
<i>Bruguiera gymnorhiza</i> (L.) Lam.	Leaves, roots, twigs, and fruits	Maceration and decoction	Quinic acid, brugierol, bruguerol A, epigallocatechin, chlorogenic acid.	AChE and BuChE enzyme inhibition	AChE: Roots, Decoction (2.56 mg GALAE/g); Twigs, Decoction (1.17 mg GALAE/g); Fruits, Decoction (3.90 mg GALAE/g); Roots, Aqueous (2.13 mg GALAE/g); Fruits, Aqueous (3.75 mg GALAE/g). BuChE: Leaves, Decoction (0.30 mg GALAE/g); Roots, Decoction (0.57 mg GALAE/g); Twigs, Decoction (0.72 mg GALAE/g); Fruits, Decoction (2.85 mg GALAE/g); Roots, Aqueous (0.32 mg GALAE/g); Fruits, Aqueous (2.19 mg GALAE/g).	[51]

Table 2. Cont.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<b>Rubiaceae</b>						
<i>Guettarda speciosa</i> L.	Leaves	Percolation with MeOH followed by partitioning with hexane and CHCl <sub>3</sub> . Aqueous layer	Iridoids and their glucosides, phenolics, glycerol derivatives, steroids, triterpenoids, and fatty acids	Thioflavin T fluorescence spectroscopy (anti-amyloidogenic activity)	50 µg/mL: Methanol (54.71% inhibition); Chloroform (65.78% inhibition)	[52]
<b>Salicaceae</b>						
<i>Populus euphratica</i> Olivier	Resins	95% EtOH which was partitioned with EtOAc affording 8 fractions by using a silica gel column with petroleum ether acetone (50:1, 35:1, 20:1, 15:1, 10:1, 7:1, 3:1,1:1) as solvents	octanorlanostane-type triterpenes, euphraticanoids A and B (1 and 2), two new trinorsesquiterpenoids, euphraticanoids C and D (3 and 4), and eight known triterpenoids (5, 6, 8–13) along with one steroid (7)	Glutamate-induced excitotoxicity in SH-SY5Y cells and antioxidative effects against H <sub>2</sub> O <sub>2</sub> in HT-22 cells	10–40 µM: Compounds 3, 4, 8, and 9 could dose-dependently protect neural H <sub>2</sub> O <sub>2</sub> cell injury on HT-22 cells, and glutamate-induced excitotoxicity on SH-SY5Y cells.	[53]

A total of sixteen species belonging to nine different plant families have been described with in vitro neuroprotective properties, where Chenopodiaceae and Juncaceae families emerged as the most represented. The aerial parts, including stems, leaves, and flowers are the plant organs that have been the focus of most investigations. In turn, a variety of extraction methods and solvents were used, with the most used in the studies being maceration and magnetic stirring, with solvents including methanol, ethanol, and aqueous acetone. Moreover, it is evident that the most active plants used for mental health treatments primarily contain a diverse array of metabolites, with phenolic compounds, flavonoids, and terpenoids being the major components. Phenolic compounds, such as flavonoids and phenolic acids, are notably prevalent across many plant species. Key flavonoids identified include apigenin, quercetin, luteolin, and catechin, while significant phenolic acids include gallic acid, salicylic acid, 4-hydroxybenzoic acid, and p-coumaric acid. Additionally, terpenoids, particularly triterpenoids, have been highlighted in some plants, such as *C. coccineum*, which contains a combination of triterpenes, steroids, lignans, and other phenolics [37], and *P. euphratica*, which includes unique euphraticanoids [53]. These metabolites often occur in synergistic combinations, which may enhance their neuroprotective efficacy. For instance, *M. crystallinum* combines flavones (apigenin, diosmin, luteolin) with phenolic acids [28], while *C. edulis* features a mix of phenolics (gallic and salicylic acids), flavonoids (quercetin), and condensed tannins [29,30]. Another notable example is *A. macrostachyum*, which contains alkaloids, phenolics, flavonoids, tannins, and fatty acids like linolenic and linoleic acids [30], demonstrating a complex blend of bioactive compounds.

In particular, salt-tolerant plants such as *Salicornia* sp., *Juncus* sp. and *Limonium* sp. have been the focus of multiple studies, indicating their significance in the context of neuroprotection [32,33,42,47–50]. For instance, *Salicornia europaea* (L.) is a species from the family Chenopodiaceae, and it has been the subject of several investigations. Karthivashan et al. [32] studied the neuroprotective activity of an enzyme-digested PhytoMeal ethanol extract (PM-EE) derived from the stem and leaves of *S. europaea*. The extract was found to exhibit inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes. Additionally, Pinto et al. [33] reported that the *S. ramosissima* by-product, extracted through Response Surface Methodology (RSM) at 80 °C/10 min, showed significant AChE enzyme inhibition. Caffeoylquinic acid derivatives, hydroxy methoxyisoflavone derivatives, isorhamnetin-3-O β-D glucopyranoside, asparagine, arginine, betaine, propionylalanine, methyl digalloyl glucopyranoside, and methoxy chromone were detected as main components in these extracts, suggesting their potential link to the reported neuroprotective properties. Juncunol, a compound isolated from *Juncus acutus* leaves, exhibited inhibitory effects on AChE and BuChE enzymes, as well as AChE inhibition in human neuroblastoma SH-SY5Y and murine microglia N9 cells [42]. The research on various *Limonium* species has demonstrated their potential in inhibiting acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE),

enzymes associated with neurodegenerative diseases like Alzheimer's. For *L. spathulatum*, extracts from leaves using ethanol and water showed significant enzyme inhibition, with water and hydroethanolic extracts exhibiting the lowest IC<sub>50</sub> values, specifically towards AChE (0.23 mg/mL) and BuChE (0.03 mg/mL), respectively, indicating high potency. Hydroxybenzoic acids, hydroxycinnamic acids, and flavonoids, detected in the leaf extracts, were associated with various bioactivities [47]. Similar research on the same species focused on the effects of aerial parts and varied extraction methods of fatty acids and phenolic compounds on enzyme inhibition, where the methanol:water extract showed strong effectiveness against AChE, with an IC<sub>50</sub> value of 3.28 µg/mL [48]. Moreover, *L. algarvense* flowers' infusions and decoctions demonstrated significant AChE and BuChE inhibition potential, with IC<sub>50</sub> values falling between 0.22 and 0.96 mg/mL. The main components found in the extracts were salicylic and gentisic acids [49]. Finally, methanol extracts from *L. delicatulum* leaves demonstrated efficacy against AChE and BuChE (EC<sub>50</sub> = 5.94 and 11.68 µg/mL, respectively), with salvianolic acid B and polydatin recognised as predominant active constituents [50]. In general, these examples showcase the various bioactive compounds and neuroprotective abilities linked to plants that can thrive in salty conditions.

In the context of salt-tolerant plants, while specific mechanistic studies on mental health are limited, the most studied targets in the scrutinized articles were acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzyme inhibition assays, as well as assays related to amyloid beta (Aβ42) self-aggregation and anti-amyloidogenic activity. This is significant as cholinesterase inhibitors are a well-established treatment strategy for neurodegenerative diseases like Alzheimer's disease. Studies on aromatic plants have shown similar inhibitory effects on cholinesterase and have provided mechanistic insights, suggesting a potential hypothesis for salt-tolerant plants as well. For instance, aromatic plants used to treat anxiety or other mental issues often act through modulation of neurotransmitter systems and enhancement of synaptic plasticity [54,55]. Similarly, amyloid-beta (Aβ42) self-aggregation also plays a pivotal role in the pathogenesis of neurodegenerative diseases, particularly Alzheimer's disease. Aβ42 peptides aggregate into toxic oligomers and fibrils, forming amyloid plaques that disrupt cellular homeostasis through oxidative stress, mitochondrial dysfunction, membrane disruption, inflammation, and synaptic dysfunction. Anti-amyloidogenic compounds inhibit Aβ42 aggregation or promote the disaggregation of preformed fibrils, thereby mitigating their toxic effects. These compounds achieve this by preventing Aβ42 monomers from aggregating, disaggregating existing fibrils, chelating metal ions that facilitate aggregation, or stabilizing non-toxic conformations of Aβ42. Understanding and targeting these mechanisms is crucial for developing effective treatments for Alzheimer's disease and other neurodegenerative disorders [56,57]. Additionally, the neuroprotective effects of plant metabolites like phenolics, flavonoids, and terpenoids in medicinal plants can be extended to several other potential mechanisms. Firstly, these metabolites can exhibit strong antioxidant activity, scavenging free radicals and reducing oxidative stress, which is crucial in combating neurodegenerative diseases [58]. Many flavonoids and phenolic acids possess anti-inflammatory properties, inhibiting pro-inflammatory cytokines and enzymes such as COX-2 and iNOS, thus mitigating neuroinflammation [59]. These compounds also inhibit enzymes like acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), thereby enhancing cholinergic transmission and offering benefits in conditions like Alzheimer's disease [54]. Flavonoids further modulate neurotransmitter systems, influencing serotonergic, dopaminergic, and GABAergic pathways to exert anxiolytic and antidepressant effects [60]. Moreover, terpenoids and flavonoids promote neurogenesis and synaptic plasticity by upregulating neurotrophic factors and activating supportive signalling pathways [61]. They also protect against neurotoxicity by stabilizing mitochondrial function and modulating intracellular calcium levels [62]. Metal chelation is another significant mechanism, where phenolics bind to metal ions, reducing metal-induced oxidative stress [63]. Lastly, certain phenolics inhibit amyloid-beta aggregation, reducing its neurotoxic effects and promoting amyloid clearance, which is particularly relevant in Alzheimer's disease [64]. These multifaceted actions highlight the potential of these plant metabolites in treating and preventing neurodegenerative and neuropsychiatric disorders.

#### 4.2. In Vivo Studies

Only a small number of researchers have assessed the neuroprotective effects of salt-tolerant plants in living organisms, focusing on six plant species from five different families, and primarily utilizing rodents for their studies. These findings are compiled in Table 3.

**Table 3.** In vivo neuroprotective activity of salt-tolerant plants.

Family/Species	Plant Organs	Extract	Main Constituents	Assay	Main Results	Reference
<b>Amaranthaceae</b>						
<i>Salicornia europaea</i> L.	Stem and Leaves	Enzyme-digested PhytoMeal ethanol extract (PM-EE) by Phyto Corporation	Caffeic acid, trans-ferulic acid, acanthoside B, isorhamnetin, irilin B carbohydrates (58.3%), uronic acids (12.8%), proteins (10.9%)	Alzheimer's like scopolamine-induced amnesic mice model	Repressed behavioral/cognitive impairment, dose-dependently regulated the cholinergic function, suppressed oxidative stress markers, regulated inflammatory cytokines/associated proteins expression and effectively ameliorated <i>p</i> -CREB/BDNF levels, neurogenesis (DCX stain), neuron proliferation (Ki67 stain)	[32]
<b>Apocynaceae</b>						
<i>Calotropis gigantea</i> Linn	Latex from aerial parts	Dried sample under sunlight (ADCG) and freeze-dried microencapsulated latex (FDCG)	Alkaloids, cardiac glycosides, tannins, flavonoids, sterols, and/or triterpenes	Apomorphine-induced climbing behavior, 1-5-HTP-induced syndrome, and MK-801-induced hyperactivity assays	FDCG significantly reduced the apomorphine-induced climbing behavior, 1-5-HTP-induced syndrome, and MK-801-induced hyperactivity in a dose-dependent manner through an interaction of dopaminergic and serotonergic receptors	[65]
<i>Apocynum venetum</i> L.	Leaves	Refluxed for 1 h in aqueous ethanol (70% v/v, 60 mL) twice	Hyperoside and Isoquercitrin	Forced swimming test (FST) with CD male rat model—acute and repeated treatment	Immobility was significantly reduced after acute pre-treatment at 125 mg/kg, and after 14 days, it reduced immobility at 30 and 125 mg/kg	[66]
"	"	"	"	Levels of serotonin (5-HT), norepinephrine (NE), dopamine (DA) and their metabolites in rat hypothalamus, striatum and hippocampus; Density of $\beta$ -adrenergic receptors in rat frontal cortex—short (2 weeks) and long (6 weeks) term administration in rat model	NE and DA levels were significantly reduced in the hypothalamus and striatum after 8 weeks of daily treatment with 15 and 60 mg/kg, respectively. In the hippocampus, the decrease in NE occurred after 2 weeks of daily treatment.	[67]
<b>Malvaceae</b>						
<i>Althaea officinalis</i> L.	Leaves	Infusion for 2 h	Hhypoalaetin-8glucoside, isoquercitrin, kaempferol, caffeic acid, p-coumaric acid, coumarins, scopoletin, phytosterols, tannins, asparagines and amino acids	6-hydroxydopamine-induced hemi-Parkinsonism (Adult male Wistar rat model)	Attenuated rotational behaviour (~50%) and protected the neurons of substantia nigra pars compacta against 6-OHDA toxicity (~30%)	[68]
<b>Nitrariaceae</b>						
<i>Nitraria tangutorum</i> Bobr	Fruit	95% ethanol for 3 h, stirring followed by fractionation	Anthocyanins (87% of cyanidin-3-[2''-(6'''-coumaroyl)-glucosyl]-glucoside)	D-Galactose-induced memory deficits (Female Sprague–Dawley rat model)	Reduced overexpression of receptor for advanced glycation end products (RAGE) and amyloid-beta42 (A $\beta$ 42) in the hippocampus	[69]
<b>Plantaginaceae</b>						
<i>Plantago major</i> L.	Leaves	Hot distilled water at 60 °C for 15 min.	Flavonoids, phenolic compounds, tannins	Pentobarbital induced Hypnosis in rat model	Doubled the sleeping time (from 42.13 to 86.57 min)	[70]

The most used plant parts are leaves, like *S. europaea*, *A. officinalis*, *P. major*, while *N. tangutorum* was the only one testing the fruit [32,68–70]. Further, several methods were used for extracting the biomass, including drying samples under sunlight, freeze-drying microencapsulated latex for *C. gigantea* [65], refluxing for 1 h in aqueous ethanol for *A. venetum* leaves [66,67], and using hot distilled water at 60 °C for 15 min for *P. major* leaves [70]. Additionally, 95% ethanol was used for 3 h with stirring for *N. tangutorum* fruit [69], and enzyme-digested PhytoMeal ethanol extract (PM-EE) was used for *S. europaea* stem and leaves [32]. The most studied family was the Apocynaceae, where *A. venetum* and *C. gigantea* were studied. The 70% aqueous ethanol extract of *A. venetum*, mainly composed of hyperoside and isoquercitrin, was tested on the forced swimming test (FST) with CD male rat models, both for acute and repeated treatment. The results of these studies demonstrated the reduction in immobility in the forced swimming test after acute pre-treatment at 125 mg/kg, and after 14 days of treatment at 30 and 125 mg/kg [66,67]. Moreover, the latex extracted from the aerial parts of *C. gigantea* decreased apomorphine-induced climbing behaviour, 1-5-HTP-induced syndrome, and MK-801-induced hyperactivity in a dose-dependent way by influencing dopaminergic and serotonergic receptor interaction [65].

Furthermore, amongst several species traditionally used for mental and nervous issues, only *P. major* has transitioned from traditional ethnobotanical practices to scientific testing. Ethnobotanical reports across European countries have highlighted the use of infusions and decoctions prepared from the leaves of *P. major* for treating ailments related to the nervous system. Building upon this traditional knowledge, Caro et al. [70] (2018) investigated the scientific basis of these reports. Utilizing a hot water extraction method to mimic traditional preparations, the study focused on the plant's impact on pentobarbital-induced hypnosis in rats, revealing that the extract notably doubled the sleeping time. This finding supports the plant's sedative effects, aligning with its historical use and demonstrating the potential of traditional medicine as a foundation for discovering therapeutic agents for neurological and mental health issues.

The in vivo assays used to test the neuroprotective activity of plant extracts are crucial for understanding their efficacy in complex biological systems. The forced swimming test (FST) with CD male rat models is used to evaluate antidepressant-like activity by measuring immobility time, indicating potential mood-enhancing effects [71,72]. The pentobarbital-induced hypnosis assay in rat models assesses sedative properties by measuring sleep duration, relevant for anxiety and insomnia treatment [73,74]. The 6-hydroxydopamine (6-OHDA)-induced hemi-Parkinsonism model in adult male Wistar rats mimics Parkinson's disease, evaluating neuroprotective effects through behavioural and neuronal integrity assessments [75]. The Alzheimer's-like scopolamine-induced amnesic mice model tests the cognitive function and memory improvement, indicating potential anti-Alzheimer's effects [76]. These assays provide valuable preclinical data on the therapeutic potential of plant metabolites, bridging the gap between in vitro studies and clinical trials.

Similarly to the in vitro tests, the major components of the most active plants are primarily phenolic compounds, flavonoids, and terpenoids. Phenolic compounds, such as caffeic acid and trans-ferulic acid, along with flavonoids like hyperoside, isoquercitrin, kaempferol, and anthocyanins, are abundantly present in these plants. Terpenoids, including sterols and triterpenes, are also significant, although less frequently mentioned. These metabolites often occur in complex combinations, contributing to the plants' neuroprotective effects. For instance, *S. europaea* contains caffeic acid, trans-ferulic acid, acanthoside B, isorhamnetin, and irilin B, along with carbohydrates, uronic acids, and proteins [32]. *C. gigantea* latex comprises alkaloids, cardiac glycosides, tannins, flavonoids, sterols, and triterpenes [65]. *A. venetum* leaves contain hyperoside and isoquercitrin [66,67], while *A. officinalis* leaves include hypolaetin-8-glucoside, isoquercitrin, kaempferol, caffeic acid, p-coumaric acid, coumarins, scopoletin, phytosterols, tannins, asparagines, and amino acids [68].

For instance, phenolics, flavonoids, and terpenoids play significant roles in the neuroprotective activities observed in various in vivo assays. Phenolic compounds, such as caffeic and ferulic acids, possess strong antioxidant properties that mitigate oxidative

stress, contributing to antidepressant-like effects [55]. Flavonoids, including quercetin and hyperoside, enhance neurotransmitter levels, promoting mood regulation and showing antidepressant activity in the forced swimming test (FST) [60,67]. These compounds also exhibit sedative and hypnotic effects, as seen in pentobarbital-induced hypnosis assays, by enhancing GABAergic neurotransmission [73,77]. In Parkinson's disease models, phenolic acids and flavonoids protect dopaminergic neurons from oxidative damage and inflammation, preserving neuronal integrity [78]. Additionally, in Alzheimer's disease models, phenolics and flavonoids inhibit amyloid-beta aggregation and enhance synaptic plasticity, improving cognitive functions [64]. Terpenoids like ginkgolides also contribute to neuroprotection by reducing neuroinflammation and oxidative stress [64]. These compounds' multifaceted actions underline their potential in treating neurodegenerative and neuropsychiatric disorders.

## 5. Conclusions and Future Research Directions

This review, for the first time, has collected data on the ethnomedicinal properties of salt-tolerant plants concerning neurological disorders and overall mental health, as well as on the existing scientific reports of their *in vitro* and *in vivo* experiments. Sixteen species from nine different plant families have been reported to possess *in vitro* neuroprotective properties, with the Chenopodiaceae and Juncaceae families being the most represented. This includes *Salicornia* sp., *Juncus* sp. and *Limonium* sp., which have been the focus of multiple studies, indicating their significance in the context of neuroprotection, with the inhibition of cholinesterases being the main biochemical target. Conversely, only six plant species from five different families were tested *in vivo*, with the Apocynaceae family being the most studied, including *A. venetum* and *C. gigantea*. Juncunol, the only pure compound, was isolated from *J. acutus* but was tested solely for its *in vitro* cholinesterase inhibitory properties. Additionally, the transition from traditional use to scientific validation is scarce, being exclusive to *P. major*, which underscores a substantial gap in this field. This oversight highlights a promising area for future research, encompassing:

**Targeted Exploration of Traditionally Used Species:** A priority for future research should be the systematic screening of salt-tolerant plants traditionally used for neuroprotective effects. This involves cataloguing species cited in ethnobotanical records and subjecting them to a phased approach of *in vitro*, *in vivo*, and eventually clinical testing. Such an approach can help prioritize species with the most promising therapeutic potential.

**Bioassay-guided Fractionation:** For species demonstrating significant activity in preliminary screenings, bioassay-guided fractionation should be employed to isolate and identify active compounds. This process involves separating extracts into fractions, testing each fraction for activity, and isolating bioactive molecules for further characterization and testing.

**In Vivo Validation of Traditional Uses:** Species that have been traditionally used for neurological conditions but have not been scientifically validated require rigorous *in vivo* testing. These studies should aim to replicate traditional use scenarios to the extent possible, providing a direct link between traditional knowledge and scientific evidence.

**Mechanistic Studies and Pathways Elucidation:** For species and compounds showing promising neuroprotective effects, detailed mechanistic studies are essential. Investigating how these plants or their constituents interact with neurological pathways, influence neurogenesis, modulate neurotransmitters, or protect against neurodegeneration can provide insights into their potential therapeutic roles.

**Integration of Traditional Knowledge and Modern Pharmacology:** Bridging traditional ethnomedicinal practices with contemporary pharmacological research can offer novel insights and approaches to neuroprotection. This includes respecting and integrating the knowledge of indigenous and local communities into research processes, ensuring that such collaborations are ethically grounded and mutually beneficial.

**Adaptation of Clinical Research Models:** Given the unique nature of traditional medicine practices, adapting clinical research models to better capture the complexity

and holistic nature of these treatments is necessary. This may involve designing clinical trials that can accommodate the multifaceted interventions typical of traditional medicine, including combination therapies and complex treatment regimens.

**Sustainability and Ethical Considerations:** As this research progresses, it is crucial to maintain a focus on sustainability and ethics, ensuring that plant resources are used responsibly and that traditional knowledge is respected and protected. This includes developing guidelines for ethical research practices, benefit-sharing, and protecting intellectual property rights in a way that honours the source communities.

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