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Neuroprotective activity of Indonesian traditional herbal medicine: A systematic review

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ABSTRACT

The brain requires good care for it regulates all systems and functions of the human body's organs. Good care can also prevent brain damage caused by the aging process and neurodegenerative diseases. Consuming herbs is one of the treatments for the brain. This study aims to provide an overview of the neuroprotective use of herbs in traditional Indonesian medicine. The method employed is a review of articles based on predetermined criteria. The plants were then reselected based on the plants used for the central nervous system (CNS) in the Cabe Puyang Manuscript. Cabe Puyang is a manuscript that describes the health benefits of various medicinal herbs. According to the criteria, 31 herbs acting as neuroprotective agents in Indonesia were discovered. The herbs were reselected based on the herbs used in the Cabe Puyang Manuscript for the CNS. Twelve herbs have been included in Indonesia's traditional medicine system for use as neuroprotectors. These herbs are *Zingiber officinale*, *Centella asiatica, Allium sativum, Andrographis paniculata, Piper nigrum, Coriandrum sativum, Piper retrofractum, Moringa oleifera, Ocimum sanctum, Kaempferia galangal, Ruta graveolens*, and *Acorus calamus*. The Cabe Puyang Manuscript mentioned all of the selected herbs used as neuroprotectors in the Indonesian system of medicine. They all demonstrated a strong antioxidative and anti-inflammatory action in brain tissues. Both actions are manifestations of neurodegenerative pathologies.

INTRODUCTION

All of the systems and functions of the human body's organs are tightly regulated by the brain. Therefore, care must be conducted throughout all stages of life to afford a healthy brain from the beginning of human life (Wang *et al*., 2020a, 2020b). Good care is necessary to provide for the proper development of all parts of the brain. Proper development is necessary as a way to control brain deterioration during the aging process.

Without it, brain deterioration may cause neurodegenerative problems. Neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Huntington's disease (HD). Examples of brain degeneration include cognitive impairment and memory loss-related illnesses of vital brain functions. Many factors contribute to the progression of the diseases, while genetic mutations and worsening environments play significant roles. An unhealthy lifestyle worsens the condition (Wang *et al*., 2020a, 2020b). Keeping an aging brain sharp is necessary since, nowadays, human beings live in a situation where their lifespan is increasing. Slowing down brain aging occurs in the healthy brain. Mild cognitive impairment in the early stages of memory loss or other cognitive ability loss happens in individuals who maintain the ability to perform most activities in their daily lives.

Data from the Indonesian Ministry of Health showed an increasing trend of neurodegenerative problems among elderly people, such as dementia, in the era of an increasing number of elderly people in 2035. The World Health Organization stated that dementia will become a serious issue as the number will triple in 2050 (Immanuel and Natalia, 2021).

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This article presents an overview of the neuroprotective properties of traditional Indonesian medicinal plants. Since its invention, original medicine manuscripts have provided various information on the health benefits of herbs for brain health. People in the community learn about the neuroprotective activity of various herbs from previous generations.

Cabe Puyang is one of the famous Indonesian manuscripts authored by Mardisiswojo and Harsono (1968). The manuscript described the health benefits of various medicinal herbs, including for brain health. Herbs used against different kinds of health problems related to the central nervous system (CNS) are grouped into herbs to combat spasms, stimulants, mental illness, vertigo, migraine, and weakness of the nervous system. Since traditional medicines have been proven to have health benefits empirically, it is important to consider their application continually. Nowadays, through advanced and modern research methods, it is becoming easier to understand the pharmacological action of herbs for brain health. Modern methods help to explore their active ingredients and mechanisms of action, metabolism, distribution, and secretion. Recent studies on some medicinal herbs from Indonesia for neuroprotection will be discussed.

Pathology of neurodegenerative diseases

In neurodegenerative diseases, protein aggregation, mitochondrial failure, glutamate toxicity, calcium load, proteolytic stress, oxidative stress, neuroinflammation, and aging are all diseases on the molecular and cellular level that destroy neurons (Gan *et al*., 2018; Kiaei, 2013). Amyloidoses, tauopathies, α-synucleinopathies, and TDP-43 proteinopathies are the most frequent neurodegenerative disorders (Dugger and Dickson, 2017).

Amyloidosis is the deposition of abnormally folded proteins in tissues. The proteins are then aggregated into insoluble fibrils and could cause organ damage (Picken, 2020). In neurodegenerative diseases, amyloid-like filamentous aggregates are predominantly located in the cytoplasm of neurons and glia. The most prevalent kind of amyloidosis is known as β-amyloid (Aβ), and it is not connected to the human brain. In addition to being an indicator of AD, it is also a sign of many other neurodegenerative diseases in older people, especially in those who have apolipoprotein E4, which is the main genetic risk factor for AD (Dugger and Dickson, 2017). A β, τ, and α-syn have overlapping protein abnormalities in a number of neurodegenerative diseases, as can be seen in Figure 1.

Tauopathy is a neurodegenerative disease defined by the buildup of dysfunctional tau protein-paired helical filaments. It is a typical morphology of protein disorder in AD. The accumulation is aggregated into neurofibrillary or gliofibrillary tangles in the human brain, and tau tangles can be seen microscopically in stained brain samples. Characteristics of the neuropathological phenotype of tauopathies are based on some factors, including anatomical areas, cell types, and the isoform of tau in the pathological deposits. New things about the disease, have already been found, like the fact that it could spread from cell to cell, which helps develop treatments (Kovacs, 2018).

Synucleinopathies are neurodegenerative diseases produced by α-synuclein aggregates. It is a 140-amino acid presynaptic protein that may play a role in synaptic vesicle trafficking. α-synuclein was formerly recognized as the primary ingredient of Lewy bodies, a neuronal inclusion observed in certain clinical disorders, such as PD. Lewy bodies appear mainly within neurons. Multiple system atrophy refers to the accumulation of α-synuclein found within oligodendrocytes. Accumulation of α -synuclein is also found in neurites, namely Lewy neuritis (Dugger and Dickson, 2017).

TDP-43 proteinopathy is the aberrant formation of inclusion bodies in the cytoplasm, nucleus, and cell processes by a nuclear protein. It is the predominant constituent of neuronal inclusions in ALS and is also identified in 25% to 50% of AD cases, primarily in limbic distribution (Dugger and Dickson, 2017). These diseases attack specific neuronal clusters with vulnerable neurons. Complex anatomical features, such as long-distance brain projections and complex synaptic connections, cause the vulnerability. Intricate neuronal structures are susceptible to metabolic shortages, necessitating a substantial amount of energy to sustain their complex operations. Since mitochondria generate the majority of the chemical energy required to power the cell's metabolic activities, it must exert more effort. Consequently, the production of adenosine triphosphate increases, leading to a rise in reactive oxygen species (ROS) creation in mitochondria. The degradation of the mitochondrial quality control and respiratory chain enzymes results in metabolic stress. Then, transporter-induced glutamate receptor dysfunction and excessive excitatory postsynaptic neurons will ensue. The subsequent accumulation of calcium within the mitochondria and endoplasmic reticulum induced metabolic stress in neuronal cells. In addition to metabolic stress, energy-hungry neurons may be more susceptible than normal neurons to various toxic chemicals, protein aggregations, and glutamate excitotoxicity. Therefore, it is necessary to restore metabolic function to protect vulnerable neurons against neurodegeneration (Muddapu *et al*., 2020).

Current natural-based medicines for neuroprotection

Many studies show that using chemical substances in modern medicine gives rise to cognitive impairments and neurodegenerative diseases associated with metabolic

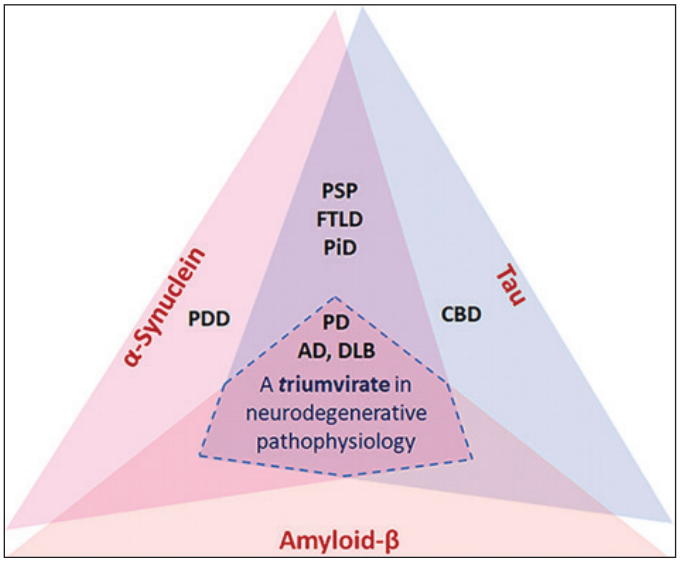

Figure 1. Aβ, tau, and α-syn have overlapping protein abnormalities in a number of neurodegenerative diseases (Sengupta and Kayed, 2022).

diseases. This is the main reason people use natural medicines, including herbal ones, to minimize possible side effects and environmental pollution. Thus, it also helps control the increasing prevalence of nervous system disorders. A recent study demonstrates the potential efficacy of herbs in the treatment of various neurodegenerative diseases, including AD and stroke. The empirical knowledge of using some herbs nowadays has already been supported by scientific explanations for neuroprotection, such as *Ginkgo biloba* and *Panax ginseng*. Such an explanation includes the pharmacological actions of the bioactive compounds for neuroprotection.

The antioxidant, anti-inflammatory, and antiapoptotic characteristics of certain herbs used in treating AD were the subject of a study. The study discovered that the bioactive compounds in herbs work on multiple targets, known as "multitarget intervention." It includes Aβ protection, induced oxidative stress, amyloid-secretion inhibition, and apoptosis. In this regard, it could be agreed that herbal medicines may have the potency to overcome the limitations of conventional medicine (More *et al*., 2013).

METHODS

Plants with neuroprotective potency were selected from Google's page using the keyword "herbs neuroprotective" and were regrouped for special plants found in Indonesia. A database of the selected plants was developed by ScienceDirect (sciencedirect.com). The selection of articles was based on some criteria:

a. Year of publication: 2011–2021
b. Article type: both research and review articles
c. Published in Q1 Scopus-indexed journals
d. Topic of selected articles should be related to the objective of the review: Neuroprotective activity of Indonesian herbal medicines
e. The selected herbs were then reselected in accordance with herbs used for CNS in the Cabe Puyang Manuscript. Table 1 describes local and scientific names, health benefits, and parts used of the herbs against CNS health problems in the Cabe Puyang Manuscript. There were 13 herbs used against spasms, 31 herbs for stimulants, 7 for mental illnesses, 27 for vertigo, and 19 herbs for the weakness of the nervous system (Mardisiswojo and Harsono, 1968).

RESULTS

Table 1 details the scientific names, health benefits, and constituents of the herbs used to treat CNS-related diseases in the Cabe Puyang Manuscript (Mardisiswojo and Harsono, 1968). There were 13 herbs used against spasms, 31 for stimulants, 7 for mental illnesses, 27 for vertigo, and 19 for weakness of the nervous system.

Table 2 lists 31 herbs used as neuroprotective agents in Indonesia. It was selected from the preliminary selection with certain criteria already determined.

Twelve herbs were reselected from the preliminary selections. Reselection was based on the herbs used for the CNS in the Cabe Puyang Manuscript (Mardisiswojo and Harsono, 1968). Table 3 describes the scientific names and local names of the reselected herbs.

Zingiber officinale (Jahe)

The plant *Z. officinale* Roscoe is the scientific name for ginger, known as "jahe" in Indonesia. Due to its pungent aroma, nutritional benefits, and pharmacological capabilities, ginger has been utilized as a food, spice, dietary supplement, and flavoring agent and in traditional medical remedies. Numerous beneficial characteristics, such as physiological and pharmacological action at the molecular level in terms of neuroprotection, were discovered (Kiyama, 2020). Ginger contains sesquiterpenes (elemene, farnesene, and zerumbone), diarylheptanoids (cineole, citral, limonene, and pinenes), phenolics (gingerols, [6]-shogaol, [6]-paradol, zingerone, and curcumin). The memory-protecting effects of gingerol, shogaol, and borneol have been tested and found to be highly effective. Other chemicals in ginger are involved in biological processes such as apoptosis, cell cycle/

Table 1. Herbs used against CNS disorders in Cabe Puyang manuscript.

CNS problem	Herbs		Part(s) used
	Indonesian name	Scientific name	
Spasm	Pulosari	*Alyxia sp.*	Barks
	Keras tulang	*Chloranthus elatior*	Roots, leaves
	Daun sudamala	*Artemisia vulgaris*	Leaves, roots
	Poko	*Mentha arvensis*	Leaves, oil
	Selasih	*Ocimum basilicum*	Leaves
	Mesoyi	*Massoia aromatica*	Barks
	Kasturi	*Hibiscus abelmoschus*	Seeds, oil
	Pala	*Myristica fragrans*	Fruits
	Kayu putih	*Melaleuca leucadendron*	Oil
	Inggu	*Ruta graveolens*	Leaves
	Ranti	*Solanum nigrum*	Fruits
	Tembelekan	*Lantana aculeata*	Roots
	Daun seribu	*Achillea millefolium*	Leave, flowers

Continued

CNS problem	Herbs		Part(s) used
	Indonesian name	Scientific name	
	Dringo	*Acorus calamus*	Rhizome
	Biduri	*Calotropis gigantea*	Leaves, flowers
	Keras tulang	*Chloranthus officinalis*	Leaves, roots
	Kesumba	*Carthamus tinctorius*	Flowers
	Rumput teki	*Cyperus rotundus*	Rhizomes
	Patikan kebo	*Euphorbia hirta*	Leaves
	Teratai gunung	*Gunnera macrophylla*	Leaves, roots
	Selasih	*Ocimum sanctum*	Leaves
	Lampes	*Ocimum sanctum*	Leaves
	Sintok	*Cinnamomum sintok*	Barks
	Saga manis	*Abrus precatorius*	Barks
	Kasturi	*Abelmoschus moschatus*	Seeds
	Kelintang	*Moringa oleifera*	Roots
	Pinang	*Areca catechu*	Fruits
	Siwalan	*Borrasus flabellifer*	Fruit juice
Stimulant	Lada	*Piper nigrum*	Fruits
	Cabe	*Piper retrofractum*	Fruits
	Daun urat	*Plantago major*	Seeds
	Incok	*Plumbago zeylanica*	Roots
	Kopi	*Coffea sp.*	Seeds, leaves
	Jeruk	*Citrus aurantifolia*	Fruit juice
	Kemuning	*Murayya paniculata*	Leaves
	Inggu	*Ruta graveolens*	Leaves
	Akar kucing	*Toddalia asiatica*	Root, fruits
	Kresek	*Dodonaea viscosa*	Leaves
	Cabe rawit	*Capsicum frutescens*	Fruits
	Terung ngor	*Solanum indicum*	Roots
	Lempoyang	*Zingiber aromaticum*	Rhizomes
	Cekur	*Kaempferia galanga*	Rhizomes
	Kina	*Cinchona sp.*	Barks
	Pulai	*Alstonia scholaris*	Barks
	Nagasari	*Mesua ferrea*	Flowers
	Lombok rawit	*Capsicum frutescens*	Fruits
	Pulai pandak	*Rauwolfia serpentina*	Stem
Mental illness	Maja	*Aegle marmelos*	Roots
	Sangketan	*Moschosma polystachyum*	Leaves, all parts
	Kaki kuda	*Hydrocotyle asiatica*	Leaves
	Lompong hutan	*Valeriana hardwickii*	Leaves
	Urang aring	*Eclipta alba*	Leaves
	Sosor bebek	*Kalanchu pinnata*	Leaves
	Rumput bolong	*Acalypha indica*	Sap/milky juice
	Bawang putih	*Allium sativum*	Tubers
Vertigo	Kayu putih	*Melaleuca leucadendron*	Oil
	Incok	*Plumbago zeylanica*	Leaves
	Legundi	*Vitis trifolia*	Leaves
	Sono kembang	*Pterocarpus indicus*	Leaves

Continued

CNS problem	Herbs		Part(s) used
	Indonesian name	Scientific name	
	Daun setan	*Leuca lavandulifolia*	Leaves
	Kacang hijau	*Phaseolus radiatus*	Seeds
	Jeruk nipis	*Citrus aurantifolia*	Leaves/fruit juice
	Asam	*Tamarindus indica*	Fruits
	Jahe	*Zingiber officinalis*	Rhizomes
	Awar awar	*Ficus septica*	Leaves/milky juice
	Janti	*Sesbania sesban*	Leaves
	Akar gamat	*Pericampylus glaucus*	Leaves
	Prasman	*Eupatorium ayapana*	Leaves
	Cemara	*Casuarina equisetifolia*	Leaves
	Inggu	*Ruta graveolens*	Leaves
	Bengle	*Zingiber cassumunar*	Rhizomes
	Sangket	*Moschosma polystachyum*	Leaves
	Kangkong	*Ipomoea reptans*	Leaves and stem
	Kelintang	*Moringa oleifera*	Roots
	Sawi	*Brassica rugosa*	Leaves
	Ketumbar	*Coriandrum sativum*	Seeds
	Trengguli	*Cassia fistula*	Flesh of fruits
	Gendarussa	*Justicia gendarussa*	Leaves
Weakness of the nervous system	Sambilata	*Andrographis paniculata*	Leaves
	Keras tulang	*Cholranthus elatior*	All parts
	Jeruk nipis	*Citrus aurantifolius*	Fruit juice
	Beluntas	*Pluchea indica*	Leaves
	Sangket	*Moschosma polystachyum*	Leaves
	Trengguli	*Cassia fistula*	Flesh of fruit
	Nenas	*Ananas comosus*	Fruit juice
	Kangkung	*Ipomoea reptans*	Leaves and roots
	Pandan wangi	*Pandanus amaryllifolius*	Leaves
	Kelintang	*Moringa oleifera*	Roots, bark
	Lampes	*Ocimum sanctum*	Leaves
	Papaya	*Carica papaya*	Roots
	Kemangi	*Ocimum basilicum*	Seeds
	Daun setan	*Leucas linifolia*	Leaves
	Kaki kuda	*Centella asiatica*	Leaves
	Cabe	*Piper retrofractum*	Fruits
	Legetan warak	*Adenostemma lavenia*	Leaves
	Gude	*Cajanus cajan*	Fruits
	Ceplukan	*Physalis angulata*	Young leaves

deoxyribonucleic acid (DNA) damage, chromatin/epigenetic regulation, cytoskeletal regulation and adhesion, immunology, and inflammation. They exert their effects through distinct signaling pathways associated with cell activities and functions, such as autophagy, cellular metabolism, and mitogen-activated protein kinase (Kiyama, 2020; Talebi *et al*., 2021).

Estrogen, specifically phytoestrogens, is one of the most important bioactive compounds in nature. Both the molecular processes and detection techniques of estrogen have been explored. Ginger active ingredients stimulate the molecular pathways of estrogen activities, such as cancer chemoprevention and treatment of menopausal syndromes, polycystic ovary syndrome, prostatic hyperplasia, endometriosis, and AD (Kiyama, 2020). Oral administration of ginger was also shown to reduce spinal neuroinflammation, lowering spared nerve injury (SNI)-induced neuropathic pain symptoms, suggesting ginger as a unique and attractive alternative for the treatment of neuropathic pain (Borgonetti *et al*., 2020).

Centella asiatica (Pegagan)

Centella asiatica (L.) Urban, famously known worldwide as gotu kola, has been used traditionally in many Asian countries, including China and India. However, in Indonesia, it is usually called by the local name "pegagan." It is a member of the Apiaceae family, and its synonyms are *Hydrocotyle asiatica* and *Hydrocotyle erecta*. Common English names are Indian Pennyworth and Asian Pennyworth (Orhan, 2012).

Empirically, the leaves are used as a salad in some parts of Indonesia, popularly named pegagan. The plant grows abundantly, and the leaves are believed by the Acehnese ethnic group in North Sumatra, Indonesia, to be a memory enhancer. Villagers of the Sundanese ethnic group in West Java Province of Indonesia have used the raw leaves as a vegetable.

Early evidence of its use for health attracts researchers to further understand its pharmacological action. External application has been proven for its skin ulcer and wound healing properties. The most famous benefit of an internal application is related to the application in the Ayurvedic tradition as a memory booster, preventing cognitive deficits and improving brain function (Gray *et al*., 2017).

Centella asiatica contains many secondary metabolites, such as essential oils and phenolic compounds like epicatechin, catechin, quercetin, kaempferol, and related glycosides. It is famous for its high content of pentacyclic triterpenoids. The saponins are asiaticosides and madecassosides, while their aglycones are asiatic acid and madecassic acid. Essential oils are also present in the aerial parts of the herb and contain a high level of sesquiterpenes and monoterpenoids (Gray *et al*., 2017).

Centella asiatica and its chemical constituents could be used to treat several neurological disorders. Research has demonstrated its efficacy against neuroinflammatory activities, oxidative stress, mitochondrial malfunction, and disruption in brain-derived neurotrophic factors (BDNF) for treating AD and PD.

Neuroinflammation occurs in AD and PD. Cytokines as proinflammatory mediators are closely related to neurodegenerative lesions manifested in AD (Alasmari *et al*., 2018). As the source of the buildup of Aβ-containing neuritic plaques and neurofibrillary tangles, the lesion altered the expression and metabolism of amyloid precursor protein (Yuan *et al*., 2020). *Centella asiatica* showed its neuroprotective effect in the context of Aβ toxicity. The result of *in vitro* test using neuroblastoma cells showed that aqueous extract could protect the cells from Aβ-induced cytotoxicity (Gray *et al*., 2017).

A study on the oxidative and antioxidant effects of *C. asiatica* showed its radical scavenging activity. This is very important since increased production of ROS can directly affect neuronal synaptic activity and neurotransmission and cause cognitive dysfunction. A study has found that the terpenoid contents of *C. asiatica* increased free radical scavengers superoxide dismutase (SOD) and glutathione peroxidase (GPX) and helped in reducing the level of ROS (Chintapanti *et al*., 2018; Gray *et al*., 2017; Tönnies and Trushina, 2017; Welbat *et al*., 2018).

The activity of triterpenoids in *C. asiatica* in reducing ROS helps prevent mitochondrial dysfunction. This is significant because ROS activates the cell death signaling pathway. Myocardial dysfunction is closely linked to AD and PD (Gray *et al*., 2017; Nataraj *et al*., 2017a; Onyango *et al*., 2017).

The asiatic acid and asiaticoside contents of *C. asiatica* showed an increasing effect on the BDNF content. BDNF helps in the maintenance of neuron survival and neurotransmitter regulation (Boondam *et al*., 2019; Chintapanti *et al*., 2018; Gopi and Arambakkam, 2017; Nataraj *et al*., 2017b). Neurodegenerative diseases cause a reduction in the concentration of this factor (Giacobbo *et al*., 2019)

Allium sativum (Bawang Putih)

Garlic is used widely in Indonesian households for daily needs. There is a growing demand for the consumption of garlic, but unfortunately, the production has shown a downward trend (Hadianto *et al*., 2019). As a member of the Alliaceae family, its

Table 2. Names of selected herbs with neuroprotective activity.

No.	Name of herbs	Data
1.	*Curcuma longa*—Kunyit	
2.	*Camellia sinensis*—The	
3.	*Zingiber officinale*—Jahe	
4.	*Centella asiatica*—Pegagan	
5.	*Allium sativum*—Bawang putih	
6.	*Nigella sativa*—Jinten hitam	
7.	*Glycyrrhiza glabra*—Akar manis	
8.	*Thymus vulgaris*—Timi	
9.	*Andrographis paniculata*—Sambiloto	
10.	*Piper nigrum*—Lada hitam	
11.	*Foeniculum vulgare*—Adas	
12.	*Acorus calamus*—Jeringau	
13.	*Coriandrum sativum*—Ketumbar	
14.	*Piper longum*—Lada panjang	Description of all plants will include:
15.	*Moringa oleifera*—Kelor	
16.	*Momordica charantia*—Pare	Scientific names, family, parts uses, traditional uses in Indonesia, chemical contents, mechanism of action as neuroprotector
17.	*Ocimum sanctum*—Kemangi	
18.	*Phyllanthus emblica*—Malaka	
19.	*Tinospora cordifolia*—Bratawali	
20.	*Syzygium aromaticum*—Cengkeh	
21.	*Morinda citrifolia*—Mengkudu	
22.	*Curcuma zedoaria*—Temu Putih	
23.	*Clitoria ternatea*—Bunga telang	
24.	*Alpinia galanga*—Laos	
25.	*Curcuma xanthorrhiza*—Temu lawak	
26.	*Kaempferia galanga*—Kencur	
27.	*Heliotropium indicum*—Sangketan	
28.	*Coffea spp.*—Kopi	
29.	*Curcuma amada*—Temu mangga	
30.	*Illicium verum*—Bunga Lawang	
31	*Ruta grafiolens*	

Table 3. Herbs with neuroprotection activity.

Herb's scientific name	Family	Part(s) used	Traditional uses	Bioactive substance(s)	Neuroprotection activity		References
					Type of CNS disorder	Mechanism of action	
Zingiber officinale	Zingiberaceae	Rhizomes	Food, spice, supplement, flavoring ingredient, medicine	Borneol, cineole, citral, limonene, pinene, elemene, farnesene, zerumbone, gingerol, shogaol, paradol, zingerone, curcumin.	AD, spinal neuroinflammation, neuropathic pain	Reduce spinal neuroinflammation, lowering SNI-induced neuropathic pain symptoms	Borgonetti *et al.* (2020); Kiyama (2020); Talebi *et al.* (2021).
Centella asiatica	Apiaceae	Leaves	Vegetable, medicine for memory enhancer, skin ulcer, wound and ulcer.	Terpenoids, catechin, epicatechin, kaempferol, quercetin, asiaticoside, madecassoside, asiatic acid and madecassic acid.	AD and PD	enhance free radical scavengers SOD and GPX, and help in reducing the level of ROS that causes neuroinflammatory activities, oxidative stress, mitochondrial dysfunction, and dysfunction in BDNF	Gray *et al.* (2017); Nataraj *et al.* (2017a, 2017b); Onyango *et al.* (2017); Tönnies and Trushina (2017); Alasmari *et al.* (2018); Chintapanti *et al.* (2018); Gray *et al.* (2018); Welbat *et al.* (2018); Boondam *et al.* (2019); Giacobbo *et al.* (2019); Yuan *et al.* (2020).
Allium sativum	Alliaceae	Tubers	Vegetable, medicine	Alliin, allicin, ajoenes, vinyldithiins,quercetin, SAC,	Neuroinflammation and nootropic	Augmenting the antioxidant defensive system, and alleviation of learning and memory deficits.	Rojas *et al.* (2011); Baluchnejadmojarad *et al.* (2017); Hadianto *et al.* (2019); Batiha *et al.* (2020); Hazzaa *et al.* (2020).
Andrographis paniculata	Acanthaceae	Leaves	Medicine	Andrographolide	AD and PD	Inhibits proinflammatory cytokine and ROS production, inhibiting microglial activation, reduces Aβ aggregation and tau hyperphosphorylation in the hippocampus.	Yang and Song (2014); Kandanur *et al.* (2019); Lu *et al.* (2019); Ketterman *et al.* (2020).
Piper nigrum	Piperaceae	Seeds	Spice, medicine	Piperine, sabinene, 3-carene, D-limonene, α-pinene, caryophyllene, β-phellandrene, α-phellandrene, α-thujene, and β-bisabolene.	Cerebral ischemic injury; PD.	Inhibits microglia activity, prevent NO, production of PGE2, iNOS, COX-2, and proinflammatory cytokines, through inhibition of the TLR4/Nf-kB pathway; reduce 6-OHDA-induced lipid peroxidation and stimulating *GSH* levels; inhibits neuronal cell apoptosis; protects dopamine neurons.	Nahak and Suhu (2011); Trivedi *et al.* (2011); Shrivastava *et al.* (2013); Hua *et al.* (2019a, 2019b); Jin *et al.* (2019); Wang *et al.* (2020a, 2020b); Amorita *et al.* (2021); Ashokkumar *et al.* (2021).

Continued

Herb's scientific name	Family	Part(s) used	Traditional uses	Bioactive substance(s)	Neuroprotection activity		References
					Type of CNS disorder	Mechanism of action	
Coriandrum sativum	Apiaceae	Seeds	Spice	Linalool, α-pinene, geraniol, camphor, γ-terpinene, and geranyl acetate	AD and PD	Reducing lipid peroxidation, improving Aβ-induced memory; decreases SOD activity, decreased production of intracellular H_2O_2, increase of GPX activity; inhibits LPS-induced production of TNF-α and IL-6 in BV-2 microglial cells.	Iwatani *et al*. (2003); Cioanca *et al*. (2013); Bhat *et al*, (2014); Prachayasittikul *et al*. (2018); Rodrigues *et al*. (2019); Caputo *et al*. (2021); Koppula *et al*. (2021).
Piper retrofractum	Piperaceae	Fruits	Spice, medicine for bronchitis, gastrointestinal ulcer, diarrhea or postpartum haemorrhage.	Piperamides, Piperolactam C, piperlongumine,	General CNS disorders	Inhibits effects of AChE and BChe.	Tappayuthpijarn *et al*. (2012); Zarai *et al*. (2013); Mgbeahuruike *et al*. (2017); Salehi *et al*. (2019); Islam *et al*. (2020); Luca *et al*. (2021).
Moringa oleifera	Moringaceae	Leaves	Vegetable, medicine	Kaempferol, quercetin, RT, isothiocyanate, tocopherols, myricetin and lectins.	AD, depression	Counteracting ROS, prevent and cure extracellular senile plaques and intracellular neurofibrillary tangles, prevent and reduce oxidative stress; decreasing tau hyperphosphorylation and decreased Aβ production.	Bajpai *et al*. (2005); Santos *et al*. (2005); Mahajan *et al*. (2007); Drazen (2012); Gupta *et al*. (2012); Inbathamizh (2012); Govardhan *et al*. (2013); Bhattacharya *et al*. (2014); Kaur *et al*. (2015); Tumer *et al*. (2015); Mahaman *et al*. (2018); Riastiwi *et al*. (2018); Yunusa and Musa (2018a, 2018b)
Ocimum sanctum	Lamiaceae	Leaves	Spice, vegetable, mosquito repellent, medicine.	Eugenol, b-caryophyllene, methyl eugenol, b-pinene ocimumosides, ursolic acid, rosmarinic acid, oleanolic acid, orientin, and vicenin.	Depression, and other types of CNS disorder	Ameliorate ChAT; inhibiting lipid peroxidation, DNA damage, ROS production, and depolarization of mitochondrial membrane; decreased MDA levels, increased GSH; decrease AChE activity in brain; increased the expression of NPY-immunoreactive cells and retained the number of neurons in each hippocampal area.	Siddique *et al*. (2014); Ittiyavirah and Hameed (2014); Jivad and Rabiei (2015); Sarangi *et al*. (2017); Venuprasad *et al*. (2017); Hening *et al*. (2018); Peshattiwar *et al*. (2020); Mataram *et al*. (2021) Rahmawati and Silaban (2021)
Kaempferia galanga	Zingiberaceae	Rhizomes	Spice, vegetables, medicine for inflammatory restlessness, stress, anxiety, and depression.	Kaempferol, diarylheptanoids	Depression and other general CNS disorders	Antioxidants, inflammation, alleviate neuroprotective symptoms.	Ali *et al*. (2018); Yao *et al*. (2018); Elshamy *et al*. (2019); Nie *et al*. (2020).

Continued

Herb's scientific name	Family	Part(s) used	Traditional uses	Bioactive substance(s)	Neuroprotection activity		References
					Type of CNS disorder	Mechanism of action	
Ruta graveolens	Rutaceae	Leaves	Medicine for inflammatory, antiallergenic, antiviral, anti-cancer, antihyperlipidemic, and anti-hyperuricemic.	RT SKM.	AD, PD, and HD, brain ischemia	Reduces levels of pro-inflammatory mediators (TNF-a, IL-6, PGE2, NO, COX-2 5-LOX, increasing levels of SOD catalase, and GPx; inhibit MAO-B; inhibit AChE and BuChE; reduce p53 expression and lipid peroxidation; increase 'endogenous antioxidant defense enzymes'; reduce serum and brain MDA levels.	Chua (2013); Gentile *et al.* (2015); Ganeshpurkar and Saluja (2017); Gullón *et al.* (2017); Enogieru *et al.* (2018); Bhattacharjee and Perumal (2019); Asgharian *et al.* (2020); Cai *et al.* (2020); Coimbra *et al.* (2020); Colucci-D'Amato and Cimaglia (2020); Dong *et al.* (2021); Bai *et al.* (2021); Joshi *et al.* (2021); Prasathkumar and Sadhasivam (2021).
Acorus calamus	Acoraceae	Rhizomes	Natural pesticide, medicine for headaches, migraines, and pain due to inflammation	Saponins, β-asarone	Amnesia, epilepsy, hallucinogenic, sedative, and neuropathic disorders	Increase antioxidant agents, decrease the expression of inflammatory cytokines such as TNF-α; inhibition of calcium channel activity; inhibition of the activity of the AChE; inhibit the formation of Aβ plague; increase BDNF in the CNS.	Muthuraman *et al.* (2011); Muthuraman and Singh (2012); De Rus *et al.* (2014); Rajput *et al.* (2014); Anand *et al.* (2017); Singh *et al.* (2017); Shelar *et al.* (2018).

scientific name is *A. sativum* and popularly known as "bawang putih," its Indonesian local name.

Garlic is aromatic, and research reported its several biological properties, including its neuroprotective potency. The presence of sulfur-containing phytoconstituents such as alliin, allicin, ajoenes, vinyldithiins, and flavonoids such as quercetin is responsible for its therapeutic properties (Batiha *et al.*, 2020). The main active compound that contributes to its neuroprotective activity is S-allylcysteine (SAC) (Rojas *et al.*, 2011). SAC is the most abundant organosulphur compound derived from garlic. SAC is water-soluble and known for having high antioxidant capacity, besides its anti-inflammatory and nootropic properties. Its antioxidant capacity effectively augment the antioxidant defensive system in streptozotocin-diabetic rats. This demonstrated the effectiveness of SAC in reducing learning and memory deficiencies (Baluchnejadmojarad *et al.*, 2017).

Garlic powder has also been studied for its efficacy against monosodium glutamate- (MSG-) induced neurotoxicity. It is indicated that the enhancement of antioxidant activity and reduction of lipid peroxidation of A. sativum can prevent MSG-induced neurotoxicity and improve short-term memory (Hazzaa *et al.*, 2020)

***Andrographis paniculata* (Sambiloto)**

Andrographis paniculata, also known as King of Bitters, grows well from mainland India and China to Southeast Asia, such as Thailand, Malaysia, and Indonesia. In Indonesia, it is known locally as "sambiloto" and has been part of an ingredient in Indonesian traditional medicine. As a member of the Acanthaceae family, the plant is widely utilized for various ailments, and this is due to its antioxidant, anti-inflammatory, and anti- or proapoptosis activities. The main active compounds that play major roles in preventing and curing diseases are flavonoids and andrographolides. Andrographolides are a labdane diterpenoid that can cross the blood-brain barrier, and this triggered various studies to reveal the action at different brain regions.

Andrographolide, a major compound, is known to have antioxidant, immunomodulatory, antihyperglycemic, antimicrobial, antiviral, anticancer, anti-inflammatory, and neuroprotective activities (Kandanur *et al.*, 2019; Ketterman *et al.*, 2020; Lu *et al.*, 2019). The emergence of activity is thought to be due to the presence of pharmacophore groups on the C-3, C-14, and C-19 chains and double bonds at C-12/13 and C-8/17, which have the potential to provide activities (Kandanur *et al.*, 2019). The presence of these pharmacophore groups ultimately makes andrographolide a compound that has a neuroprotective potential equivalent to phenolic compounds (Yang and Song, 2014).

Studies on the efficacy of andrographolide in combating AD showed some mechanisms. One of them is the reduction of Aβ aggregation and tau hyperphosphorylation in the hippocampus of aged degus (Lindsay *et al.*, 2020). Aggregation and deposition of Aβ usually accompany microglia-mediated neuroinflammation in AD pathogenesis. The aggregation itself triggers the generation of proinflammatory chemicals via microglial hyperactivation. This is the cycle of neuronal injury and degeneration; hence, neuroinflammatory response inhibition becomes a treatment method for AD.

PD is a neurodegenerative disease of the CNS, and the specific mechanism of the disease's origin or progression is not entirely understood. However, evidence indicates that neuroinflammatory response in the brain is a crucial mechanism in the etiology of PD. Since overactivation of microglia results in the generation of proinflammatory mediators, suppression of microglia has been shown to protect neurons from damage *in vitro* and *in vivo* models of PD. Previous research has demonstrated that andrographolide inhibits the generation of proinflammatory cytokines and ROS. Therefore, andrographolide may alleviate PD symptoms by reducing microglial activation (Lu *et al*., 2019).

Piper nigrum (Lada Hitam)

Black pepper (*Piper nigrum*) is a member of the Piperaceae family and is known as the King of Spices (Ashokkumar *et al*., 2021). It is native to India, and Indonesia is one of the world's largest pepper-producing countries. It also is the second-largest area of pepper cultivation (Amorita *et al*., 2021).

The Javanese ethnic of Indonesia named it "merica," while the ethnics of the Sumatra Island of Indonesia named it "lada." The plant has a round fruit and single seed with a spicy and sharp taste. In some countries, such as India and China, pepper is considered to have medicinal properties. The chemical constituents are alkaloids, phenols, tannins, coumarins, saponins, flavonoids, glycosides, and essential oils (Nahak and Suhu, 2011; Trivedi *et al*., 2011).

The major constituents of essential oil of black pepper are 3-carene, sabinene, D-limonene, caryophyllene, α-pinene, α-phellandrene, β-phellandrene, β-bisabolene, and α-thujene. Piperine, the main active ingredient of the fruit, is an alkaloid that gives a characteristic pungent sensory effect to the pepper. It has been reported of its medicinal properties, such as antidepressive, anti-inflammatory, antioxidant, and antiepileptic (Wang *et al*., 2017). It also has antiplatelet aggregation and antiatherogenic properties (Hua *et al*., 2019a, 2019b, 2019c).

Piperine also has the potential for neuroprotection. Some research to explore further its cerebral brain functioning is being conducted (Ashokkumar *et al*., 2021). An investigation into the effects of oral piperine treatment on cerebral ischemia injury in rats revealed a decrease in the area of cerebral injury, an improvement in behavioral impairment, and a decrease in the severity of cellular damage following permanent middle cerebral artery occlusion injury. This demonstrates that piperine is effective in providing neuroprotection by regulating apoptotic processes. Globally, ischemic stroke contributes to long-term impairment and morbidity, making neuroprotection crucial (Wang *et al*., 2017). Black pepper can inhibit microglia activity, prevent nitric oxide (NO), production of prostaglandin E2, inducible NO synthase, cyclooxygenase-2, and proinflammatory cytokines, through inhibition of the Toll-like receptor 4/nuclear factor-kB pathway to prevent cognitive and neurodegenerative disorders (Jin *et al*., 2019).

Piperine possesses antioxidant properties via inhibiting 6-hydroxydopamine (6-OHDA)-induced lipid peroxidation and boosting glutathione (*GSH)* levels. In addition, it suppresses neuronal cell death, exhibiting a protective effect via antiapoptotic and anti-inflammatory pathways in 6-OHDA- induced PD (Shrivastava *et al*., 2013). Piperine also has a cytoprotective effect, nuclear factor-erythroid factor 2-related factor 2 activation, and upregulation of related phase II antioxidant enzymes, such as heme oxygenase-1 and NAD(P)H quinone oxidoreductase 1 and protects dopamine neurons, thereby attenuating PD (Wang *et al*., 2020a, 2020b).

Coriandrum sativum (Ketumbar)

Coriandrum sativum (Apiaceae) is known as coriander or Chinese parsley. In Indonesia, its local name is "ketumbar," and the fruit is mixed with other ingredients in preparing local dishes. Local people are seldom aware of the medicinal value of the fruit and other parts of the plant. The plant is adapted from the Mediterranean area and is acclimatized in many countries with a temperate climate.

The main constituents of essential oil of the plant are α-pinene, linalool, geraniol, γ-terpinene, camphor, and geranyl acetate (Cioanca *et al*., 2013). The seeds contain lipids, vitamins, and minerals, such as potassium, phosphorus, calcium, magnesium, zinc, and sodium (Bhat *et al*., 2014; Iwatani *et al*., 2003). The bioactive chemicals of coriander showed a variety of biological activities, including antioxidant, neuroprotective, and anti-inflammatory effects.

Linalool is the primary component of seeds and has been shown to influence various important pathogenic pathways. It is found that the neuroprotective property of coriander mainly relates to the potent antioxidant activity of coriander. It includes neuroprotective, antioxidant, analgesic, anti-inflammatory, anticancer, anxiolytic, anticonvulsant, hypnotic, and antidiabetic (Prachayasittikul *et al*., 2018).

Linalool can be useful as a neuroprotective by reducing lipid peroxidation, oxidative damage, anti-inflammatory, antidepressant, and anxiolytic in the presence of interactions of GABA receptors (Prachayasittikul *et al*., 2018). Coriander can improve locomotor, balance, and coordination and reduce mercury-induced oxidative stress (Rodrigues *et al*., 2019).

Coriander is useful in improving Aβ-induced memory by attenuating oxidative stress. Linalool decreased SOD activity and decreased the production of intracellular H_2O_2 with a simultaneous increase of GPX activity. This could decrease the stimulation of lipid peroxidation and protein oxidation, implying that coriander possesses strong antioxidant properties (Cioanca *et al*., 2013). Coriander treatment inhibited lipopolysaccharides (LPS)-induced production of TNF-α and IL-6 in BV-2 microglial cells in a concentration-dependent manner, indicating that *C. sativum* fruit extract might be beneficial in delaying the progression of neuroinflammation and oxidative stress-mediated neurodegeneration seen in PD (Koppula *et al*., 2021).

Linalool was able to counteract the reduction of mitochondrial dehydrogenase activity and the increase in intracellular ROS production and caspase-3 activation induced by Aβ1-42 oligomers. Linalool can interact with N-methyl-d-aspartate receptors and inhibit acetylcholine release. It modulates some voltage-gated calcium channel subtypes and their electrophysiological properties. Such modulation and modification exert anxiolytic and neuroprotective effects on linalool as a natural product of potential interest in treating AD (Caputo *et al*., 2021).

***Piper retrofractum* (Cabe Jawa)**

Piper retrofractum is one of the members of the genus *Piper* of the Piperaceae family. The Indonesians named it "cabe Jawa" or "cabe Jamu." Empirically, it is used mainly as one of the important ingredients in traditional Indonesian drinks and is believed to give a warming sensation. Its elongated-shaped fruits are believed to have some medicinal benefits and are traditionally used for bronchitis, gastrointestinal ulcers, diarrhea, or postpartum hemorrhage (Mgbeahuruike *et al*., 2017; Salehi *et al*., 2019). Studies revealed that spices from the family Piperaceae are rich in bioactive compounds, such as piperamides, lignans, flavonoids, and essential oils (Yadav *et al*., 2020). Therefore, they can show multiple pharmacological actions with antioxidant, anti-inflammatory, and neuroprotective effects (Salehi *et al*., 2019; Yadav *et al*., 2020).

It is known from a previous study that the total flavonoid content of *P. retrofractum* is high compared to green and black peppers (Zarai *et al*., 2013). Piperolactam C and piperlongumine were solely found in *P. retrofractum*, and the study also revealed the total antioxidant potency of the fruit (Luca *et al*., 2021). The neuroprotective of *P. retrofractum* is closely related to its moderate anti-butyrylcholinesterase (BChe) effect of *Piper* spices, with values ranging from 0.60 mg galanthamine equivalents (GALAE)/g in *P. retrofractum* to 3.11 mg GALAE/g in black pepper (Luca *et al*., 2021).

The anticholinesterase (AChE) inhibitor of *Piper* sp. has rarely been reported. Another study showed that the methanolic extract from fruits of *P. nigrum* and *P. retrofractum* showed IC50 values of 11.133 and 14.08 µg/ml against AChE inhibitor, respectively (Tappayuthpijarn *et al*., 2012).

***Moringa oleifera* (Kelor)**

Moringa (M. oleifera) is a member of the Moringaceae family, a native plant from Africa and Asia. It is cultivated for its nutritious pods, edible leaves, and flowers and has also been known for its health benefits. In Indonesia, its local name is kelor, and it has been used as a vegetable. But, up untill now, people have never realized its health benefits as a functional food (Riastiwi *et al*., 2018).

Research that has been conducted revealed its richness in bioactive compounds, which include flavonoids, vitamins, carotenoids, polyphenols, glucosinolates, isothiocyanates, tannins, and saponins. Such richness may explain its various health benefits, which have been proven by its pharmacological actions (Vergara-Jimenez *et al*., 2017).

The antioxidant potential of different parts of *M. oleifera* is chiefly ascribed to the presence of ascorbic acid, β-carotene (Mahajan *et al*., 2007), kaempferol, rutin (RT), quercetin, and isothiocyanate from leaves (Bajpai *et al*., 2005; Gupta *et al*., 2012; Tumer *et al*., 2015); tocopherols, lectins, and myricetin from seeds (Govardhan *et al*., 2013; Mahajan *et al*., 2007; Santos *et al*., 2005); phytosterols and from flowers (Inbathamizh, 2012). Its antioxidant property could explain its pharmacological action against neurological disorders, and this is because of its ability to counteract ROS. However, a previous study showed the potency of *M. oleifera* in preventing and curing extracellular senile plaques and intracellular neurofibrillary tangles found in neurological disorders such as AD. According to the study, hyperhomocysteinemia induced AD-like pathology in rats. Homocysteine is one of the major risk factors for AD (Drazen, 2012). The result showed the ability of the extract to prevent and reduce oxidative stress, which helps prevent cognitive impairment, and decrease neurodegeneration, such as decreased tau hyperphosphorylation and Aβ production (Mahaman *et al*., 2018).

Kaur *et al*. (2015) conducted current research on the antidepressant effects of *M. oleifera* on laboratory rats. The antidepressant properties of the alcoholic extract of *M. oleifera* were coupled with fluoxetine (an antidepressant), and the result was a reduction in the rats' depressive condition. It was also recognized that the extract behaved similarly to the family of drugs known as selective serotonin reuptake inhibitors. Similar evidence of the antidepressant action of *M. oleifera* extract has been documented elsewhere (Bhattacharya *et al*., 2014; Yunusa and Musa, 2018a, 2018b).

***Ocimum sanctum* (Kemangi)**

Ocimum sanctum L. belongs to the Lamiaceae family. The plant was originally introduced in India and has now spread worldwide, including Indonesia. In Indonesia, O. sanctum is known by the name "kemangi."

Some pharmacological actions of the plants are antimicrobial, antidiabetic, antistress, hepatoprotective, anticarcinogenic, anti-inflammatory, immunomodulatory, radioprotective, analgesic, cardioprotective, antioxidant, and mosquito repellent (Rahmawati and Silaban, 2021; Siddique *et al*., 2014). Its neuroprotective effect was known through the activity of *O. sanctum* hydroalcoholic extract against H_2O_2 in inducing neuronal cell damage through its antioxidative defense mechanism (Venuprasad *et al*., 2017).

A previous study has been conducted to evaluate the protective effect of *O. sanctum* extract (OSE) against trimethyltin (TMT) challenge by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide, reduction assay in cultured human embryonic kidney-293 (HEK-293) cell, and excessive ROS formation induced by TMT caused cell death (Gunasekar *et al*., 2001). It is already described that the choline acetyltransferase (ChAT) enzyme also plays a crucial role in neuroprotection in the cells.

Pretreatment with OSE is capable of ameliorating ChAT. By preventing lipid peroxidation, DNA damage, ROS generation, and mitochondrial membrane depolarization, OSE can preserve cell viability (Venuprasad *et al*., 2017). Several studies have demonstrated the neuroprotective and antistress properties of polyphenols and flavonoids, which are the principal bioactive components of herbal extracts. OSE has a neuroprotective impact by improving cell viability and sustaining ChAT expression in HEK-293 cells as an *in vitro* model of neurodegenerative disorders, as determined by Hening *et al*. (2018).

The major bioactive components of O. sanctum are ursolic acid, flavonoids, rosmarinic acid, and tannins. Essential oil contents are eugenol, methyl eugenol, β-pinene, β-caryophyllene, and ocimumosides. Flavonoids include ursolic acid, oleanolic acid, orientin, and vicenin (Sarangi *et al*., 2017; Venuprasad *et al*., 2017). Flavonoid, phenolic, and fatty acid metabolites in O. sanctum exhibit antioxidant effects (Venuprasad *et al*., 2017).

Ursolic acid in O. sanctum has shown antioxidant effect through significantly decreased methane dicarboxylic aldehyde (MDA) levels, increased *GSH* (Jivad and Rabiei, 2015; Sarangi *et al*., 2017), protection of TH positive neurons from degeneration, and significantly obviated the complex I inhibition and promoted mitochondrial biogenesis (Ittiyavirah and Hameed, 2014; Peshattiwar *et al*., 2020). Other activities of O. sanctum were decreased AChE activity in rat brains (Peng *et al*., 2021), increased expression of neuropeptide Y (NPY) immunoreactive cells, and retained the number of neurons in each hippocampal area (Mataram *et al*., 2021).

***Kaempferia galanga* (Kencur)**

Kaempferia galanga is a member of the Zingiberaceae family and is named "kencur" among Indonesians. It grows easily and has been used through generations as a spice in daily dishes and for health purposes. The research found its medicinal benefits, including inflammatory restlessness, stress, anxiety, and depression (Elshamy *et al*., 2019; Yao *et al*., 2018).

One of the active chemicals of *K. galanga* is kaempferol, a type of flavonoid with anti-inflammatory, antioxidant, and neuroprotective properties (Nie *et al*., 2020). A methanol extract of *K. galanga* rhizomes showed antioxidant activity in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and NO radical scavenging assays in a concentration-dependent manner. The antioxidant activity was demonstrated through its essential oil extracts, which have considerable DPPH radical scavenging activity (Ali *et al*., 2018). Compared to indomethacin, which has anti-inflammatory properties, the chloroform, cyclohexane, and ethyl acetate extracts with diarylheptanoids obtained from *K. galanga* demonstrated a significant reduction of LPS-induced NO in macrophage RAW 264.7 cells. *Kaempferia galanga* extracts and purified components have also alleviated neuroprotective symptoms (Elshamy *et al*., 2019; Yao *et al*., 2018).

***Ruta graveolens* (Inggu)**

Inggu is the Indonesian name for the Rutaceae species *R. graveolens*, and the name in English is Rue. It has been used as a part of traditional medicines in Indonesia, especially by people of the Central Javanese Javanese ethnic group.

Skimmianine (SKM, 83) is a quinoline alkaloid isolated from *R. graveolens* L. Compound 83 (5 mg/kg, i.p.) exhibited potential edema inhibition in a carrageenan-induced acute illness model. Its efficacy was superior to that of the positive control diclofenac as it significantly decreased levels of proinflammatory mediators (TNF-a, IL-6, PGE2, and NO), as well as COX-2 and 5-LOX activity; antioxidant effect demonstrated by elevated levels of SOD, catalase, and GPx; decreased levels of thiobarbituric acid reactive substances and nitrites (Bai *et al*., 2021; Prasathkumar and Sadhasivam, 2021).

One of the bioactive flavonoid compounds, RT, has been identified and isolated from the plant extract (Gullón *et al*., 2017; Prasathkumar and Sadhasivam, 2021). RT-rich plants have been used in traditional medicine for centuries in the form of a drink or food. Because of its versatile nature, RT is now a well-known constituent of more than 130 registered medicinal preparations (Chua, 2013). RT, also known as rutoside, QE-3-rutinoside, and vitamin P, is a dietary polyphenolic bioflavonoid extracted from fruits, and many Chinese medical herbs, such as *Fagopyrum tataricum* (tartary buckwheat), Flos Sophorae (Huai Mi), and *R. graveolens* (Yun Xiang) various pharmacological activities, including antioxidant, antiallergenic, anti-inflammatory, anticarcinogenic, antiviral, and superoxide radical potential (Enogieru *et al*., 2018), antiapoptotic, cardioprotective, vasoprotective, antihyperlipidemic, nephroprotective, antihyperuricemic, neuroprotective, hepatoprotective, and anticancer properties have been reported for RT (Cai *et al*., 2020; Dong *et al*., 2021; Joshi *et al*., 2021).

The neuronal activity of *R. graveolens* and its key RT metabolites are not restricted to a single function but encompass a wide range of actions. Moreover, some are especially significant because they can interfere with pathogenic pathways implicated in neurodegenerative mechanisms' start and/or progression, such as those in PD, AD, and HD. *Ruta graveolens* inhibits monoamine oxidase B (MAO-B) in PD, according to research examining the plant's impact on neurodegenerative disorders (Bhattacharjee and Perumal, 2019; Coimbra *et al*., 2020).

Previous studies have reported that the successful application of *R. graveolens* in an *in vivo* murine DA model as an acetylcholinesterase (AChE) inhibitor (Colucci-D'Amato and Cimaglia, 2020) and BuChE inhibitor is the hexane extract of *R. graveolens* at a concentration of 400 g/ml. This extract had a dose-dependent inhibitory activity, and inhibition was higher than 50% at a concentration of 100 g/ml, the lowest concentration used (Bhattacharjee and Perumal, 2019; Coimbra *et al*., 2020). RT has demonstrated neuroprotective properties against brain ischemia. RT administration reduces "ischemic neuronal apoptosis" as a result of decreased p53 expression and lipid peroxidation and increased "endogenous antioxidant defense enzymes." RT inhibits proinflammatory cytokine activity by decreasing microglial TNF-a and IL-1b production. As indicated by the suppression of oligomeric b-amyloid cytotoxicity, this action appears to be effective in treating AD (Ganeshpurkar and Saluja, 2017). Regular intake of natural food sources, such as groats or buckwheat noodles, has been reported to be potentially effective in protecting against neuronal loss in AD (Enogieru *et al*., 2018).

Among different medicinal plants, the highest clinical evidence was observed for *R. graveolens*, encouraging its potential efficacy in MS symptoms (Coimbra *et al*., 2020). Extracts of *R. graveolens* and RT, due to their strong antioxidant activity, increased serum and brain antioxidant capacities and reduced serum and brain MDA levels (Asgharian *et al*., 2020).

Research showed the activity of the aqueous extract of *R. graveolens* in inducing death in different glioblastoma cell lines (U87MG, C6, and U138). Glioblastoma multiforme is a brain tumor with a poor prognosis (Gentile *et al*., 2015).

***Acorus calamus* (Dringo)**

Acorus calamus of the Araceae family, known in Indonesia as jeringau or dringu, is a plant widely used for various purposes, such as beverages and as nutritious ingredients. Traditionally, it is used to treat headaches, migraines, and pain due to inflammation in Indian and Southeast Asian medical systems, including in Indonesia (Anand *et al*., 2017; Muthuraman *et al*., 2011; Muthuraman and Singh, 2012). The activities were due to the contents found in the plant, including flavonoids, tannins,

saponins, polyphenols, and essential oils. Research supports its utilization due to its potency to reduce blood lipid levels and in neuropharmacology for amnesia, epilepsy, hallucinogenic, sedative, and neuropathic disorders (De Rus *et al*., 2014; Muthuraman *et al*., 2011).

The mechanism of action on the neuropharmacological activity is due to antioxidant, anti-inflammatory, and calcium ion inhibition activities of the chemical content of the plant. The contents included saponin and asarone compound groups (De Rus *et al*., 2014; Muthuraman and Singh, 2012). Saponins and β-asarone may act as antioxidant agents, decreasing the expression of inflammatory cytokines such as TNF-α and inhibiting calcium channel activity (Muthuraman *et al*., 2011; Rajput *et al*., 2014; Singh *et al*., 2017). Another mechanism is the inhibition of the activity of the acetylcholinesterase (AChE) enzyme, which indirectly inhibits the formation of Aβ plague (Anand *et al*., 2017; Rajput *et al*., 2014). *Acorus calamus* is able to increase BDNF in the CNS responsible for improving memory (Shelar *et al*., 2018). However, *A. calamus* needs special attention to the β-asarone known to show a good natural pesticide. Therefore, *A. calamus* is categorized as a toxic plant (Rajput *et al*., 2014; Singh *et al*., 2017).

DISCUSSION

Indonesia is blessed with huge biodiversity, which is the main reason behind the application of herbs for health purposes in the daily lives of people in the community. Almost all the herbs for neuroprotection that have been selected and included in the Cabe Puyang Manuscript are popular and have been used as spices in traditional dishes, vegetables, and beverages and in traditional medicine. Historically, most of the herbs originated from various parts of the world, including South East Asian regions, but nowadays, they are grown abundantly in many parts of Indonesia. This indicated the existence of cultural exchanges among traders from many parts of Asian countries, including China, Thailand, Myanmar, and Malaysia. The exchange of culture covers a vast area, including health issues. Historically, exchange on the application of traditional oriental medicine in China and India, for example, existed and could be traced back to some original manuscripts of Indonesia. It included various forms of herbal medicine.

Rhizomes of the Zingiberaceae family, *Zingiber officinalis* and *K. galanga*, grow in many parts of the country, while certain areas produce better quality. Research has shown that they act as antioxidants and anti-inflammatory agents, among other things. Ginger constituents exert neurological effects through specific signaling pathways associated with cell functions. The essential oil content of *K. galanga* showed its neuroprotection activity through antioxidant action. Both are popular spices in local dishes and traditional drinks. Wedang jahe, the local name for ginger tea, is believed by some to help with energy enhancement, while its action as a neuroprotector is not known. *Kaempferia galanga* is popular and often used to help cure coughs that cause hoarse voices. This is the reason for their regular usage among people in the community. From the empirical use supported by scientific data, regular usage is the most important prerequisite to enjoying the health benefits of herbs.

Centella asiatica is one of the adaptogenic agents, and research proved its pharmacological activity as a memory enhancer. Leaves are eaten as a daily salad in the western part of Java Island, Indonesia. People from the northern part of Sumatera Island use it as a vegetable and believe its action to be a memory enhancer.

Andrographis paniculata is an adaptogenic agent. It tastes bitter and has been used as an ingredient in a traditional drink, famously named paitan drink. Paitan means bitter in the Javanese language. People believe that drinking can help control blood sugar and cholesterol. Because research has shown that it promotes brain health, drinking it regularly should be encouraged. Andrographolide, as the major compound, showed antioxidant, anti-inflammatory, and neuroprotective activities.

Piper retrofractum grows well in some parts of the country, such as Madura Island in East Java Province, and is a very popular spice. It is often used as an ingredient in some traditional drinks, such as cabe lempuyang drink, which is effective against many health problems, especially during recovery from illnesses. Regular use of the drink may help in improving brain performance and controlling the degeneration of the brain caused by its richness in bioactive compounds.

Allium sativum, P. nigrum, and coriander are part of daily Indonesian dishes. Coriander has a strong oxidative property. The piperine content of *P. nigrum* and the SAC content of *A. sativum* are strong neuroprotective agents. Therefore, their usage supports their benefits in controlling brain health.

Moringa oleifera and *O. sanctum* are well-known vegetables used by people, especially in rural areas. They often eat the leaves of *O. sanctum* without understanding its health benefits. People who live in big cities just take a small amount of *O. sanctum* as a salad. The study found flavonoids and polyphenols as their main active compounds and proved the neuroprotective and antistress activities of the leaves. Nowadays, the leaves of *M. oleifera* are especially popular among people who live in urban areas. They know its high nutrient content, including vitamin C. The research found its antioxidant property that could explain its pharmacological action against neurological problems. As they grow well in the surrounding areas, people should be encouraged to consume both leaves as vegetables to maintain brain health.

Acorus calamus is a special herb among Javanese people, especially in Central Java. Traditionally, they believe the magical power of the rhizome can throw away evil spirits. But, research indicates its antianxiety and antistress properties. Saponin and β-asarone groups showed the antioxidant and anti-inflammatory properties of the rhizome, which explain its effectiveness in preventing memory loss.

Ruta graveolens is not popular. Its local name is "inggu." Research is being conducted to find the pharmacological activity, such as against hepatitis viruses. However, recent research indicates the action of extract and RT, its active compound, in enhancing memory function and learning capability in animal brain cells.

CONCLUSION

Some herbs have been included in the traditional medicine system of Indonesia to be used as neuroprotectors. The Cabe Puyang Manuscript of Indonesian Traditional Medicine categorized the herbs into those used for different health problems related to the CNS. They are grouped into herbs to combat spasms,

stimulants, mental illness (insane), vertigo, migraines, and weakness of the nervous system. All of the selected herbs used as neuroprotectors in the Indonesian system of medicine were mentioned in the Cabe Puyang Manuscript. In this review, all of them showed a strong indication of their action as antioxidative and anti-inflammatory in brain tissues. Both actions are examples of the pathologies of neurodegeneration. The actions help in understanding their health benefits for the brain's health through the synergistic action of the chemical contents of the herbs. From such findings, it is important to encourage people to use them naturally throughout their lives. More research should be encouraged to understand the other actions of the herbs related to neuroprotective actions, such as against protein aggregations in the brain.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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