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Naturally Occurring Chemicals against Alzheimer's Disease

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Chapter 3.2.19

Convolvulus prostratus

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Introduction

Globally, neurologic and mental disorders are severe health challenges. They are particularly common in developing countries, in which the cultural aspects and poor or limited healthcare facilities make it more important to use traditional medicines. Neurological disorders are caused by a dysfunction in part of the nervous system or brain, resulting in physical and/or psychological symptoms. They are generally classified according to the location, cause, and type of dysfunction, and usually described as central and/or peripheral nervous system disorders. They are congenital, acquired, and idiopathic (unknown cause). Globally, neurological disorders are the main cause of mortality and constitute about 12% of total deaths. Some examples of neurological disorders are Alzheimer's and other dementias, multiple sclerosis, Parkinson's disease, cerebrovascular disease, migraine, neuroinfections, neurological injuries, nutritional deficiencies, neuropathies, tetanus, poliomyelitis, meningitis, Japanese encephalitis, epilepsy, etc. In lower-/middle-income countries, neurological disorders constitute about 16.8% of total deaths, while they account for 13.2% of total deaths in economically strong countries. According to an estimation from 2005, among the neurologic disorders, Alzheimer's and other dementias caused about 2.84%, 0.46%, 0.41%, and 0.34% of the total deaths in high, upper-middle, low, and lower-middle income countries, respectively, in 2005 (WHO, 2006). Alzheimer's disease (AD) was first identified by a German pathologist and psychiatrist Alois Alzheimer in 1906 in a 50-year-old woman (Berchtold and Cotman, 1998). AD causes brain cells to degenerate; it starts slowly but the condition worsens with time. This disease is the cause of 60%–70% cases of dementia in which a patient is unable to function

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independently due to a continuous decline in thinking and social skills (WHO, 2017; Burns and Iliffe, 2009). In 2015, about 30 million people were reported as having Alzheimer's disease worldwide (WHO, 2017; Querfurth and LaFerla, 2010). In 2005, a panel of Alzheimer's Disease International (ADI) estimated 24.3 million dementia patients globally, with 4.6 million new cases annually and that this number would double every 20 years to 81 million by 2040. In developed countries, it is estimated that the number of AD patients will increase by up to 100% by the year 2040, however, in China, India, and other South-East Asian countries, this increase may be as much as 300% (WHO, 2006). AD is counted among the most financially costly diseases, mainly in developed countries (Bonin-Guillaume et al., 2005; Meek et al., 1998). Although currently available drugs for AD can temporarily improve symptoms, there is no permanent treatment available (WHO, 2017). Besides the genetic differences in 1%−5% patients, the actual cause of AD remains unknown. Hypothetically, there may be many causes of AD, such as a reduction in the synthesis of the neurotransmitter acetylcholine (Mathew and Subramanian, 2014), extracellular amyloid β (Aβ) deposition (Hardy and Allsop, 1991), the formation of intraneuronal neurofibrillary tangles of hyperphosphorylated τ protein (Kizhakke et al., 2019), poor functioning of the blood−brain barrier (Deane and Zlokovic, 2007), smoking (Cataldo et al., 2010), air pollution, oxidative stress (Moulton and Yang, 2012; Xu et al., 2014), dysfunction of oligodendrocytes (Bartzokis, 2011), gum disease (Miklossy, 2011), and fungal infection (Pisa et al., 2015).

The genus *Convolvulus* is a major group of the Convolvulaceae family of angiosperms or flowering plants; it has up to 72 species that are distributed worldwide. *Convolvulus prostratus* Forssk. is one of the highly valuable medicinal plant used in the treatment of human ailments. It is commonly known as prostrate bindweed and aloe weed. *Convolvulus pluricaulis* Choisy and *Convolvulus pluricaulis* var. *macra* Clarke are synonyms of *Convolvulus prostratus* Forssk (The Plant List, 2013). It is a prostrate, spreading, perennial, wild herb. The stems are 10−40 cm long, prostrate or ascending, and densely velvety with appressed to spreading hairs. The leaves are 0.8−3 cm long and 1.5−6 mm broad, nearly stalkless, linear to oblong, lance-shaped or inverted-lance shaped, and wedge-shaped at the base. Flowers are develop in 1−3 flowered cymes on stalks of up to 3 cm long. Bracts are 3−7 mm long and linear to lance-shaped. The flowers are pale pink or white, the style is 2−4 mm long, while stigma-lobes are 3−5 mm long. The capsule is 3−4 mm in diameter and round in shape. Seeds are 2−2.5 mm long, numbering 2−4, and are dark brown (Flowers of India, 2019). The flowering season is September to October. It is distributed in Egypt, Qatar, Oman, Saudi Arabia, the Sinai Peninsula, Yemen, United Arab Emirates, Pakistan, Nepal, India, south Algeria, Libya, Somalia, Morocco, Mali, Sudan, and the Cape Verde Islands (Catalogue of Life, 2019). All parts of the plant are known to have therapeutic benefits and have long been used in indigenous medicine, mainly in the

treatment of epilepsy, hepatic disorder, CNS-related problems, cardiac diseases, respiratory disorder (chronic bronchitis and asthma), fever, skin treatment, hair loss, infectious diseases, and also as a nervine tonic and brain tonic to improve memory (Agarwa et al., 2014).

In India, it is found throughout the country and is known as Shankhpushpi, which is one of the most popular herbs in Ayurveda. According to Ayurveda, it is a laxative, brain tonic, aphrodisiac, and cures psychological diseases. It is astringent in taste, hot in potency, acts as a tissue vitalizer, boosts memory power, promotes luster and vigor, and is an appetizer. It alleviates disease of three Dosas, epilepsy, evil spirits, poverty, skin disease, worm infestation, and poisons (Sitsram, 2015). It is cold in potency and Rasa is bitter. It improves the intellect and quality of the voice. It controls the affections of evil spirits/planets and bestows power to subdue others (Sankhyadhar, 2012). Several bioactive compounds (Fig. 3.2.19.1) have been reported in *Convolvulus prostratus* such as shankhpushphin, convolvine, convolamine, convolidine, convoline, phylabine, confoline, sterol I–II, β-sitosterol, stigmasterol, scopoletin, ayapanin (herniarin), scopolin, caffeic acid, ferulic acid, lupeol, 20-oxodotriacontanol, tetra-triacontanoic acid, 29-oxodotriacontano, volatile oil, etc. (Basu and Dandiya, 1948; Bihaqi et al., 2009; Malik et al., 2016; Irshad and Khatoon, 2018). Some other studies indicate the existence of several other compounds, namely 1,2-benzenedicarboxylic acid, 10-bromodecanoic acid, 1-octadecanesulphonyl chloride, 2-butanone, 2-pentanol, ascorbic acid, cinnamic acid, cyclononasiloxane, cyclononasiloxane, octadecamethyl, decanoic acid, eicosane, heneicosane, nonacosane, octatriacontyl, pentafluropropionate, pentanoic acid, phthalic acid, pyrimidine, silane, squalene, sulfurous acid pentadecyl 2-propyl ester, tridecane, and vitamin E in *C. prostrates* (Rachitha et al., 2018).

Several other species are also known as Shankhpusphi in India, and are used in the place of *C. prostrates* and are commercially available, they are *Clitoria ternatea* L., *Evolvulus alsinoides* (L.) L., *Tephrosia purpurea* (L.) Pers., and *Canscora alata* (Roth) Wall. (syn. *Canscora decussata* (Roxb.) Schult. & Schult.f.), etc. (Sethiya et al., 2009; Irshad and Khatoon, 2018). It is an important ingredient of several herbal formulations such as Remem (Zydus Industries, India), Abana (The Himalaya Drug and Co, India), Tirukati,

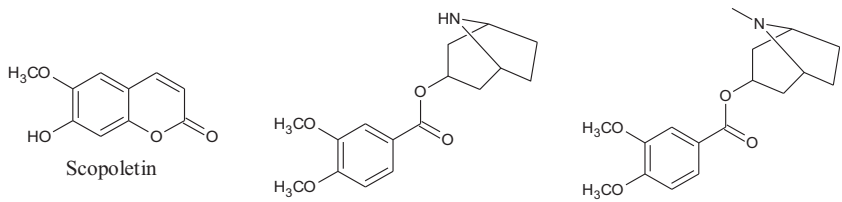

FIGURE 3.2.19.1 Structure of selected bioactive compounds of *C. prostrates*.

Ayumemo (Welexlabs, India) (Agarwa et al., 2014), Brahmi Ghrta, Agastya-haritaki Rasayana, Brahma, Rasayana, Manasmitra Vataka, Gorocanadi Vataka, Brahmi Vati (API, 1999), Dabur Shankhpushpi, Unjha Shankhpushpi, Baidyanath Shankhpushpi, etc.

Pharmacological activities of *C. prostratus*

Anti-Alzheimer's activity

Effect on amyloid β (Aβ) inhibition

The in vitro inhibitory activity of alcoholic extract of leaves on Aβ (amyloid peptide) production and amyloid precursor protein modulation was screened in mouse neuroblastoma cells expressing Swedish (N2a-Swe) APP. MTT assay was also done to determine the toxic concentration of the extract. The alcoholic extract showed greater inhibitory action on Aβ generation; therefore, it was chosen for further examination of APP modulation. The extract was found to be inactive against the multiplication rate as it did not affect cell viability at concentrations of 4, 12, and 36 μg/mL. The extract showed no effect except reducing Aβ production without amyloid precursor protein modulation (Liu et al., 2012). A methanol extract of the whole plant was tested for β-amyloid (2.5 μM)-induced neuroprotection on a neuroblastoma Neuro-2a cell line. The extract (10−200 μM) increased cell viability and the highest concentration (200 μM) showed better effect against neurotoxicity induced by β-amyloid in the brain cell line. The extract also possessed antioxidant activity, acetylcholinesterase, and lipoxygenase enzyme inhibition (Sethiya et al. (2019)).

Effect on acetylcholinesterase and lipoxygenase inhibition

The methanol extracts of the whole plant (0.1 mg/mL) were tested for AChE inhibitory activity using Ellman's microplate colorimetric method. The extract showed 40.6% ± 5.4% inhibition of acetylcholinesterase with an IC_{50} value of 234 μg/mL. The IC_{50} for physostigmine was 0.075 μg/mL (Mathew and Subramanian, 2014). The methanol extracts of the whole plant (50, 100, 150, 200, and 250 μg/mL) were tested for their acetylcholinesterase inhibition against β-amyloid ($A\beta_{1-40}$ 2.5 μM) induced neurotoxicity on a neuroblastoma cell line (Neuro-2a). The IC_{50} values of extract for acetylcholinesterase inhibition were 107.99 and 4.68 μg/mL for galantamine, used as a standard in microplate assay (Sethiya et al., 2019). The study also found that the extract showed lipooxygenase (LOX) inhibitory activity against β-amyloid-induced neurotoxicity on Neuro-2a cells with an IC_{50} value of 81.76 μg/mL. The IC_{50} value for rutin (positive control) was recorded as 4.21 ± 0.17 μg/mL.

Effect on neuroprotection

The methanol, ethanol, and water extracts of the whole plant (1.5−50 μg/mL) and quercetin (standard drug) displayed cytoprotective activity when tested against cytotoxicity induced by hydrogen peroxide (H_2O_2) in human IMR32

neuroblastoma cell lines. Among the tested extracts, methanol extract significantly decreased H_2O_2-induced cell death. A noteworthy reduction in neurofilament (NF-200), heat shock protein (HSP70), and mortalin expression have been recorded in the cultures treated with a combination of methanolic extract and H_2O_2. The levels of first-line defense antioxidants viz. SOD, CAT, GPX, and GSH were increased, whereas lipid peroxidation was decreased with both quercetin and the methanol extract. The study suggested the protective effect of *Convolvulus prostratus* was caused by induction of antioxidant machinery of the cells (Dhuna et al., 2012). The ethanolic leaf extract was also studied for the same effect in SHSY5Y cells. The pretreatment of ethanol extract (50 μg/mL) showed 50% cell survival against 100 μM H_2O_2 challenge for 24 h and it also diminished the lactate dehydrogenase leakage. The pretreatment with ethanol extract improved and regulated the antioxidant and apoptosis markers (SOD, CAT, caspase-3, and p53 inhibited the generation of reactive oxygen species and mitochondrial membrane depolarization) (Rachitha et al., 2018).

The aqueous root extract was evaluated for neuroprotective effects against neurotoxicity induced by aluminum chloride in rat cerebral cortex. The extract potential to inhibit the toxicity was compared with standard drug rivastigmine tartrate (1 mg/kg). The elevated enzymatic activity of AChE (~60%) was reduced when the aqueous extract was administered daily at a dose of 150 mg/kg with aluminum chloride (50 mg/kg) for 3 months and this dose also inhibited the decline in Na^+/K^+ ATPase activity which resulted from the aluminum intake. The extract of root preserved the levels of mRNA in muscarinic receptor 1, choline acetyltransferase (ChAT), and nerve growth factor (NGF)-tyrosine kinase A receptor. The extract also improved the upregulated expression of cyclin-dependent kinase 5 (CDK5) induced by aluminum (Bihaqi et al., 2009). The neuroprotective effect of aqueous roots extract (150 mg/kg) against scopolamine (1 mg/kg)-induced neurotoxicity was screened in the cerebral cortex of male Wistar rats. As a standard drug, rivastigmine tartrate (1 mg/kg, p.o.) was used. Pretreatment with aqueous root extracts significantly decreased the scopolamine-induced increase in the transfer latency in the elevated plus maze, while in the Morris water maze, the extract administration ameliorated the loss of spatial memory induced by scopolamine. Significant inhibition was observed by the extract in the activity of acetylcholinesterase within the cortex (~46%) and hippocampus (~56%). Administration of rivastigmine tartrate also inhibited elevated acetylcholinesterase activity by ~24% in the cerebral cortex and ~30% in the hippocampus. The extract elevated the diminished activities of glutathione reductase (GR), glutathione (GSH) and superoxide dismutase (SOD) within the cortex and hippocampus induced by scopolamine (Bihaqi et al., 2011). In a neuroprotective study, the treatment with aqueous root extract (150 mg/kg) to scopolamine (2 mg/kg, i.p.) treated rats decreased the increase in tau protein and mRNA levels, and AβPP (β-amyloid precursor protein) levels followed by

a decrease in amyloid β levels. The results were compared with rivastigmine tartrate (1 mg/kg p.o.), which was used as a positive control (Bihaqi et al., 2012). The neuroprotective action of aqueous extract (root) against human microtubule-associated protein tau (hMAPτ) induced neurotoxicity in an AD *Drosophila* model was studied. A separate study by Kizhakke et al. (2019) also found a neuroprotective effect of aqueous root extract against hMAPτ-induced neurotoxicity in the *Drosophila melanogaster* (Oregon K) strain. The extract was found to control hMAPτ-induced early death. The extract also increased the lifespan and reduced the level of τ protein in tauopathy *Drosophila*. The extract treatment also enhanced the antioxidant enzyme action, ameliorated the oxidative stress induced by τ, and restored the depleted acetylcholinesterase action.

Effect on cognitive function

The effect of ethanol extract of aerial parts, its ethyl acetate, and aqueous fractions (100 and 200 mg/kg p.o.) were evaluated for nootropic activity. The administration of the extract and fractions for 7 days potentially increased the number of avoidance responses in the training trials and retention trials. A dose of 100 mg/kg of extract and fractions was found to be statistically significant, while the results were increased with a higher dose, i.e., 200 mg/kg. The step-down latency in the passive avoidance test was significantly increased by extract and fractions. The ethanol extract, ethyl acetate, and aqueous fraction increased the inflexion ratio to 13.14, 13.00, and 14.68 at the dose of 100 mg/kg, and 17.42, 14.29, and 15.66 at the dose of 200 mg/kg, respectively, as compared to the control group (3.69). The results were compared with the standard drug piracetam (100 mg/kg p.o.). Treatment with the extracts for 15 days showed better retention and recovery than the vehicle-treated animals in a dose-dependent manner against scopolamine-produced amnesia. The decrease in the number of avoidance responses was observed after administration of scopolamine butylbromide (0.3 mg/kg i.p.) on days 9−15 30 min before the daily dosing of the extract and fractions. The animals treated with 100 mg/kg extract as well as fractions took 5−7 days, while animals treated with 200 mg/kg of the same extracts as well as fractions took 3−4 days only to get to the point of reversal, signifying better retention and recovery. In an active avoidance test, the animals treated with extract and fractions showed a remarkable increase in the percentage ARs as compared to the vehicle. These findings suggested the extract and fraction from aerial parts of *C. prostratus* enhance learning and memory retention (Nahata et al., 2008).

The effects of pretrial and posttrial administration of ethanol extract (whole plant) on learning and memory in young and aged mice were evaluated by an elevated plus maze test and by measuring acetylcholinesterase activity. In pretrial administration of the extract, the effect was measured in acute, subchronic, and chronic studies. The animals were treated with distilled water

orally (control), piracetam 10 mg/kg, i.p. (standard), and ethanol extract at doses of 100 and 200 mg/kg, p.o. (test). In an acute study in young mice, transfer latency (TL) was noted 60 min after drug administration and again after 24 h. A dose-dependent improvement of memory was observed in extract-treated animals as compared to the vehicle-treated control group when tested on the second day. The extract (200 mg/kg, p.o) showed significantly higher percent retentions (81.42%) than piracetam (48.7%). In a subchronic study in young mice, TL was noted 60 min after drug administration on the third day and again after 24 h in all groups. Multiple treatments with the extract for 3 days showed a significant dose-dependent increase in percentage retentions as compared to the control group. The same effect was observed in piracetam-treated animals. The extract showed a more prominent effect of 84.2% as compared to piracetam 75.9%. In a chronic study in aged mice, TL was noted 60 min after drug administration on the seventh day and again after 24 h. Significant lower percentage retention (3.7%) in aged mice was seen as compared to young mice (18.3%). Mice aged 18−20 months exhibited higher transfer latency (TL) values on the first and second days as compared to young mice, showing impairment in learning and memory. Pretreatment with extract for 7 days improved memory as a significant increase in percent retention as compared to control aged mice. Significantly higher retention (55.3%) was observed at a dose of 200 mg/kg as compared with piracetam (which was 42.84%). To evaluate the effect of posttrial administration of the extract on memory the same treatment was given to animals after training them on an elevated plus-maze. During acquisition trials, latency times were similar across all experimental groups. However, posttrial administration of extract revealed a significant decrease in latency times during retention trials. The percent retention of memory after 24 h in the control group was significantly less than that of the extract-treated groups during these trials. The effect on acetylcholinesterase activity was also screened. Hippocampal regions associated with the learning and memory functions exhibited an increase in acetylcholinesterase activity in a dose-dependent manner in Cornu Ammonis 3 (CA3) area with extract treatment. The principal mechanism of these extract actions may be due to their antioxidant, neuroprotective, and cholinergic properties (Sharma et al., 2010).

The nootropic activity of aqueous-methanol extract (whole plant) at doses of 50, 100, 200, and 400 mg/kg for 30 days was studied against amnesia induced by scopolamine hydrobromide (3 mg/kg, p.o.). The activity was tested using elevated plus-maze (EPM) and step-down models. As a standard drug, piracetam (100 mg/kg) was administered orally. In the EPM test, a decrease in the transfer latency indicated the memory-enhancing action of the tested drug. In the EPM model, the extract showed memory-enhancing action at all tested doses, and at the dose of 100 mg/kg the activity was maximum. When compared to animal training-day latency, the extract showed a 70% reduction

in transfer latency. In the step-down passive avoidance model, the extract (100 and 200 mg/kg) profoundly improved the step-down latency. The results at 100 mg/kg were similar to piracetam and were significantly changed from vehicle-treated groups. Moreover, CPE also exhibited significant action at the higher doses (200 and 400 mg/kg), in comparison to controls (Malik et al., 2011). Three compounds, scopoletin, scopolin, and ayapanin (coumarins), isolated from chloroform and ethyl acetate fractions at doses of 2.5, 5, 10, and 15 mg/kg, p.o. were tested for memory-enhancing activity against amnesia induced by scopolamine. As a standard drug, donepezil (1 mg/kg, p.o.) was used. Compounds of scopoletin and scopolin significantly and dose-dependently diminished the amnesic action induced by scopolamine in both elevated plus maze and step-down paradigms. At the dose of 15 mg/kg, the effect of both compounds was similar to that of donepezil. Ayapanin was found to be inactive at all tested doses. However, no significant activity on locomotor action was shown by any of the tested compounds. Both scopoletin and scopolin exhibited significant reversal of increased acetylcholinesterase activity induced by scopolamine, at doses of 10 and 15 mg/kg the activity was comparable to that of donepezil (Malik et al., 2016). The nootropic action of methanol extract (whole plant) at a dose of 400 mg/kg, p.o. was tested against scopolamine (0.3 mg/kg, i.p.) induced memory retrieval. The administration of extract decreased the number of avoidance responses of scopolamine-induced amnesia when compared to piracetam (100 mg/kg p.o.) (Sethiya et al., 2019).

Activity against other CNS-related disorders

Depression

The consecutive 1-week treatment of methanolic extract prepared from the aerial parts decreased immobility time and increased the sucrose preference index and the number of rearings in chronic mild stress rats at oral doses of 50 and 100 mg/kg. The results were found to be comparable to those of standard drug fluoxetine at a dose of 10 mg/kg. The extract also reversed the increased elevated levels of IL-1β, IL-6, TNF-α, alanine transaminase, and aspartate transaminase in rats. In addition, this extract also reestablished the noradrenaline and serotonin levels in the hippocampus and prefrontal cortex of experimental rats. This study suggested that the exerted antidepressant-like effect of methanol extract could be facilitated by antiinflammatory action, reestablishing liver biomarkers or mono-aminergic responses in stressed animals (Gupta and Fernes, 2019). An aqueous-methanol extract of the whole plant at a dose of 400 mg/kg showed an antidepressant effect by decreasing the immobility period by 37% in experimental animals. The extract improved the immobility time to 156, 167, and 191 s at doses of 100, 200, and 400 mg/kg, respectively. A known antidepressant drug, imipramine (12.5 mg/kg), was used as a positive control (Malik et al., 2011). A chloroform fraction of the

ethanolic extract of whole plant showed a significant reduction in the immobility time of mice at oral doses of 50 and 100 mg/kg without showing any effect on locomotor activity. This activity was found to be comparable to that of the standard drugs fluoxetine (20 mg/kg) and imipramine (15 mg/kg). The study concluded that the antidepressant-like effect of the chloroform fraction in mice was through the interaction with adrenergic, dopaminergic, and serotonergic systems (Dhingra and Valecha, 2007).

The chloroform, ethanol, and aqueous extracts of the aerial parts were evaluated for their neuropharmacological activity in mice. The extracts (500 mg/kg) were given orally 30 min before thiopental sodium (40 mg/kg) administration. A dose of 1 mg/kg of diazepam was used as a standard. The study showed that only aqueous and ethanol extracts had promising results in general behavior models, while the chloroform extract was less active (Siddiqui et al., 2014).

Stress

The aqueous extract was evaluated for antistress potential, and the stressed animals were post-treated with 100, 150, and 200 mg/kg b.w. of the aqueous extract which significantly restored altered serum cortisol, lipid peroxidation levels, and body weight, compared with the stress control group. The stress was experimentally induced using a cold water forced swimming stress model. The significant dose-dependent antistress activity was observed in this study. This effect was due to its neuroprotective and antioxidant potential (Yuvaraj et al., 2018). The oral administration of methanol extract of aerial parts at a dose of 100 mg/kg showed a potent anxiolytic effect in conditioned avoidance response (CAR) induction of experimental stress test, when the extract was given 45 min before the test. The extract significantly lowered the stress-induced epinephrine level and potentiated more prolonged sleeping time (Sethiya et al., 2009).

Anxiety

The ethyl acetate fraction of ethanolic extract from the aerial parts was tested for central nervous system activity in rat and mouse models. The extract at a dose of 100 mg/kg showed an anxiolytic effect and increased the open-field exploratory behavior. At a dose of 200 mg/kg, ethyl acetate fraction potentially decreased the neuromuscular coordination. Diazepam (1 mg/kg i.p.) was taken as a reference drug. The aqueous fraction was also used in this study but it was not found to be effective at doses of 100 and 200 mg/kg (Nahata et al., 2009).

The ethanol and chloroform extracts of the aerial parts at doses of 500 mg/kg showed anxiolytic-like effects in mice by increasing the total time spent and the open arms in the elevated plus-maze models. The results were compared with an anxiolytic drug, diazepam (1 mg/kg) (Siddiqui et al., 2014). A similar study by Malik et al. (2011) studied the aqueous-methanol extract of

the whole plant (50, 100, 200, and 400 mg/kg) to evaluate the anxiolytic effect. The extract exhibited significant anxiolytic action at all dose levels. The effect of extract at the dose of 100 mg/kg was comparable to the standard drug, diazepam (2 mg/kg). The treatment of animals with the extract showed an average of 9.4 entries in the open arms.

Huntington's disease

An ethyl acetate fraction obtained from the methanolic extract of the whole plant showed neuroprotective activity by attenuating body weight loss, enhancing locomotor activity, grip strength, and gait abnormalities in nitropropionic acid-induced Huntington's disease in rats at a dose of 20 mg/kg. The extract also reduced the elevated malondialdehyde and nitrite levels, and reestablished the superoxide dismutase and decreased the glutathione enzyme action in the striatum and cortex. This study revealed that the extract showed a neuroprotective effect through accelerating brain antioxidant defense mechanisms in nitropropionic acid-treated rats (Kaur et al., 2016).

The hydromethanol extract of whole plant (200 mg/kg) and its ethyl acetate (15 and 30 mg/kg), butanol (25 and 50 mg/kg), and aqueous (50 and 100 mg/kg) fractions were significantly in attenuated 3-nitropropionic acid-induced reduction in locomotor activity, memory, grip strength, oxidative defense, and body weight of mice in 15 days. This study suggested that *Convolvulus prostratus* has a protective effect against 3-nitropropionic acid-induced neurotoxicity and can be developed as a drug to treat Huntington's disease (Malik et al., 2015).

Epilepsy (seizure disorder)

The anticonvulsant action of chloroform, ethanol, and aqueous extracts of the aerial part was evaluated against pentylenetetrazol-induced seizures in mice. The extracts were orally administered at a dose of 500 mg/kg body weight, 30 min before the subcutaneous injection of pentylenetetrazol (80 mg/kg). Diazepam, at a dose of 2.0 mg/kg i.p., was used as a standard drug. The ethanol, chloroform, and aqueous extract showed highly efficacious protection against pentylenetetrazol-induced clonic convulsions (453.5, 673.8, and 544.1 s) while the absence of any convulsion was observed in the diazepam-treated groups (Siddiqui et al., 2014). The methanol extract of the whole plant was evaluated for anticonvulsant activity in a seizure model. The extract at doses of 500 and 1000 mg/kg reduced the mean recovery time from convulsion but did not abolish the hind limb extension. The results were compared with phenytoin which was used as a standard drug (Verma et al., 2012).

CNS stimulation

Aqueous-methanol extract of the whole plant (100, 200, 400, and 600 mg/kg) was studied for CNS-depressant activity by measuring the locomotor activity

using an actophotometer. As a standard drug, diazepam was administered orally at a dose of 10 mg/kg. The extract gave a significant CNS-depressant activity in a dose-dependent manner. A higher dose (400 and 600 mg/kg) gave an average of 27% and 45% decrease, respectively, in locomotor activity (measured as a decrease in the number of counts), whereas diazepam showed a 52% reduction in activity (Malik et al., 2011). Similarly, chloroform, ethanol, and aqueous extracts of aerial parts were also evaluated for locomotor activity using the same mouse model. As compared with the positive control group (amphetamine, 2 mg/kg), ethanol and aqueous extracts (500 mg/kg) showed a significant reduction in motor activity (Siddiqui et al., 2014). The effect of water-soluble alcoholic extractives of different parts of the plant on the potentiation of barbiturate hypnosis was tested in albino rats (300 mg/kg, i.p.). The maximum barbiturate hypnosis potentiation (sleeping time) was shown by the leaf and flower extractives. A comparison of the activity of plant parts when collected in different seasons (rainy, winter, spring, and summer) was also carried out. The activity was found to be higher when the plant was collected in the spring season while it was lower in the rainy season (Mudgal, 1975).

Alcohol addiction

Shankhpushpi Churna, a marketed formulation (100 and 200 mg/kg) gave dose-dependent activity against acute alcohol withdrawal anxiety in Swiss albino mice screened by an elevated plus-maze test. Diazepam at 1 mg/kg was used as a standard drug. Both Shankhpushpi (200 mg/kg) and diazepam (1 mg/kg) were shown to have comparable anxiolytic potential. However, pretreatment with $GABA_A$ antagonist prevented Shankhpushpi-mediated reversal of withdrawal anxiety. Treatment with $GABA_B$ agonist and Shankhpushpi did not give any significant change in withdrawal anxiety compared with Shankhpushpi-treated animals. These results suggested that Shankhpushpi may reverse ethanol withdrawal anxiety in a $GABA_A$-dependent manner.

On chronic ethanol consumption (21 days), the effect of Shankhpushpi was evaluated using a two-bottle choice protocol of voluntary drinking. The effect was also evaluated on cortico-hippocampal GABA levels. After 30 days of alcohol treatment, animals showed a significant increase in cortico-hippocampal GABA as compared with the control group. Shankhpushpi treatment at a dose of 200 mg/kg for 10 days showed a significant increase in GABA as compared with alcohol-consuming animals. This significance was further increased in the diazepam-treated group as compared with the alcohol group. Animals treated with Shankhpushpi showed a significant decrease in ethanol and water intake as compared with the control group after day 24 or 4 days post-Shankhpushpi therapy. This was comparable with diazepam-treated animals, which also presented a significant decrease in ethanol intake. However, administration with $GABA_A$ blocker to animals followed by

Shankhpushpi failed to show a decrease in ethanol and an increase in water intake till day 30. These findings also suggested that Shankhpushpi prevented chronic ethanol intake and showed antiaddictive potential, which may be mediated by $GABA_A$ receptors (Heba et al., 2017).

Effect on oxidation and oxidative stress

It is well-established that antioxidants are extensively used as health-promoting agents which can protect from many age-related ailments. According to Kamat et al. (2008), there is enough evidence that antioxidants are able to prevent CNS-related diseases. The total phenolic content in methanol leaves extract in 50, 100, and 200 μg/mL was determined to be 0.2092, 0.2380, and 0.3608 mg GAE/g, respectively. The radical-scavenging activity of the extract was recorded to be 52.56% and for standard (butylated hydroxytoluene) to be 93.48% at the highest concentration of 100 μg/mL. The IC_{50} values of 90.56 and 29.02 μg/mL were calculated for the extract and standard, respectively (Balaji et al., 2014). The methanol extract of the whole plant was evaluated for antioxidant activity by DPPH assay and the IC_{50} value of the extract was observed at 41.00 μg/mL as compared to 2.03 μg/mL of ascorbic acid which was used as a standard (Verma et al., 2012). In another study, the significant antioxidant effect was observed with ethanol extract of aerial parts, its ethyl acetate and aqueous fractions, in comparison of ascorbic acid. In a dose-dependent manner, the best superoxide radical-scavenging action was displayed by the ethanol extract followed by the ethyl acetate and aqueous fractions (Nahata et al., 2009). The methanol extracts of the whole plant (0.1 mg/mL) showed 21.9% inhibition of DPPH with an IC_{50} 275 μg/mL. As a positive control, gallic acid and ascorbic acid were used, which showed IC_{50} values of 1 and 2.5 μg/mL, respectively (Mathew and Subramanian, 2014). Four subfractions (FrA, FrB, FrC, and FrD) collected from chloroform and ethyl acetate fractions of methanol extract of the whole plant were evaluated for antioxidant potential. The IC_{50} were 61, 51, 100, and 91 μg/mL, respectively, while the IC_{50} for ascorbic acid was recorded as 40 μg/mL. As a pure compound, scopoletin was obtained from FrB on further purification (Kaur et al., 2016). The extract showed IC_{50} values of 25.46, 26.94, and 22.11 μg/mL in DPPH, FRAP assay, and phosphomolybdenum complex method, respectively. As a standard, vitamin E displayed IC_{50} values of 13.62, 12.39, and 4.41 μg/mL in the respective methods (Sethiya et al., 2019).

Clinical evidence to support CNS-related activities of *C. prostrates*

Sankhapuspi has been used as a brain tonic mainly for improving memory for the past several years. Today, a number of formulations are available in the market which contain *Convolvulus prostrates* as a major component. Its potency against CNS-related disorders has been proven clinically. The effect of

oral administration of Sankhapuspi Rasayana (3 g three times a day for 6 weeks) in patients with anxiety disorders was evaluated in a clinical study and the effect was compared with the Jaladhara treatment (30 min daily for 6 weeks). Jaladhara treatment provided 67.49% relief on the Hamilton scale, whereas Sankhapuspi Rasayana provided 72.06% relief. The study also proved that 12.5% patients gained marked improvement and 87.5% patients showed moderate improvement in the Jaladhara group, and in the Sankhapuspi Rasayana group, 47.7% patients showed marked improvement and 58.3% patients showed moderate improvement. Therefore, the overall effect of Sankhapuspi Rasayana for management was better than Jaladhara treatment, as it provided a comparative improvement in anxiety, irritability, inability to relax, lack of concentration, disturbed sleep, loss of memory, palpitations and headache, dryness of mouth, upset stomach, and restlessness. Sankhapuspi Rasayana was made from Sankhapuspi Churna processed with 7 Bhavana of Sankhapuspi Kwath (Dass, 2012). Dandekar et al. (1992) observed an encouraging improvement of seizure control and reduction in plasma phenytoin levels in patients who were continuously taking Sankhapuspi for a long time.

The antihypertensive action of *Convolvulus prostrates* was determined in a randomized, single-blind, active-controlled clinical study. In this study, the aqueous extract of *Convolvulus prostrates* at a dose of 3 g (in a gelatin capsule) was orally administered (twice daily) in combination with Gokhru (*Tribulus terrestris*) 7 g (once a day) for 28 days. The combination of benzthiazide (25 mg) and triaterene (50 mg) was given as a control. After 28 days of therapy, significant activity was noticed in both the experimental and control groups (Rizwan and Khan, 2014).

Toxicity studies

The continuous use of the *Convolvulus pluricaulis* plant for the treatment of many ailments for hundreds of years has confirmed its clinical safety. There are many preclinical studies available that support its nontoxic nature within a dose limit. Its aqueous leaf extract was found to be safe up to a dose of 2000 mg/kg in an acute oral toxicity study in rats. Histopathology showed that the extract is also safe for the brain, heart, and liver (Ravichandra et al., 2013). Similarly, its ethanolic and aqueous extracts at a dose of 5000 mg/kg did not show any toxicity or behavioral changes in rats during an acute oral toxicity study (Agarwal et al., 2014).

Conclusion

Convolvulus pluricaulis, popularly known as Sankhpuspi in Ayurveda, has been used as a brain and nervine tonic for the past several years, mainly in India and other South Asian countries. Its remarkable effect on CNS-related

activities makes it an important plant for the treatment of Alzheimer's disease. There are many preclinical studies available which support its role against AD, however, clinical trials, particularly for AD, are not available. Hence, there is a need for further preclinical and clinical studies to enable its use for the treatment of AD.

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