ISSN 2515-8260 Volume 09, Issue 07, 2022

A Systematic Review On Convolvulaceae Plants With Central Nervous System Efficacies

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INTRODUCTION

The central nervous system (CNS) is the control centre of the body. It integrates information received to coordinate and influence the body's activity. Central nervous system disorders, such as neuralgia, dementia, epilepsy, anxiety, and insomnia, profoundly debilitate human behavioral, social, and cognitive functions (1,2). Besides accounting for 39% of deaths worldwide, CNS disorders also result generally in poor quality of life (1,3). Moreover, CNS disorders place a severe challenge on healthcare systems. An extensive study by the European Brain Council estimated the total cost of brain disorders across Europe at 798 billion pounds in 2010 (4). Despite the significant impact of CNS disorders on individuals and society, new drug development in this field of medicine remains limited. Treatments for CNS disorders, such as depression and schizophrenia, are still largely based on substances identified in the 1950s (5). Therefore, novel and active chemical substances for the treatment of CNS disorders are to be discovered.

Plants have been used by humans since immemorial times to cure disorders and to promote relief from ailments (6). The traditional usage of medicinal plants by indigenous healers has been valuable for community health care in many cultures (6). Medicinal plants are valuable sources of alternative therapy per se, but a wide range of secondary metabolites can also be potentially used for the treatment and prevention of disorders. Nearly 51% of approved drugs directly or indirectly originated from natural products since 1980 (6,7). Among plant medicines used in

ISSN 2515-8260 Volume 09, Issue 07, 2022

CNS disorder treatments historically, many are proven effective by modern pharmacological studies (8,9). Meanwhile, plenty of natural metabolites identified from medicinal plants have demonstrated efficacy in invivo or in vitro models, suggesting their therapeutic potential on CNS disorders (10). However, a large majority of medicinal plants have not been investigated for their pharmacological activities and represent a potential source for providing new lead compounds for CNS disorder treatments (7-10).

Convolvulaceae, known commonly as bindweed or morning glory family, is a family comprising approximately 1,600–1,700 species grouped in 55–60 genera. The family is nearly cosmopolitan in distribution, but its members are primarily tropical plants (11). Convolvulaceae plants are commonly present as herbaceous vines, but some plants are also trees, shrubs, or herbs. Many species of Convolvulaceae have been reported to possess CNS efficacies throughout the world. The seeds of Turbina corymbose and Ipomoea violacea are known as ololiuhqui and tlitliltzin, respectively, in the Aztec language and were used to attain a state of mind suitable for divination in religious ceremonials in ancient Mexico (11). Convolvulus pluricaulis and Evolvulus alsinoides, two important sources of Indian medicine Shankhpushpi, were used to treat several CNS disorders, including insanity, epilepsy, nervous debility, and memory impairment (11). Cuscuta Chinensis Lam., a traditional Chinese medicine used to tonify the livers and kidneys, is used as a CNS depressant in India (12). Recently, extensive studies have been conducted on the CNS efficacies of Convolvulaceae species, such as Argyreia Nervosa (11), C. pluricaulis (13), and Ipomoea batatas (14). Several reviews were published on some specific Convolvulaceae species or genera (11). However, a systematical and comprehensive review of the ethnopharmacology and pharmacology properties of the CNS-active Convolvulaceae species has not been performed.

Originally, ergoline alkaloid derivatives were isolated from lower fungi and were shown to exhibit diverse and remarkable CNS activities, especially in the treatment of migraine or Parkinson's disease (15). In the 1960s, Hofmann and Tscherter defined ergoline alkaloids in higher plants, specifically in some Convolvulaceae plants (15). Since then, a large number of genera belonging to Convolvulaceae, including Argyreia (15), and Ipomoea, have been searched for the existence of ergoline alkaloids, based on the idea that ergoline alkaloids are the main bioactive constituents responsible for the psychotomimetic effects of Convolvulaceae plants. In recent years, with the development of phytochemical research, other CNS active compounds have been identified from Convolvulaceae plants, including flavonoids, coumarins, lignans, and resin glycosides, greatly enriching the understanding of the CNS efficacies of Convolvulaceae plants.

This review study not only focuses on the medicinal uses and pharmacological studies of CNS-active Convolvulaceae plants but also summarizes the isolated biological compounds from several Convolvulaceae species. In addition, the crosstalk among the medicinal uses and pharmacological and phytochemical studies provides theoretical guidance for the medicinal

ISSN 2515-8260 Volume 09, Issue 07, 2022

utilization of Convolvulaceae plants and might lead to the discovery of novel active chemical substances for CNS disorder treatments.

MEDICINAL USES

Argyreia Nervosa

A. Nervosa (syn. Argyreia speciosa) is native to the Indian subcontinent and was introduced to numerous areas worldwide, including Hawaii, Africa, Deccan, and the Caribbean. Although its seeds are now recognized as a hallucinogen and are found to contain the highest concentration of ergoline alkaloids in the entire family, its roots are the traditional medicinal parts used in India since ancient times. The roots have been regarded as a nervine tonic, which was used to improve intellect and prevent the effects of age (16).

Convolvulus species and Evolvulus species

Shankhpushpi is considered one of the best brain tonics in Ayurvedic pharmacopeia. C. pluricaulis (syn. Convolvulus microphyllus) and E. alsinoides, two medicinal plants belonging to different genera in Convolvulaceae, are the main sources of Shankhpushpi. C. pluricaulis is mostly used in North India, whereas E. alsinoides is used in South India. Despite belonging to different genera, they share similar therapeutical effects on CNS disorders including insanity, epilepsy, nervous debility, and memory impairment. Evolvulus nummularius, another Evolvulus plant morphologically similar to E. alsinoides, is also regarded as a substituent source of Shankhpushpi to improve memory according to the literature. In addition, Convolvulus arvensis was traditionally used to treat epilepsy in north Pakistan (17).

Cuscuta species

Chinese Dodder or Tu Si Zi, the seed of Cuscuta australis and C. Chinensis is a commonly used traditional Chinese medicine for improving sexual function, tonifying the livers and kidneys, and reducing urination. It is also used to treat cognitive impairment in many Chinese formulations, such as the Five Seeds Combo and Zuo Gui Wan pill. Moreover, the whole plant of C. Chinensis has been used widely as a CNS depressant in traditional Indian medicine to treat various brain disorders such as epilepsy, insanity, mania, and melancholy for several centuries. Cuscuta reflexa is a substitute for C. Chinensis in China, the seeds of which are also used as Tu Si Zi. In India, the seeds of C. reflexa are reported to possess a sedative effect, and the whole plant is used for the treatment of mental disorders such as melancholy, insanity, and epilepsy. Moreover, the stem of the Cuscuta epithymum is recorded to treat epilepsy in Iran (18).

Ipomoea species

The genus Ipomoea, with approximately 500–600 species, comprises the largest number of species within Convolvulaceae. Due to the hallucinogenic content of ergoline alkaloids in the seeds, a lot of Ipomoea species were used by ancient people to attain a state of mind suitable for divination during religious ceremonies and magical rituals in Central America and Africa. For instance, the seeds of I. violacea, known as tlitliltzin in the Aztec language, are still used even today by certain natives in Mexico. In Latin American countries, the seeds and leaves of some Ipomoea species, such as Ipomoea alba, Ipomoea pescaprae, and Ipomoea purpurea, are also used during religious ceremonies. Two to four seeds of I. alba crushed in water and taken at night result in vivid dreams as reported in Zimbabwe (19).

In addition to their use as a hallucinogenic, Ipomoea species are also used in the treatment of nervous disorders. Ipomoea Aquatica and I. batatas, two important consumed foods, are used to treat nervous debility and madness in India and Zimbabwe, respectively. The smoke of burned roots of Ipomoea leptophylla is used in the treatment of nervousness. The roots of Ipomoea tyrianthina and Ipomoea stans were used to treat convulsions and epilepsy in Mexico. The roots of Ipomoea ommaneyi are used to treat convulsions and epilepsy in Zimbabwe. Moreover, the whole plants of Ipomoea eriocarpa are used to treat epilepsy in India (20).

Merremia species

Merremia dissecta was first discovered in the Caribbean islands. As a medicine, the crushed leaves of M. dissecta are recommended by Cubans as a sedative for use in tisanes. Merremia emarginata, which is also called Convolvulus reniformis, Evolvulus emarginatus, Ipomoea reniformis, or Merremia gangetica is the twining herb therapeutically used to treat neuralgia and epilepsy in India. In addition, the fruits of Merremia tridentata are used to treat epilepsy in India (21)

Operculina turpethum

Operculina turpethum is a well-known medicinal herb traditionally used in the Unani system of medicine to treat various disorders. During the flowering season, the roots of the plants are shed to be used as a drug. It is reported to possess several neurological effects in the Unani system of medicine, such as brain evacuant and brain tonic, and to be used to treat CNS disorders such as insanity, epilepsy, and pain (22).

Pharbitis nil

The seed of Pharbitis nil (syn. Ipomoea nil), with the common Chinese name of Qian Niu Zi, is one of the most powerful purgative drugs used in China and Japan. Although there are no related records on the utilization of P. nil in CNS disorders in China, it is used to treat Alzheimer's disease (AD) in Unani. Eminent Unani scholars believed that P. nil as a purgative agent could be used to slow the progression of AD by removing deranged material from the brain tissue (23).

Turbina corymbosa

T. corymbosa also called Rivea corymbosa or Ipomoea corymbosa is a large scandent twining woody vine distributed throughout Latin America from Mexico to as far south as Peru. The seeds

ISSN 2515-8260 Volume 09, Issue 07, 2022

are known as ololiuhqui and are used as a narcotic by the Aztecs and neighboring Indians. In addition, ololiuhqui is also used to attain a state of mind suitable for divination during religious ceremonies and magical healing practices. According to our research, a total of eight species are suggested to possess hallucinogenic effects as a part of their traditional usage. Meanwhile, 21 species are used to treat head or body pain; about 14 species are used to treat epilepsy; about 11 species are suggested to possess a CNS depressant effect that could be used to treat madness, insanity, or nervousness; about nine species are regarded as a brain tonic. Other plants are used for senselessness, brain evacuant, narcotic, and some other mental distributions (24).

PHARMACOLOGICAL EFFECTS

A total of 144 published articles referred to the CNS efficacies of (46 Convolvulaceae species. According to their curative effects, the CNS efficacies of Convolvulaceae species can be categorized as follows: analgesic, antidementia, anxiolytic or antistress, antiepileptic, sedative-hypnotic, neuroprotective, and other effects.

Analgesic effect

Pain is an unpleasant sensory and emotional feeling accompanying existing or impending tissue damage. Pain sensation involves the active regulation by excitatory and inhibitory circuits in the CNS, controlled primarily by nuclei in the brainstem that can either diminish or exaggerate pain depending on mood, cognitive function, and memories. Most of the studies investigated the in vivo analgesic effects of Convolvulaceae species using mouse or rat models, except for an in vitro study evaluating the antimigraine effect of Ipomoea pestigridis. The methanol extract of the stems of Argyreia argentea was evaluated for its analgesic effect against pain induced by acetic acid and formalin in Swiss albino mice. The extract at the doses of 1.0, 1.5, and 2.0 g/kg produced an inhibition of 12.66%, 16.04%, and 23.60% in acetic-acid-induced pain and 19.3%, 24.5%, and 31.0% in formalin-induced pain. The roots, leaves, and aerial parts of A. Nervosa are all investigated for the analgesic effect in the tail-flick test, acetic-acid-induced writhing test, or hot-plate test, which showed positive. A study reported that the ethanol extract of the fruits of Calonyction aculeatum showed remarkable analgesic activity, which they suggest to be related to the malondialdehyde and prostaglandin E2 reduction and superoxide dismutase level increase (25).

Antidementia effect

Dementia is a chronic condition in which progressive cognitive impairment leads to functional disability. This condition has become a global health challenge along with an aging world population. AD, the most common type of dementia, represents 60–80% of cases. Pathologically, AD is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits. Altered cholinergic function and induction of neuroinflammation and oxidative stress are also prominent features of AD. These researches comprise 31 in vivo studies, 20 in vitro studies, and 3 clinical studies.

ISSN 2515-8260 Volume 09, Issue 07, 2022

The roots of A. Nervosa display antiamnesic effects in different animal models, including scopolamine/diazepam/5-HT-treated, aging, and normal Swiss albino mouse models). Hanumanthachar et al. (2007) have found that the extract of the roots of A. Nervosa could reduce the whole-brain acetylcholinesterase (AChE) activity (26) Bodhankar and Vyawahare (2008) found that the extract of the roots of A. Nervosa could reduce brain dopamine levels, including AChE, dopamine, 5-HT, and noradrenaline. These results suggested the potential usage of A. Nervosa in AD (27). C. pluricaulis shows antidementia effects in vitro, invivo, and clinical studies reported that C. pluricaulis could improve scopolamine-induced learning and memory dysfunction by decreasing AChE activity and inhibiting oxidative stress in the cortex and hippocampus (28). Bihaqi et al. (2012) also reported that the C. pluricaulis extract could attenuate scopolamine-induced increased protein and messenger RNA levels of tau, β-amyloid precursor protein levels, amyloid β-protein (Aβ) levels, and histopathological changes in the rat cerebral cortex (29). In a clinical study, patients treated with Shankhpushpi tablets (made of powder and juice of C. pluricaulis) showed the significant result in auditory delayed, visual delayed, auditory recognition, and visual recognition tests compared with the placebo group, suggesting an enhancement in long-term memory. The antidementia mechanism was tested in vitro. L. F. Liu et al. (2012) evaluated a lot of Ayurvedic and traditional Chinese medicines and found that the leaves of C. pluricaulis showed remarkable inhibition of Aβ40 and Aβ42 productions. Interestingly, C. pluricaulis did not affect the secreted amyloid precursor protein levels, suggesting the extract of C. pluricaulis does not reduce Aβ through amyloid precursor protein modulation (30). Mathew and Subramanian (2012) reported that C. pluricaulis could prevent the aggregation of Aβ and dissociate preformed Aβ fibrils at a concentration of 100 μg/μl. Mathew and Subramanian (2014) also reported that the ethanol extract of the whole plants of C. pluricaulis could inhibit AChE activity with a 50% inhibitory concentration (IC50) value of 245 ± 32.4 μg/ml. In addition, in a large-scale screen for activity, the methanol extract of the aerial parts of Convolvulus pilosellaefolius showed an AChE inhibitory ratio of 10.4% at a concentration of 50 μg/ml, suggesting the potential utilization of C. pilosellaefolius in the treatment of AD (31). According to Khare, Chaudhary, et al. (2008), the whole plants of C. cretica reduced whole-brain malondialdehyde and nitric oxide (NO) levels and decreased whole-brain AChE activity, leading to an improvement of memory impairment in scopolamine-treated mice (32).

Anxiolytic and antistress activities

Anxiety is a normal reaction simulated by stress. Clinically, excessive anxiety often presents in the form of discrete discomfort, which is very common and often comorbid with other psychiatric and medical illnesses. Most anxiolytic drugs used in the clinic have many side effects, such as sedation, muscle relaxation, and anterograde amnesia, leading to a search for alternative medicines.

According to several researchers, different extracts of the roots of A. Nervosa exhibited antistress effects. The roots of A. Nervosa could decrease stress-induced ulcers; increase survival time; decrease aspartate transaminase, alanine aminotransferase, and creatine kinase levels; and restore the adrenal gland and spleen weight. Moreover, the result from a study suggested that the ethanol extracts of the roots of A. Nervosa exhibited maximum effect to increase the number of entries and time spent in the open arm, suggesting the most effective anxiolytic activity. As two important sources of Shankhpushpi, C. pluricaulis and E. alsinoides both show anxiolytic activities in various animals (33). Malik et al. (2011) report that aqueous methanol extracts of the whole plants of C. pluricaulis and E. alsinoides show the maximum anxiolytic activity at doses of 100 and 200 mg/kg, respectively (34). Nahata et al. (2009) suggested that the ethyl acetate fraction of the ethanol extracts of C. pluricaulis and E. alsinoides showed the best anxiolytic activities, which were correlated with their antioxidant effects (35). According to the Thomas et al. (2015) research, the methanol extract of the whole plants of C. reflexa could decrease the number of entries into closed arms, increase the number of entries into open arms, increase the time spent in open arms and light chamber, and increase the number of crossings into light and dark chambers at doses of 200 and 400 mg kg−1 day−1 in Swiss albino mice (36).

Antiepileptic activity

Epilepsy, a common chronic neurological disease, affects 1–2% of the world population. In 67% of patients, seizures can be successfully controlled with anticonvulsant medications, whereas 33% remain refractory to medical therapy. Therefore, there is an unmet medical need for new antiepileptic drugs with higher safety and efficacy.

Several researchers reported that the hydroalcoholic extract of the roots of A. Nervosa could delay the onset of convulsions, inhibit the lethality in pentylenetetrazole-treated mice, and reduce the hind limb extension in maximal electroshock-treated mice at doses of 100–400 or 500 mg kg−1 day−1. The aerial parts of four Convolvulus plants Co. arvensis, Convolvulus hirsutus, C. pluricaulis, and Convolvulus suendermannii, together with the whole plants of C. pluricaulis, all show anticonvulsant activities in various seizure models, including metrazole-induced seizure, strychnine-induced seizure, pentylenetetrazole-induced seizure, or maximal electroshock seizure. In the genus Cuscuta, the aqueous extract of the whole plants of C. Chinensis could decrease the clonic phases of electrically induced seizures at a dose of l,000 mg kg−1 day−1. The 80% methanol extract of Cuscuta planiflora could delay the onset of a seizure, decrease the mortality rate, and enhance seizure protection. The leaf extract of C. reflexa could reduce the duration of convulsion and inhibit tonic extension convulsion, whereas its stem extract could increase the level of catecholamines and enhance the level of γ-aminobutyric acid (GABA), glutamine, and glutamate contents in the brain at doses of 25–75 mg kg−1 day−1 (37).

The sedative–hypnotic effect

ISSN 2515-8260 Volume 09, Issue 07, 2022

Insomnia is commonly defined as a state of poor sleep quality caused by difficulties in sleep initiation or maintenance despite being in a proper sleep-inducing environment. Approximately 9–15% of the general population worldwide has been reported to suffer from insomnia symptoms accompanied by daytime activity consequences.

Galani and Patel (2009) reported that the hydroalcoholic root extract of A. Nervosa could prolong pentobarbital-induced sleeping time at doses of 100–500 mg/kg. The leaf extract of Argyreia populifolia showed a sedative effect in a gender-dependent way. The extract had no sedative effect on male and estrous rats. In contrast, all three doses (2.5, 5.0, and l0.0 ml/kg) of the extract showed sedative effects in diestrus rats, whereas in proestrus rats, the highest dose induced marked sedation. The ethanol extract of the flowers of Co. arvensis showed a tranquilizing activity in the rotating rod and traction tests in mouse models. The activity is attributed to the flavonoid contents. In addition, the whole plants of C. pluricaulis also exhibited a sedative effect and potentiated pentobarbitone-induced sleeping time at doses of 40–120 mg/kg. The aqueous extract of the whole plants of C. Chinensis also showed a sedative effect, which could potentiate pentobarbitone-induced narcosis and survival time under hypoxia at a dose of l,000 mg/kg (

38). Pal et al. (2003) reported that the petroleum ether extract of the stems of C. reflexa could potentiate pentobarbitone-sodium-, diazepam-, and meprobamate-induced sleeping times at doses of l00–160 mg/kg (39).

Neuroprotective activity

The CNS contains a remarkable array of neural cells. Exposure to natural or artificial toxic substances alters the nervous system, causes damage to nervous tissues, and eventually induces CNS disorders. The production of reactive oxygen species (ROS) and reactive nitrogen species is part of the natural physiological reaction in the brain. However, under pathological conditions, excessive production of ROS and reactive nitrogen species leads to oxidative stress and nitrosative stress, respectively. Both types of stress damage lipids, proteins, and DNA and lead to the destruction of membranes and organelles. As mentioned earlier, some Convolvulaceae species exhibit neuroprotective activities in specific CNS disorder models. The roots of C. pluricaulis prevent aluminum-induced neurotoxicity in male Wistar rats. The aqueous extract decreases the elevated enzymatic activity of AChE, inhibits the decline in Na+ /K+ ATPase activity, prevents the accumulation of lipid and protein damage, and ameliorates the upregulated protein expression of Cdk5. In addition, in the H2O2-induced cytotoxicity in the IMR32 neuroblastoma cell line, the methanol extract of C. pluricaulis remarkably decreases H2O2-induced cell death due to the induction of the antioxidant machinery. The seeds of C. Chinensis show antineuroinflammatory activities both in vitro and in vivo. In the lipopolysaccharide (LPS)-stimulated BV-2 microglial model, the 80% aqueous ethanol extract of the seeds of C. Chinensis remarkably decreases the production of NO, prostaglandin E2, tumor necrosis factor α, interleukin 1β, and interleukin 6. In the cerebral ischemia-reperfusion injury model of rats, the flavonoid fraction of C. Chinensis inhibits the inflammatory cytokine secretion and expression and reduced the inflammation of brain tissue. In addition, the flavonoid fraction of C. Chinensis seeds also exhibits antioxidant activity and reduced cell death in H2O2-treated PC-12 cells (40).

Other bioactivities

Four species were recorded to possess other CNS activities, including antidepressant effect, anti-Huntington's disease, and anti-PD. The whole plants of C. pluricaulis show antidepressant activity at doses of 25–100 mg kg^{-1} day^{-1} (41, 42). The chloroform fraction of the ethanol extract reduced the immobility time and reversed the reserpine-induced extension of the immobility period in the forced swim test and tail suspension test. The methanol extract of the whole plants of C. pluricaulis could attenuate the 3-nitropropionic-acid-induced reduction in locomotor activity, grip strength, memory, body weight, and oxidative defense, suggesting a promising use against Huntington's disease (43).

Conclusion

CNS disorders account for 12% of deaths worldwide and represent a huge challenge for healthcare systems. Plenty of Convolvulaceae species are used to treat CNS disorders in traditional medicine and might be used as alternative medicines. This review provides systematic information on the medicinal uses, pharmacology, and phytochemistry of the Convolvulaceae species with CNS efficacies. According to these studies, 54 species have been used as folk medicine to treat CNS- related disorders throughout the world, suggesting a wide utilization of this family of plants. In addition, great progress in the pharmacology and phytochemistry of the CNS-active Convolvulaceae species has been made. However, more exploratory research is still needed to gain a better understanding of the CNS efficacies of this family. Moreover, more clinical trials are needed for the large-scale utilization of these species in medicine.

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ISSN 2515-8260 Volume 09, Issue 07, 2022

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