



Review on *Evolvulus alsinoides* and a brief outlook in to the neuroprotective activity of *Convolvulaceae* plants

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Abstract

Evolvulus alsinoides Linn (EA) is well known for its memory enhancement, antiepileptic and immunomodulatory properties in Ayurveda, The traditional Indian system of medicine. The plant belongs to the family Convolvulaceae. Convolvulaceae family comprising about 1,600-1,700 species grouped in 55-60 genera, and most of the species are reported to have an effect on CNS. The plant has shown wide range of pharmacological activities such as antioxidant, anti-amnesic, anticonvulsant, antidepressant, immunomodulatory, anti-inflammatory, anti-diabetic, antihypertensive, antimicrobial activities etc. This review will highlight the morphological characters, chemical constituents, and the reported pharmacological activities of *Evolvulus alsinoides* (*E. alsinoides*). A review of the literature studies was also carried out to summarize available evidences on Convolvulaceae plants with neuroprotective and anti-amnesic activity. According to this report many of the plants belong to Convolvulaceae family improve CNS function. Even though great progress has been made on the pharmacological studies, more exploratory research and clinical trials are still needed to gain a better understanding of the CNS efficacies of this plant family.

Keywords: anti-amnesic, *Evolvulus alsinoides*, neuroprotective, shankhpushpi

Introduction

Natural products are gaining popularity as potential therapeutic agents because of their wide margin of safety [1]. In developed and developing countries plant materials are used as home remedies, over-the-counter drug products, raw materials for the pharmaceutical industry, and also which constitute an important portion of the worldwide drug market. According to the report of World Health Organization, around 80% of the population in the world using traditional medicines and in India more than 75% of the population residing in rural areas utilizing medicinal plants. Hence traditional medicines still play very important role in health care system. *Evolvulus alsinoides*, one of such plants extensively used in the Indian traditional (Ayurveda) system of medicine and other parts of the world for the treatment of various diseases. *E. alsinoides* is also known as the slender dwarf morning-glory. It is commonly known as Shankhpushpi/Sankhaholi [2]. The scope of this review is to summarize the reported pharmacological activities of *Evolvulus alsinoides* and a brief outlook into the evidences on Convolvulaceae plants with neuroprotective and anti-amnesic activity. According to this report many of the plants belong to Convolvulaceae family improve CNS function. Even though great progress has been made on the pharmacological studies, more exploratory research and clinical trials are still needed to gain a better understanding of the CNS efficacies of this plant family.

Vernacular names and etymology

Vernacular names of Shankhpushpi in different states of the country is given in the following table no.1 [3].

Botanical description

Evolvulus alsinoides is a flowering annual or perennial herb with small woody rootstock. It is often prostrate, very slender, relatively branched, spreading or ascending, generally exceptionally hairy herb.

Stem: spreading, thin, bushy and about 30 cm in length or more.

Leaves

are plenty, elliptic-oblong to oblongovate in shape with 8-14 mm long and 5-7 mm wide, mucronate apex, silky hairs on both surfaces; petiole is short about 3 mm long.

Inflorescence: flowers are solitary and bluish in colour, size: 6-8 mm in diameter, lean peduncle, bracts are narrow of size about 5 mm long and 0.75 mm wide. Pedicel is 2-10 mm long. Calyx contains 5 sepals, which are lanceolate in shape. Corolla is rotate or funnel shaped.

Fruits

Globose capsule of 3-4 mm in length which is usually 4 seeded.

Seeds: are ovoid in shape with pale brown to black in color. Pollination is by means of insects and seeds are dispersed by winds.

Habitat

It has a normal pantropical distribution surrounding tropical and warm temperate regions of Australia, Asia, Indomalaya, Polynesia, Sub-Saharan Africa and the Americas. It is an ordinary weed growing wild in open grassy places all over India climbing to the 6000ft in the Himalayas and subtropical countries of the world [2-4].

Table 1: Vernacular names of shankpushpi

Scientific Name	<i>Evolvulus alsinoides</i> (Linn.)
Bombay	Sankhavali
English	Slender dwarf morning glory
Gujarati	Kalisankhavali
Hindi	Shyamkranti, sankpushpi
Malayalam	Vishnukranti
Marathi	Vishnukanta
Punjabi	Kodyali, Sankpushpi
Sanskrit	Vishnukranti, Vishnugandhi
Tamil	Vishnukarandi, vishukaranthi
Telugu	Vishnukranta, kancakura
Unani	Sankhaholi

**Fig 1:** *Evolvulus alsinoides* Linn

History: *Evolvulus* is a small genus composed of about 10-15 species extensively scattered in Asian and American countries and some of its species used medicinally. *Evolvulus alsinoides* is well-known Ayurvedic crude drug that have significant role in traditional medicinal system of India owing to its memory improving properties. In addition to its historical indigenous use some preparations containing the plant decoction are extensively commercialized as nerving tonic (Shankpushpi) in Asia. Moreover, the plant extracts have been used for the treatment of a number of ailments including bronchitis, asthma, brain disorders like insanity, epilepsy, nervous disability, and scrofula [5].

Phytoconstituents: *E. alsinoides* is reported to contain alkaloids, steroids, flavanoids and coumarins as active constituents which is responsible for its biological effects. The major therapeutic agents present in the plant are evolvine, pentatriacontane, triacotane, β -sitosterol, glycoflavone, 4' methoxyvitexin, p-hydroxybenzoic, vanillic, protocatechuic and gentistic acids and quinines. Others are caryophyllene, tetradecanoic acid, myristic acid, pentadecanoic acid, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, nonane dioic acid, dibutylester, azelaic acid, l-(+)-ascorbic acid 2,6 -dihexadecanoate, heptadecanoic acid, phytol isomer, oleic acid, 9-octadecenoic acid, octadecanoic acid, steric acid, squalene, hexadecanoic acid, Cis-11,14-eicosadienoic acid methyl ester [6].

Pharmacological activities: *Evolvulus alsinoides*, whole parts of the plant is widely used in Ayurveda. The important pharmacological activities reported are:

Antioxidant activity: may be due to the presence of antioxidant phytochemicals like polyphenolics, steroids and

triterpenes. The ethanolic extract of *E. alsinoides* possess significant antioxidant activity which is evaluated by using *in-vitro* assay methods such as scavenging activity of ferric reducing antioxidant power (FRAP), hydrogen peroxide and inhibition of lipid peroxidation [7]. Gomathi et.al assessed the free radical scavenging activity by *in vitro* methods like reducing power assay, total antioxidant activity, hydroxyl radical scavenging assay, and nitric oxide radical scavenging assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) reduction, superoxide radical scavenging activity and 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) scavenging activity using ascorbic acid as reference standard. The extract exhibited significant activities in all antioxidant assays related with the reference antioxidant.

Anticonvulsant activity: Methanolic extract of *Evolvulus alsinoides* produced 50-100% protection in mice against pentylenetetrazole (PTZ) induced seizure at doses of 100-400mg/kg, indicate its efficiency against myoclonic and absence seizures. *E. alsinoides* significantly attenuated electrically induced seizure in mice, shows its potential against generalized tonic clonic seizures [2].

Antiamnesic activity: The plant is well known brain tonic and hence indicated in nervous debility and insanity. The following studies strongly support the neuropharmacological potential of the herb. Alcoholic extracts of *Evolvulus alsinoides* (250 mg/kg body weight) showed significant nootropic activity when compared to *Convolvulus pluricaulis* in a study conducted by Rawat *et al* performed in elevated plus maze and jumping box model using wistar strain rats [2]. Another study conducted by Siripurapu *et al.* also supports the above statement. Crude ethanolic extract of EA showed noticeable improvement in the peripheral stress markers and scopolamine induced dementia in rodents this indicated the adaptogenic and antiamnesic properties of the herb [8]. Yellamma *et al.* reported the neuroprotective effect of *Evolvulus alsinoides* extract on cholinergic system and claim that this study may lead to the discovery of safe and novel anti-Alzheimer's compounds [2].

Anti-anxiety activity: *Evolvulus alsinoides* markedly relieved the anxiety symptoms without producing any side effects, in a single blind placebo controlled study conducted using 60 patients with anxiety neurosis [9]. In a different study the whole herb extract was subjected to anxiolytic activity, revealed that at doses of 100, 200 and 400 mg/kg it showed anxiolytic activity and most significant activity was observed with dose of 200 mg/kg (20.4 s in open arm, $p < 0.001$) when compared to the vehicle-treated group [10].

Antidepressant activity: *E. alsinoides* showed reduction in immobility period in test group when compared to animals of control group at doses 50 and 100mg/kg doses and increase in mobility period at higher doses indicates significant antidepressant activity in the above mentioned doses. The test was evaluated by means of forced swim despair test and imipramine was used as standard [3].

Anti diabetic activity: The plant extract was administered orally for 45 days to streptozocin induced diabetic rats showed significant antioxidant activity and also increased the insulin level in the pancreas [11].

Anti-hypertensive activity: The herb is a valuable drug for cardiovascular disorders with symptoms such as dyspnoea, palpitations etc. Methanolic extract of the plant significantly lowered blood pressure in adrenaline induced hypertension in rats and also produced noticeable effect in DOCA salt induced hypertension in mice. The study also revealed that the extract do not interfere with pulse rate and its probable mechanism of action similar to that of Enalapril^[12].

Immunomodulatory activity: This activity of Shankpushpi (*Evolvulus alsinoides*) was studied in adjuvant induced arthritic (AIA) rat model. The inflammation is induced by Complete Freund's Adjuvant (CFA) mechanism in right hind paw of the animals followed by the administration of the extract through intraperitoneal route. The anti-inflammatory response of the extracts was evaluated by determining the parameters like lymphocyte proliferation and histopathological severity of synovial hyperplasia, found that there was noticeable reduction in inflammation and edema. Moreover inhibition of nitric oxide synthase (NOS) enzyme was noticed in treated animals when compared to controls. These interpretations suggest that the herbal extracts caused immunosuppression in AIA rats and hence it can be recommended as an alternative approach to the treatment of arthritis^[13].

Anti-inflammatory activity: Chloroform and ethyl acetate extracts of *Evolvulus alsinoides* showed a graded and dose dependent reduction in inflammation when compared with standard drug at dose of 12.5mg/kg body weight. But the drug was found to be effective in acute inflammation mediated by prostaglandins, histamine and 5- hydroxy tryptamine^[4].

Antibacterial activity: Highest activity was observed with ethanolic extract of *E.alsinoides* the zone of inhibition produced at concentration 1025mg/ml, for Klebsiella pneumonia(38mm), Pseudomonas aeruginosa (33 mm), Salmonella typhi (30 mm),Escherichia coli (26 mm) and Staphylococcus aureus (8mm) respectively^[14].Methanolic extract of *Evolvulus alsinoides* showed broad spectrum of antimicrobial activity against gram positive and negative bacteria and fungi

Antimalarial activity: In order to perform enzyme inhibition study, lactate dehydrogenase enzyme was cloned from Plasmodium falciparum 3D7 strain and expressed in Escherichia coli BL₂₁ (DE3) by using expression vector pET28a and recombinant protein was purified by Ni-affinity chromatography. Recombinant plasmodium falciparum lactate dehydrogenase (PfLDH) and bovine lactate dehydrogenase were diluted with phosphate buffered saline (pH 7.4) containing 1 mg/ml bovine serum albumin and 1 mmol/L phenyl methane sulfonyl fluoride to a final concentration of 18 kU/L. 30 ml from this stock solution was used for determining PfLDH activity and the concentration of methanolic extract of *E. Alsinoides* taken was 50 mg/ml. Methanolic extract of *E. alsinoides* reduced PfLDH activity to (25.04±0.51%)which is statistically significant since the P value<0.001 levels^[4].

Anthelmintic activity: The antianthelmintic property of the plant was cited in the traditional ethanomedicinal literature. In a study conducted by G.K Dash et.al revealed that the

ethanolic extract of *Evolvulus alsinoides* was found to be more convincing than the reference standard piperazine citrate^[2].

Neuroprotective and Antidementia Effect of Plants Belong to Convolvulaceae Family

Neuroprotective activity: The CNS comprises of an outstanding collection of neural cells. Exposure to either natural or artificial toxic substances damage the nervous tissue by generating reactive oxygen species (ROS)or oxidative stress and reactive nitrogen species or nitrosative stress and eventually lead to CNS disorders. Both types of stress damage lipids, proteins, and DNA thereby cause destruction of neuronal membranes and organelles. Here, we summarize the neuroprotective effect of Convolvulaceae species against exogenous neurotoxins, oxidative stress, and neuro in flammatory models^[15].

Convolvulus pluricaulis (C. Pluricaulis): The aqueous extract of roots of *Convolvulus pluricaulis* was found to inhibit aluminium-induced neurotoxicity *in vivo* by using male Wistar rats, where it lowers the elevated enzymatic activity of acetyl cholinesterase (AChE), restore the diminished Na⁺ /K⁺ ATPase activity and also prevent lipid and protein damage. Moreover it also rectify the upregulated protein expression of Cyclin dependent kinase 5 (Cdk5)^[16]. In addition, the methanolic extract of C. Pluricaulis extremely decreases hydrogen peroxide -induced cell death in the IMR-32 neuroblastoma cell line, as a result of stimulation of the antioxidant machinery^[17].

Cuscuta chinensis: In both *in vitro* and *in vivo* studies seeds of *Cuscuta chinensis* (*C. Chinensis*) is showed antineuro inflammatory activity. An aqueous ethanolic extract (80%)significantly decreased the production of NO, prostaglandin E₂, tumour necrosis factor α , interleukin 1 β , and interleukin-6 in lipopolysaccharide (LPS)-stimulated BV-2 microglial model^[18]. In the cerebral ischemia-reperfusion injury model of rats, the flavonoid (Kaempferol) fraction of *C. Chinensis* reduced the secretion and expression of inflammatory cytokines¹⁸.Additionally, the flavonoid fraction of *C. chinensis* seeds also show evidence of antioxidant activity and reduced cytotoxicity in hydrogen peroxide treated PC-12 cells^[19].

Ipomoea aquatic: In the genus *Ipomoea*, *Ipomoea. aquatica* leaves show neuroprotective activity. In a study involving carbofuran- induced neurotoxicity. The extract decreased elevated lipid peroxidation levels in plasma and erythrocyte membrane and cholesterol levels in brain and plasma, also minimized histopathological degenerative changes of liver^[20]. Moreover the hydro alcoholic extract of the plant exhibit antioxidant& anticholinesterase activity. The anti Alzheimer's disease effect is due to the presence of chlorogenic acid^[21].

Ipomoea batatas: Choi *et al.* in 2013 investigated the protective effect of sweet potato extract against hydrogen peroxide-induced oxidative stress and cytotoxicity on the pheochromocytoma cell line (PC12). The antioxidant activity was determined by using 2, 20 -azino-bis (3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assay. The antioxidant chemical was found to be 2,4-di-tert-butylphenol. Also investigated the effect of 2,4-di-

tertbutylphenol on amyloid-beta peptide ($A\beta_{1-42}$)-induced learning and memory impairment in mice and revealed that it enhanced alternation behavior in mice injected with ($A\beta_{1-42}$). These results recommend that sweet potato extract could be protective against $A\beta$ -induced neurotoxicity, perhaps it may be due to the antioxidant component, 2,4-di-tert-butylphenol [22]. The anti-neuroinflammatory potential was also evaluated in (lipopolysaccharide) LPS-activated BV-2 microglial cell lines. It was found that it decreased production of pro-inflammatory mediators such as nitric oxide, inducible nitric oxide synthase, cyclooxygenase-2 enzyme and tumour necrosis factor-- α (TNF- α) mediated via blockade of extracellular regulated protein kinase, c- Jun N-terminal kinase, and nuclear factor kappa B signaling [23].

Antidementia activity: Dementia is a chronic condition in which progressive impairment of memory leads to functional disability [24]. This condition has developed over all health problem along with an aging world population. AD accounts for 60-80% of dementia. Pathologically, AD is characterized by deposition of intracellular neurofibrillary tangles and extracellular amyloid protein in the neurones. The important features of AD are oxidative stress, neuro inflammation and distorted cholinergic function [25].

Argyreia speciosa: *Argyreia speciosa* showed significant reduction in whole brain acetyl cholinesterase (AChE) activity of both young and aged mice compared to Piracetam, scopolamine and control groups of mice. This indicates that *Argyreia speciosa* has significant nootropic and anti-amnesic activity [26].

Convolvulus pluricaulis: Bihagi *et al.* in 2012 stated that, in rats, *Convolvulus pluricaulis* (*C. pluricaulis*) have found to reduce oxidative stress, acetyl cholinesterase activity, also prevent histopathological changes in the cortex and hippocampus and thus improve scopolamine-induced learning and memory impairment. He also reported that the above effect may be due to decreased protein synthesis messenger RNA levels of tau, β -amyloid precursor protein levels and amyloid β -protein ($A\beta$) levels [27]. In a clinical study, patients treated with Shankhpushpi tablets (made of powder and juice of *Convolvulus pluricaulis*) revealed significant improvement in auditory and visual function compared with the placebo group, suggestive of an improvement in long-term memory [28].

L. F. Liu *et al.* in 2012 reported that the mechanism of antidementia effect of the leaves of *C. pluricaulis* may be due to inhibition of $A\beta_{40}$ and $A\beta_{42}$ production [29]. Mathew and Subramanian *et al.* in 2012 reported that *C. pluricaulis*, at 100 $\mu\text{g}/\mu\text{l}$ concentration could prevent the aggregation of $A\beta$ and dissociate preformed $A\beta$ fibrils [30]. They also reported in 2014 that the ethanol extract of the whole plant of *C. pluricaulis* could inhibit acetyl cholinesterase activity (AChE) and the half maximal inhibitory concentration was found to be $245 \pm 32.4 \mu\text{g}/\text{ml}$ [31]. A coumarin derivative scopoletin may be responsible for its memory enhancing activity [32].

Convolvulus pilosellaefolius: In another study, the methanol extract of the aerial parts of *Convolvulus pilosellaefolius* at a concentration of 50 $\mu\text{g}/\text{ml}$, showed 10.4% reduction in the activity of acetyl cholinesterase enzyme, suggesting its potential application in the treatment

of Alzheimer's disease (AD) [33]. According to Khare, Chaudhary, *et al.* in 2014, the whole plants of *Cressa. Cretica* improved memory impairment in scopolamine-treated mice possibly through reducing malondialdehyde and nitric oxide (NO) levels and AChE activity [34].

Cuscuta: In the genus *Cuscuta*, the three species *Cuscuta chinensis*, *Cuscuta japonica*, and *Cuscuta. reflexa* showed anti-amnesic activity in various mouse models [35-37]. The hydroalcoholic extract of the aerial parts of *Cuscuta Chinensis* possess AChE inhibitory activity and the IC50 value was found to be $478.07 \pm 0.42 \mu\text{g}/\text{ml}$ [38].

Ipomoea: In the genus *Ipomoea*, *Ipomoea aquatica*, *Ipomoea asarifolia*, *Ipomoea involucreta*, and *Ipomoea muricata* all possess AChE inhibitory activities and the IC50 values are 49.03, 120, 42.5, and 39.67 $\mu\text{g}/\text{ml}$, respectively [21,39,40].

Ipomoea aquatic: Anti- AD and nootropic effects were observed with the methanolic extract of the leaves of *Ipomoea aquatica* in young, old, and $A\beta$ -induced neurotoxicity in Swiss albino mice [41].

Ipomoea Batatas: In both *in-vitro* and *in- vivo* studies the ethanolic extract of the roots of *Ipomoea Batatas* (*I. batatas* or sweet potato) exerts antioxidant effect and also reversed $A\beta$ -induced neurotoxicity, imply its anti-AD potential [42]. Purple sweet potato colour (PSPC) or purple sweet potato anthocyanin constituent of *I. Batatas* was reported to improve the cognitive performance, a study of D-galactose induced oxidative stress in rats. Activation of phosphatidyl inositol 3-hydroxy kinase pathway, suppression of cytochrome-C-mediated apoptosis may be the possible mechanism for survival of neurons [43]. Also found that the same drug attenuates cognitive deficits in domoic acid induced neurotoxicity by promoting oestrogen receptor- α -mediated mitochondrial biogenesis signaling and regulating the expression of phagocyte oxidase proteins [44]. Additionally, Sasaki *et al.* in 2013 reported that caffeoylquinic acid (CQA)-rich purple sweet potato extract either used alone or along with anthocyanin, exhibited neuroprotective effect on mouse brain and can enhance the spatial learning and memory of senescence-accelerated prone mouse strain (SAMP8) [45].

Conclusion

Central nervous system (CNS) disorders play a major impact on individual lives and represent a huge challenge for health care systems. The status of herbal medicines is also increasing due to their perceived efficacy, safety and affordability. Plenty of Convolvulaceae species are used to treat CNS disorders in conventional medicine and might be used as alternative medicines. *Evolvulus alsinoides* is used in traditional medicine in East Asia, India, Africa and Philippines to cure fever, cough, cold, venereal diseases, adenitis and dementia. *Evolvulus alsinoides* use is also reported in the treatment of neurodegenerative diseases, asthma and amnesia. Various *in- vivo* and *in- vitro* studies have been performed with EA to prove its pharmacological actions like anti amnesic, antihypertensive, anti-convulsant, antimicrobial, anti-oxidant, anti-inflammatory and many other mentioned above, supports the traditional use of this

medicinal herb. It has also been noticed that many plants under Convolvulaceae family possess neuroprotective and anti-amnesic activity suggesting wide utilization of this family of plants in CNS disorders. Further in-depth research and clinical trials should be encouraged in this family of plants for isolation and characterization of the bioactive compounds responsible to validate the efficacy of the drug against various CNS disorders.

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Conflict of Interest

All the authors declare that there is no conflict of interest.

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