Pharmacological and Neuroprotective Activity of Smilax zeylanica, *Carissa* macrocarpaandThespesia lampas

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ABSTRACT

Brain tumors, stroke, and other neurodegenerative diseases are some of the most predominant medical conditions in developed countries, and they put a financial burden on the healthcare system. Neurodegenerative disorders are believed to affect about 3.1 percent of the population aged 70-79 years in Western countries, but just 0.7 percent of citizens of the same age in India. The World Health Organization recommends that people increase their intake of foods, herbs, and fibers to lower their risk of neurological disorders. A variety of medicinal plants have been recorded in literature as being used in local health ceremonies to treat brain disorders. The effect of active phytochemical constituents of different sections of *Smilax zeylanica*, *Carissa macrocarpa*, and *Thespesia lampas* on neuronal activity and various disease conditions was explored in this study.*Smilax zeylanica* contain phytochemicals such as alkaloids, tannins, triterpenoids, sterols, flavonoids, and compounds like diosgenin and β-sitosterol in the fruit used for theiranalgesic, anticonvulsant, antiepileptic, antidepressant andanti-cataleptic activities. *Carissa macrocarpa*contains flavonoids, coumarins, xanthones, chalcones, and ligninsthat are well-known for their cancer-fighting abilities, hepatoprotective properties, and antifungal properties.*Thespesia lampas*is rich in glycosides, phenols, tannins, hormones, saponins, flavonoids, sugars, β-sitosterol and quercetin. This plant's roots have been found to have anti-diabetic, anti-hyperlipidemic, hepatoprotective, antioxidant and anthelmintic effects.

INTRODUCTION

Brain tumors, stroke, and other neurodegenerative diseases are among the most common healthcare problems in developing countries, and they are a financial strain on the healthcare system. More than 10 million people worldwide suffer from neurological diseases per year, with the number predicted to increase in the future (Gourie-Devi, 2014).Since brain function continues to deteriorate with age due to neurodegenerative mechanisms, researchers are looking for cellular and molecular targets that can help the brain perform properly.In Western countries, about 3.1 percent of the population aged 70–79 years is thought to be susceptible to neurodegenerative diseases, while in India, the prevalence of disease in people of equal ages is 0.7 percent. The discrepancy is largely due to variations in lifestyle and dietary patterns dependent on the use of multiple ingredients (Wyss-Coray, 2016).

Herbs are natural ingredients. Thetherapeutic active chemical agent in herbs varies based on a number of variables such as from person to person, potential decoction to the use of herbal extracts in compliance with Western mainstream medicine practices. Modern medication system has anextensive history of development: it is the collection of methods founded on ideas, values, and interactions from multiple traditions and periods that are used in the preservation of wellbeing, as well as the avoidance, detection, enhancement, and treatment of illnesses (Firenzuoli & Gori, 2007; Yuan et al., 2016).

Treatment of brain diseases is one of the biggest medical issues in the lack of adequate treatment using traditional medicine. The WHO suggests that people raise their consumption of foods, herbs, and fibers as a way to decrease their risk of neurological disorders (Dreher, 2018). There is a relevant product section that may lead to wellbeing in addition to the nutrients available in fresh fruits and green vegetables, such as fiber, carbenoids, and phytosterols (Decloedt, 2017).Polyphenols, on the other hand, play an important function in the treatment of pathogenic bacteria and fungi, as well as providedefenseagainst a variety of stressors both biotic and abiotic. They are a normal part of the human diet, and research shows that they are connected to the cooperative regulation of a variety of health-linked factors, including cognitive function (Kennedy, 2014).

Flavonoids are recognized for their antioxidant properties, which help to reduce oxidative stress, which is thought to be one of the reasonsfor central nervous system disorders. They may also modify the functions of enzymes and receptors, making them multi-target botanical therapeutics or medicines (Grosso, 2013).Glycosides has a number of functions in living organisms. Many plants store inactive glycosides which will be activated by processlike enzyme hydrolysis, which breaks down the sugar component of the chemical, and making it active so that it can be used further. Medicinally, all of these plant glycosides are included.

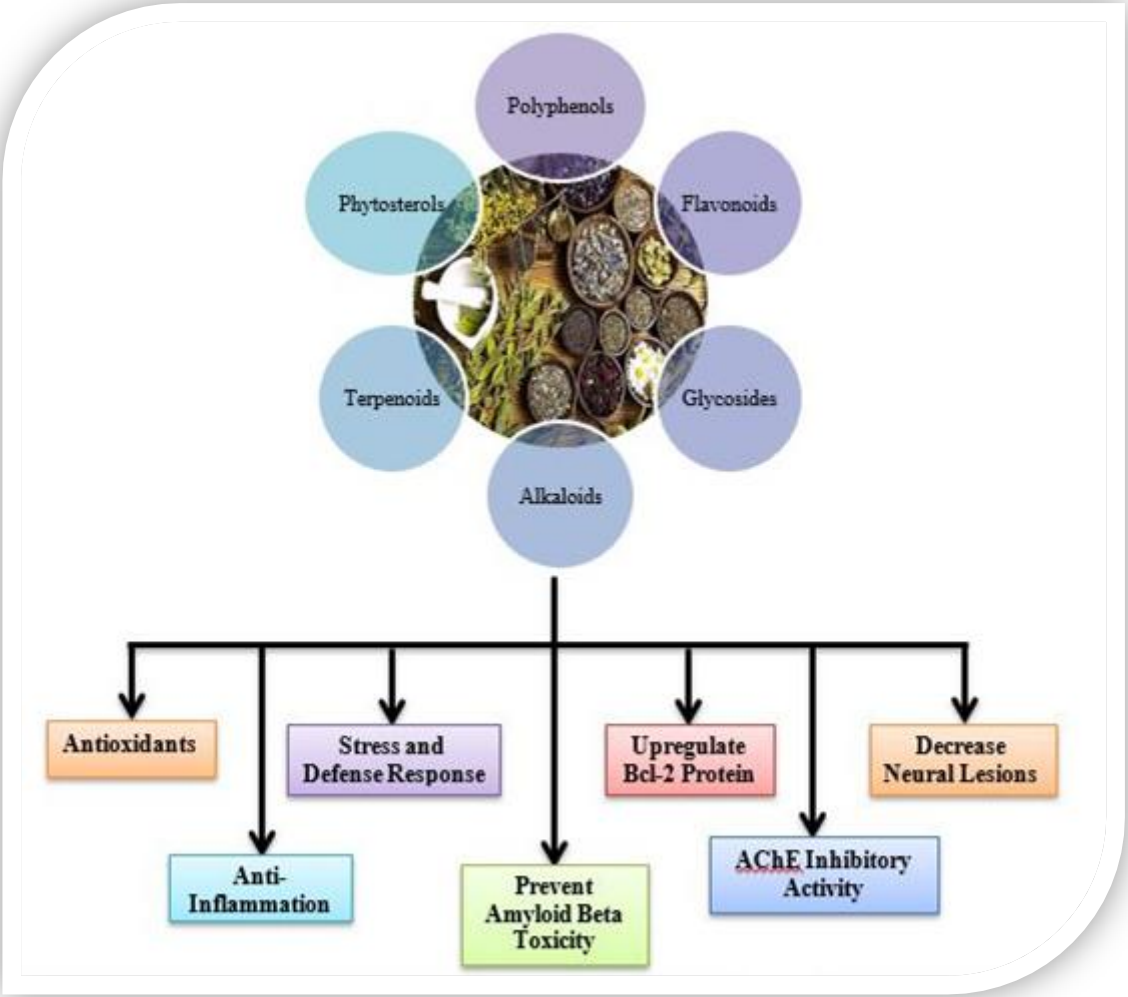

Fig. 1: Plant Secondary Metabolites and their Uses

Literature has recorded the use of a number of herbal plants in local health rituals to cure brain disorders (Tabish, 2008). Many herbal plants used as folk-lore medicines to cure brain diseases, on the other hand, have yet to be researched. The effect of active phytochemical constituents of different sections of *Smilax zeylanica*, Carissa macrocarpa, and Thespesia lampas on neuronal activity and cognitive functions were explored in this study.

Selected Plants with High Secondary Metabolites Targeting Brain

Smilax zeylanica

*Smilax zeylanica*is a member of the monocotyledon Smilacaceae genus, which includes around 350 herbaceous, climbing, and vine plants, as well as shrubs with creeping high branches. *Smilax zeylanica* is a tropical and subtropical plant that is commonly employed in herbal treatmentacross the globe as diuretic and also for the prevention of syphilis and rheumatism (Hirota et al., 2016).

Chemical Compounds in *Smilax zeylanica*

Smilax zeylanica contain a diverse range of phytochemical types such as flavonoids, phenolic compounds, alkaloids, saponins, tannins, and glycosides. HPTLC and GC-MS studies have detected phytochemicals such as triterpenoids, sterols, and compounds like diosgenin and β-sitosterol in the fruit (Uddin et al., 2015; Dhanya Shree et al., 2018).

Apart from nitrogen, sodium, phosphorus, potassium, magnesium, copper, iron, manganese, and zinc, the leaves of *Smilax zeylanica* contain the largest amount of calcium (838.8 mg/100g of DW.) (Mahadkar et al., 2012).

Calcium is the most essential mineral nutrient for plant growth out of all the mineral nutrients. From fertilization to differentiation to organogenesis, calcium signaling pathways play a critical role in development. Ca^{2+} signals are essential controllers of manysynaptic functions in the nervous system, including neuronal network forming and maturation, as well as long-term memory (Leclerc et al., 2012).

By using Sephadex LH-20 chromatography with silica gel, the constituents of *Smilax zeylanica* rhizomes were extracted and distilled, and their architectures were elucidated using spectral analysis. Thirteen compounds were isolated and classified as kaempferol, kaempferol-5-O-beta-D-glucopyranoside, kaemperol-7-O-beta-D-glucopyranoside, dihydrokaempferol-5-O-P-D-glucopyranoside, vanillic acid 3, 5- Diosgenin, β-sitosterol, rutin, smilagenin, trans-so-eugenol, engeletin, isoengeletin, 3, 5, 4'-trihydroxystibene, sarsapogenin, hydroxytyrosol, and squalene were also reported in the fruit (Xu et al., 2008; Dhanya Shree et al., 2018).

Pharmacological Activities of *Smilax zeylanica*

Smilax zeylanica tuber, stem, root, and leaves, used alone or in conjunction with other plants in some formulations (such as paste and decoction) are used to treat a variety of human and veterinary ailments around the world. *Smilax zeylanica* extracts have previously been shown to possess antinociceptive, anti-inflammatory, antimicrobial, antifungal, estrogenic, and antiestrogenic properties, according to previous research (Mahadkar et al., 2012; Nithyamala, 2013; Dhanya Shree et al., 2018).

Venereal infections such asboils, abscesses, rheumatism, psoriasis, dysentery and swellings are among the diseases for which the herb has historically been used. *Smilax zeylanica* is known to be a possiblecomplementary source for the Chopachinee (Ayurvedic drug) (Mahadkar et al., 2012).The following arethe descriptions of the plant's different neuro-pharmacological properties.

Analgesic Activity

Jena et al. used the tail immersion process to assess the analgesic efficacy of several extracts (petroleum ether, chloroform, and methanol) of *Smilax zeylanica* leaves. Many of the extracts had analgesic efficacy equal to that of a standard drug (aspirin). Methanolic extract outperformed all other solvent extracts in terms of analgesic activity (Jena et al., 2011).

Nithyamala et al. tested the analgesic efficacy of *Smilax zeylanica* root powder in albino mice using the hot plate procedure and the acetic acid mediated writhing method. In the hot plate process, oral administration of root greatly improved reaction time in a dose-dependent fashion. Writhing produced by acetic acid was also inhibited by the root powder. Hossain et al. tested the analgesic ability of an ethanolic extract of *Smilax zeylanica* leaves in albino mice using an acetic acid-induced writhing procedure. In mice, extract administration reduced the amount of writhing which was dependent on dose, implying that the leaf extract has analgesic efficacy(Nithyamala, 2013).

Anticonvulsant Activity

Using laboratory animal models, Jena et al. studied the anticonvulsant efficacy of leaves of *Smilax zeylanica* Linnin mice. Strychnine-induced tonic convulsions in albino mice were used to test the extracts' anticonvulsant efficacy. In mice, both of the extracts reduced the induced convulsions. In addition to other extracts, the ethyl acetate extract of *Smilax zeylanica*was found to possessincreased anticonvulsant efficacy (Jena et al., 2011).

Antidepressant Activity

Using forced swimming test (FST) and tail suspension test (TST) methods, Ahemad et al. assessed the anti-depressive efficacy of *Smilax zeylanica* Linn after two weeks of administration (TST). The anti-depressive effect of *Smilax zeylanica* Linn was studied further by testing monoamine levels in the striatum, cortex, hypothalamus, and hippocampusof mice, as well as MAO-A inhibition function. *Smilax zeylanica*decreased mice's immobility period in both the FST and TST, while also increasing 5-HT levels in the cortex, striatum, hippocampus, and hypothalamus and norepinephrine levels. *Smilax zeylanica* has an antidepressant-like effect after two weeks of administration. The mechanism of action of *Smilax zeylanica*antidepressive effect seemed to include a rise in monoamine levels (Ahemad et al., 2016).

Anti-epileptic activity

Madhavan et al. studied the antiepileptic function of alcoholic and aqueous extricates of the roots and rhizomes of*Smilax zeylanica* Linn. in swiss albino mice using the Pentylenetetrazole (PTZ) and Maximal electrical shock (MES) convulsion models. Alcohol extract at doses between 300 and 600 mg/kg greatly decreased the length of the extensor process and the time it took to recover in MES-induced seizures. At doses of 300 and 600 mg/kg, aqueous extract

dramatically and dose-dependently shortened the length of the extensor process. Recovery time was greatly reduced. Both extracts at 600 mg/kg greatly postponed the occurrence of convulsions in PTZ-induced seizures. The study concluded that *Smilax zeylanica* Linn. is a valid botanical source for the Chopachinee, an Ayurvedic medicationused to treat epilepsy (Madhavan et al., 2008).

In mice, Vijayalakshmi et al. investigated ethanolic and ethyl acetate extricates of *Smilax china* rhizome (EESC and EAF, respectively) for its anticonvulsant efficacy and neurotoxicity against maximal electroshock and pentylenetetrazole induced epilepsy, and neurotoxicity by employing the rotarod procedure. EESC at 400 mg/kg dose and EAF at all 200 and 400 mg/kg dosage have greatly shortened the length of hindleg extension in the MES procedure (Vijayalakshmi, 2011).

Anti-Cataleptic Activity

By testing behavioral and biochemical parameters, Ahemad et al. elaboratedin the haloperidol-induced catalepsy rats, the non-catalepticefficacy of the ethanolic root extricate of *Smilax zeylanica*. In male albino rats, catalepsy was induced by administering haloperidol (1 mg/kg). All of the drug-treated groups saw a substantial decrease in cataleptic scores as comparison to the haloperidol-treated group, with the *Smilax zeylanica*(500 mg/kg) treated group showing the greatest reduction. *Smilax zeylanica* reversed haloperidol-induced catalepsy in rodents, according to behavioural experiments and biochemical calculations.The antioxidant potential of haloperidol has helped to reduce oxidative stress and catalepsy caused by the drug (Ahemad et al., 2012).

Carissa macrocarpa

Carissa macrocarpa, also known as Natal plum, is a native herb of KwaZulu-Natal, South Africa. Wide, lushgreen and permanent leaves, oval edible fruit and star-shaped white flowers define this ornamental shrub (Khalil et al., 2015).

The hydroethanolic extract contained thirty polyphenols, including flavan-3-ols, phenolic acids, and flavonol glycosides compounds. Manyresearch papers on the phenolic profile of the Carissa have identified the existence of antioxidant activities and various phenolic compounds such hydroxycinnamic acid, hydroxybenzoic acids, xanthones, coumarins, stilbenes, chalcones, lignans and lignins. Mango and natal plum (2:1) fruit leathers had the greatest levels of kaempferol, catechin, epicatechin, apigenin, quinic acid, cyanidin-3-O-sambubioside, cyanidin-3-O-glucoside chloride, quercetin-3-O-rhamnosyl glucoside, luteolin, and chlorogenic acids, as well as in vitro antioxidant action. Fruit leather of 100 g contains carbohydrate (63.51 g), total sugar (40.85 g), fat (0.36 g), and energy (269.88 calories), according to proximate study. In declining order, the fruits also contained calcium, magnesium, iron, manganese, copper, lead, selenium, nickel, and zinc (Moodley et al., 2012).

There have been no previous research papers on leaves, stems, or flowers of *Carissa macrocarpa*. A few studies on the antibacterial, cytotoxic and antioxidant properties of various extracts derived from stem and leaves have been found. There is still no information on *Carissa macrocarpa* flowers. The chemical compounds present in *Carissa macrocarpa* are well-known for their tumor-fighting abilities, hepatoprotective properties, and antifungal properties (Carocho & Ferreira, 2013; Martins et al., 2015; Pereira et al., 2016).

Because of the existence of numerous phytochemical compounds such as flavonoids, triterpenoids, saponins, tannins, glycosides and anthraquinones, *Carissa macrocarpa* branches, buds, and roots have been employed as an antioxidant and antimicrobial agent, and the leaves as cytotoxic compound (Abbas et al., 2014; Khalil et al., 2015; Khalil et al., 2018).

Thespesia lampas

Thespesia lampas, also known as ‘Ranbhendi,' is a medicinal plant of the family Malvaceae. It's been discovered all over India and in Eastern Tropical Africa. It's a reddish-brown perennial undershrub with reddish brown bark. Flavonoids, glycosides, tannins, phenolic compounds, saponins, hormones, proteins, amino acids,and sugars were discovered in preliminary phytochemical research. Dodecanoic acid, tetradecanoic acid, n-hexadecanoic acid, and 9-tetradecenal fatty acids were detected in *Thespesia lampas*stems by GC-MS analysis, and HPTLC fingerprinting exposed the existence of β-sitosterol and quercetin (Chumbhale & Upasani, 2016).

The fruit and roots of *Thespesia lampas* are used to cure gonorrhea, syphilis and jaundice in herbal medicine. Antimicrobial, antioxidant and anti-lipoxygenase properties have been discovered in the herb. This plant's conventional use as a hepatoprotective agent has not been verified. This research was conducted in order to gain insight into the usefulness of *Thespesia lampas*in the development of a successful hepatoprotective drug (Subramoniam et al., 2015). This plant's roots have been found to have anti-diabetic, anti-hyperlipidemic, hepatoprotective, antioxidant and anthelmintic effects (Jayakar & Sangameswaran, 2008; Sangameswaran et al., 2008; Sangameswaran et al., 2008; Kumaraswamy & Satish, 2008; Sangameswaran et al., 2009; Kosalge & Fursule, 2009).

Plant	Chemical Compounds	Therapeutic Uses
Smilax zeylanica	Kaempferol, kaempferol-5-O-beta-D-glucopyranoside, kaemperol-7-O-beta-D-glucopyranoside, dihydrokaempferol-5-O-P-D-glucopyranoside, vanillic acid 3, 5- Diosgenin, β-sitosterol, rutin, smilagenin, trans-so-eugenol, engeletin, isoengeletin, 3, 5, 4'-trihydroxystibene, sarsapogenin, hydroxytyrosol, and squalene	Analgesic, anticonvulsant antiepileptic, antideprassant, anti-cataleptic activities
Carissa macrocarpa	Hydroxycinnamic acid, hydroxybenzoic acids, xanthones, coumarins, stilbenes, chalcones, lignans, lignins,kaempferol, catechin, epicatechin, apigenin, quinic acid, cyanidin-3-O-sambubioside, cyanidin-3-O-glucoside chloride, quercetin-3-O-rhamnosyl glucoside, luteolin, and chlorogenic acids,	Antioxidant, cytotoxic, antibacterial properties,cancer-fighting abilities, hepatoprotective, and antifungal properties
Thespesia lampas	Flavonoids, glycosides, tannins, phenolic compounds, saponins, hormones, proteins, amino acids, sugars, and fatty acids	Treat gonorrhea, jaundice, and syphilis in herbal medicine.Antimicrobial, antioxidant and anti-lipoxygenase, anti-diabetic, anti-hyperlipidemic, hepatoprotective, and anthelmintic effects

CONCLUSIONS

Nature has gifted us with useful herbal compounds that have great promise in the treatment and prevention of lethal diseases and lifestyle-related illnesses, such as neurodegeneration. Phytonutrients' role in coping with neurodegeneration and preventing dementia has been well-documented in many studies. According to the findings of a comprehensive literature review, the plants mentioned above are widely used ethnobotanically and have a broad variety of pharmacological practices. The plants have long been used to cure a variety of illnesses.Several portions of the plants have been shown to have a variety of neuro-pharmacological functions, according to research. The existence of numerous phytochemicals in the plants, such as alkaloids, terpenoids, flavonoids, and other phenolic compounds, may have contributed to the plant's pharmacological activities and therapeutic ability. Overall, the phytochemicals present in the chosen plants proved to be a potential candidate for developing therapeutic agents for neurological disorders. To retrieve active concepts from the plant and study their biological processes, further pharmacological experiments will be performed.

ACKNOWLEDGEMENTS

One of the authors M. Kavitha and PM Reddy is thankful to UGC-New Delhi, India for financial support in the form of Start-up grant and Head, Department of Chemistry, Osmania University, Hyderabad, India for providing laboratory facilities.

AVAILABILITY OF DATA AND MATERIALS

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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