

Antiepileptic and Antioxidant Activity of Some Medicinal Plants: A Review

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ABSTRACT

Medicinal plants are the oldest form of healthcare known to mankind. Antioxidants are considered to be important in fighting against the damages done by the free radicals produced due to oxidative stress. Antiepileptic drugs help to minimize or to irradiate the convulsive shocks and seizures as a result of abnormal and excessive nerve cell activity. Standardized, well established *in vitro* and *in vivo* methods are available for experimental evaluation of antioxidant and antiepileptic agents. A step wise procedure from *in vitro* and *in vivo* seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing. This review has focused on some herbal drugs with both antioxidant and antiepileptic property such as *Brassica nigra*, *Bacopa monniera*, *Ficus religiosa*, *Convolvulus pluricalis*, *Jatamansi* and *Acorus calamus*.

Keywords: Epilepsy, antioxidants, *Brassica nigra*, *Jatamansi*, *Acorus calamus*.

INTRODUCTION

Epilepsy is a CNS disorder characterized by recurrent transient attack of disturbed brain function that results in motor (convulsive) and sensory (seizure) episodes¹. The word epilepsy is from Ancient Greek "to seize, possess, or afflict. Epilepsy as the result of brain injury, stroke, brain tumors, infections of the brain and birth defects. Epileptic seizures are the result of excessive and abnormal nerve cell activity in the cortex of the brain. The diagnosis involves imaging the brain and performing the blood tests. Epilepsy can often be confirmed with an electroencephalogram (EEG)^{2,3}. Seizures are controllable with medication in about 70% of cases. In those whose seizures do not respond to medication, then surgery, neuro stimulation, or dietary changes may be considered. Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed. Epilepsy is more common in older people^{1,4}.

Antioxidants or inhibitors of oxidation are the compounds which retard or prevent the oxidation and usually prolong the life of the oxidisable matter. An antioxidant act by slowing or preventing the oxidation process which damages the cells in the body, by getting oxidized itself. Thus an antioxidant can also be termed as a reducing agent. Antioxidants are considered to be important in fighting against the damage done by free radicals produced due to oxidative stress. Although the human body has its own defense mechanism against oxidative stress, these become weak with age or in the case of illness. The antioxidant defense system in the body can protect the body when the amount of free radicals is within the physiological level.

When balance is shifted towards more free radicals, it leads to oxidative stress, which may result in tissue injury and subsequent diseases. Antioxidants are being widely used and studied for their role in the treatment and prevention of disease. Antioxidants are used for treating brain injuries such as reperfusion injury and traumatic brain injury as they arrest lipid peroxidation in the brain. They are also being investigated as possible treatment agent against Alzheimers and Parkinsons disease⁵⁻⁷. In this study we are reviewing some medicinal plants that have potent antioxidant and antiepileptic activity.

Brassica nigra

Synonym

Black mustard, brown mustard, red mustard

Taxonomic Classification⁸

Kingdom: Plantae

Phylum: Spermatophyte

Subphylum: Angiospermae

Class: Dicotyledonae

Tribe: Brassiceae

Family: Brassicaceae

Genus: Brassica

Species: Brassica nigra

Description

Brassica nigra, black mustard, is an annual herbaceous plant. It grows up to 2 m (a little over 6 ft), with many branches. The lower leaves are dentate (toothed), pinnatifid (deeply lobed) or lyrate (deeply lobed, but with an enlarged terminal lobe and smaller lateral lobes), and are often hairy, at least on the underside. Upper leaves on flowering stems are narrow and oblong. In contrast to

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many *Brassica* species, the leaves are little if at all glaucous (waxy). Many-seeded, opens lengthwise, 4-edged, 1–2 cm (0.4–0.8 in.) long silique, parallel to stem, terminated by a 2–3 mm (0.08–0.12 in.) long, seedless beak. Stalk 2–5 mm (0.08–0.2 in.). Mustard family plants bear a great resemblance to each other and they often also mutate.

The yellow, four-parted and cross-shaped flowers, occur in many racemes (spikelike cluster) and produce 4-sided siliques capsular fruit that dehisces (splits open) when mature that may be up to 2.5 cm (1 inch) long. Each silique contains 2 to 12 or more reddish brown to black round seeds. A single plant may produce thousands of seeds, which must be harvested by hand or mechanically before they fully ripen, because the siliques spontaneously split and disperse the seeds when they are mature^{9,10}.

Parts used

The medicinal parts were the seeds from which oil is extracted.

Chemical Constituents

Phytochemical screening showed that the plant contained alkaloids, flavonoids, glycosides, carbohydrates, sinapine, myrosin, sinigrin, inositol, albumins, gums and colouring matters. The total phenol content in the plant was 6.67 mg/g of gallic acid 11–12. It contained fatty oil (30–35%), proteins (40%), phenyl propane derivatives: including sinapine (choline ester of sinapic acid, 1%), and glucosinolates: chiefly sinigrin (allylglucosinolates, 1–5%). Grinding the seeds into powder and then rubbing with warm water releases the volatile mustard oil, allyl isothiocyanate. Total phenol content of methanol extract was found to be 171.73 ± 5.04 gallic acid equivalents and the total flavanoid content was 7.45 ± 0.0945 quercetin equivalents. The predominant phenolic compounds determined by HPTLC were gallic acid, followed by quercetin, ferulic acid, caffeic acid and rutin. It also consist of volatile oil, anthraquinones, flavanoids, tannins¹¹.

Antiepileptic Activity

The antiepileptic activity of methanolic extract of *Brassica nigra* seeds was investigated on maximal electroshock induced seizures (MES), Pentylene tetrazole (PTZ), Picrotoxin (PIC) and bicuculline induced seizures in mice. It was found that the extract (200 and 400 mg/kg, orally), significantly prolonged the onset of tonic seizures and reduced the duration of incidence of seizures in PTZ, PIC and bicuculline induced seizure models, while in MES model, the extract showed significant effect in abolishing tonic hind limb extensions by inhibiting voltage dependant Na^+ channels or by blocking glutaminergic excitation mediated by the N-methyl- D-aspartate (NMDA) receptor. The anti-epileptic effect of the methanolic extract of *Brassica nigra* seeds (75, 150 and 300 mg/Kg; ip) was evaluated in pentylenetetrazole (PTZ) - induced kindling in mice. The methanolic extract of *Brassica nigra* seed reduced the intensity and duration of seizure. In addition, the *Brassica nigra* extract increased the SOD and NO levels and decreased the MDA level in the brain tissues^{12,13}.

Antioxidant Activity

The total antioxidant capacity of the extract was found to be 97.08 mg/g of ascorbic acid. *Brassica nigra* showed IC₅₀ value of 63.09 µg/ml whereas the standard antioxidant showed IC₅₀ value 14.45 µg/ml in DPPH method. The standard antioxidants ascorbic acid, gallic acid and quercetin showed the reducing power 485.75%, 736.30% and 763.01%, respectively whereas *Brassica nigra* showed the value 263.69%. IC₅₀ value in NO scavenging activity of the extract was found to be 118.21 µg/ml whereas ascorbic acid showed the value 5.47 µg/ml and quercetin had the value 15.24 µg/ml. The antioxidant activity of methanol extract of *Brassica nigra* seeds, and leaves was demonstrated with a wide range of concentration, 10–500 µg/ml. It was increased with the increase in concentration. Callus obtained from hypocotyl explants of *Brassica nigra* was investigated for its antioxidant activity and antibacterial activity against 4 pathogenic bacterial strains (*E. coli*, *Staphylococcus aureus*, *Ps. Aureogenosa* and *K. pneumonia*). It was generally observed that antioxidant activity and antibacterial activity were higher in calli obtained under light incubation conditions than calli obtained under dark incubation conditions or the mother plant parts from which calli were induced. It is also observed that older calli accumulated more amounts of total phenolics, exhibited higher antioxidant activity and stronger antibacterial activity¹⁴.

Bacopa monniera

Synonym

Indian pennywort

Taxonomical Classification

Kingdom: Plantae

Order: Lamiales

Family: Scrophulariaceae

Genus: *Bacopa*

Species: *Bacopa monniera*

Description

Bacopa monniera (synonyms: *Lysimachia monnieri* L. Cent., *Gratiola monnieri* L., *Monniera cuneifolia* and *Herpestis monniera* L.) which commonly known as (bacopa, brahmi, and thyme leaved gratiola), belongs to the Scrophulariaceae family, was distributed in the warmer and wetlands regions of the world. It was used in traditional medicine to treat various nervous disorders, as a brain tonic to enhance memory development, learning, and concentration, and to provide relief to patients with anxiety; it is also used in digestive complaints, for skin disorders, and as an antiepileptic, antipyretic, and analgesic¹⁵.

Chemical constituents

Bacopa monniera contained alkaloid brahmine, nicotine and herpestine. Bacosides A[3-(α -L-arabinopyranosyl)-O- β -D-glucoopyranoside-10, 20-dihydroxy-16-keto-dammarene] was isolated from *Bacopa monniera*. Triterpenoid saponins, saponins A, B and C and pseudojubenin glycoside were also isolated from *Bacopa monniera*. They identified as 3-O- α -L-arabinopyranosyl -2-O- α -L-arabinopyranosyl -jujubogenin, 3-O- [α -L- arabinopyranosyl - (1 \rightarrow 2)- α -L-arabinopyranosyl]pseudojubenin, 3-O- β -D-glucopyranosyl (1 \rightarrow 3)-{ α -L-arabinofuranosyl-(1 \rightarrow 2)}- α -



Figure 1: *Brassica nigra*



Figure 2: *Bacopa monniera*



Figure 3: *Ficus religiosa*



Figure 4: *Convolvulus pluricaulis*



Figure 5: *Nardostachys jatamansi*



Figure 6: *Acorus calamus*

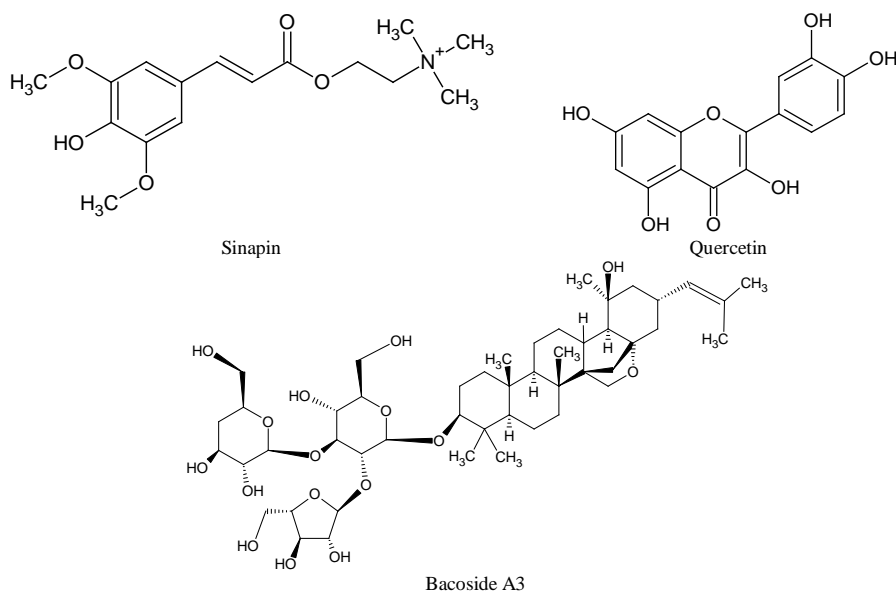
Larabinopyranosyl] pseudojubilogenin and 3-O-[α -L-arabinofuranosyl-(1 \rightarrow 2)- β -Dglucopyranosyl] pseudojubilogenin. Bacopasides I, II, III, IV and V were also isolated from *Bacopa monniera*, which identified as 3-O- α -L-arabinofuranosyl-(1 \rightarrow 2)- β -D-glucopyranosyljubilogenin, 3-O- β -D-glucopyranosyl(1 \rightarrow 3)- α -Larabinopyranosyl jubilogenin, 3-O- β -D-glucopyranosyl(1 \rightarrow 3)- α -L20 arabinofuranosyl pseudojubilogenin. *Bacopa monniera* also contained betulinic acid, D-mannitol, stigmasterol, β -sitosterol and stigmasterol¹⁶

Antiepileptic Activity

For all the different models studied with a mechanism of action similar to that of benzodiazepines (GABA Crude plant extract of *Bacopa monnieri* or bacosides have also shown anticonvulsive action. It possessed neuroprotective effects in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring in association with pilocarpine-induced epilepsy.⁽¹⁵⁾ The ethanolic extract of *Bacopa monniera* was tested for anticonvulsant activity using different convulsive models (pentylenetetrazol, maximal electroshock and strychnine-induced convulsion in rats, as well as hypoxic stress-induced convulsions in mice and lithium-pilocarpine-induced status epilepticus). The ethanolic extract of *Bacopa monniera* was administered as 50 and 55 mg/kg orally for rats and mice, respectively 2 and 4 hours before the respective convulsive stimuli. The ethanolic extract of leaves produced significant anticonvulsant activity agonist¹⁷.

Antioxidant Activity

The total phenolic content of aqueous extract of *Bacopa monniera* measured by Folin ciocalteu was found to be 58 mg gallic acid equivalent/g, while, in hydrogen peroxide scavenging method the IC50 value was found to be 254.70 μ g/ml. The antistress effect of bacosides of Brahmi (*Bacopa monnieri*) was studied in adult male Sprague Dawley rats by administering oral doses of 20 and 40 mg/kg for 7 consecutive days. Bacosides, at both doses, didn't induce significant changes in the expression of Hsp70 in all studied brain region, while stress alone produced significant increase in the Hsp70 expression in all brain regions. A significant decrease in the activity of superoxide dismutase was evident in the hippocampus with the lower dose of bacosides, while an increase in the activity of SOD was observed in the brain regions with the higher dose. An increase in the activity of cytochrome P450 (P450) dependent 7-pentoxoresorufin-o-dealkylase (PROD) and 7-ethoxyresorufin-o-deethylase (EROD) was observed in all the brain regions after exposure to stress alone and with both doses of bacosides, although the magnitude of induction of P450 expression was less with a higher dose of bacosides. Interestingly, stress in the animals pretreated with bacosides for 7 days resulted in a decrease in Hsp70 expression in all the brain regions with a significant decrease occurring only in the hippocampus. Likewise the activity of SOD was found to be further reduced in all the brain regions in the animals treated with the lower dose of bacosides followed by stress. However, when animals exposed to stress after treatment with the higher dose of bacosides, a significant increase in the enzyme activity was observed in the cerebral cortex and in the rest of the brain while the activity of SOD was reduced



to a much greater extent in the cerebellum and in the hippocampus. Likewise, the activity of P450 enzymes was found to be restored to almost control levels in the animals exposed to stress and pretreated with the higher dose of bacosides, while a lesser degree of induction, compared with animals treated with bacosides or stress alone, was observed in the animals pretreated with the lower dose of bacosides and exposed to stress. These data indicated that bacosides has potential to modulate the activities of Hsp70, P450 and SOD and allowing the brain to be prepared to act under adverse conditions such as stress^{18,19}.

Ficus religiosa

Taxonomical Classification

Kingdom: Plantae

Subkingdom: Viridiplantae

Family: Moraceae

Species: *Ficus religiosa*

Description

Ficus religiosa (L.) is a large perennial tree, found throughout the plains of India largely planted as an avenue and roadside tree especially near temples. It is a popular bodhi tree.

It has got mythological, religious, and medicinal importance in Indian culture. Traditionally the bark is used as an, antiviral, astringent, antidiarrhoeal, antibacterial, antiprotozoal, in the treatment of gonorrhoea, ulcers, and the leaves used for skin diseases. The leaves reported antivenom activity and regulates the menstrual cycle. Fruits are used as laxatives, latex is used as a tonic, and fruit powder is used to treat asthma. The tree fruits in summer and the fruits get ripened by rainy season.

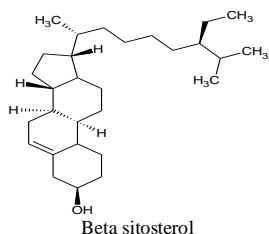
Chemical Constituents

The stem bark of *F. religiosa* are reported phytoconstituents of alkaloids and flavonoids, β -sitosterol-D-glucoside, phenols, tannins, steroids, vitamin K, n-octacosanol, methyl oleanolate, lanosterol, stigmasterol, lupen-3-one. The active constituent from the root bark *F. religiosa* was found to be β -sitosterol-D-glucoside, which showed a peroral hypoglycemic effect in diabetic rats. The fruits contain essential amino acids, isoleucine, and phenylalanine. The seeds contain phytosterolin, β -sitosterol, and its glycoside, albuminoids, carbohydrate, fatty matter, coloring matter, caoutchouc. *F. religiosa* fruits contain flavonols namely kaempferol, quercetin, and myricetin. Leaves and fruits contain carbohydrate, protein, lipid, calcium, sodium, potassium, and phosphorus. The aqueous extract of dried bark of *F. religiosa* has been reported to contain tannins, phytosterols, flavonoids, furanocoumarin derivatives namely bergapten and begapten. The fruit of *F. religiosa* contained appreciable amounts of total phenolic contents, total flavonoid, and percent inhibition of linoleic acid. Generally higher extract yields, phenolic contents, and plant material antioxidant activity were obtained using aqueous organic solvents²⁰.

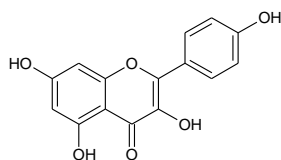
Antiepileptic Activity

F. religiosa methanolic extract of figs had anticonvulsant activity against maximum electroshock (MES) and picrotoxin induced convulsions in a dose-dependent manner. *F. religiosa* extract showed a significant protection in MES and picrotoxin induced convulsion models in a dose-dependent manner. There was a significant decrease in the duration of tonic hind limb extension at all the three doses of extract (25, 50, and

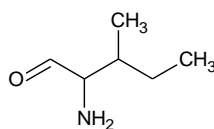
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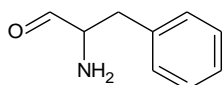
Beta sitosterol



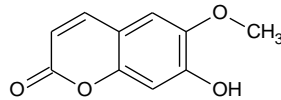
Kaempferol



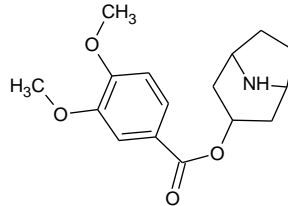
Isoleucine



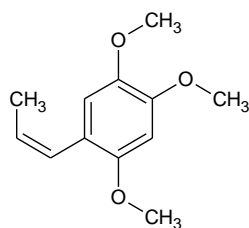
Phenyl alanine



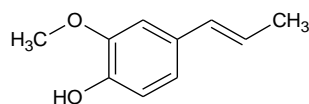
Scopoletin



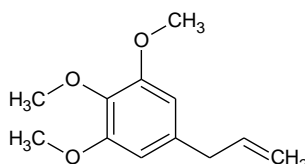
Convolvine



Alpha asarone



Isoeugenol



Elemicine

100mg/kg) in MES model with maximum protection observed at 100mg/kg dose, as compared to control group. The anticonvulsant activity of the extract at 100mg/kg was comparable to phenytoin-treated group; Treatment with extract caused a dosedependent delay of the latency to clonic convulsions in picrotoxin-induced convulsion model. Significant increase in the latency to clonic convulsions was observed only at 50 and 100mg/kg dose of extract as compared to control group. *F. religiosa* extract increased the threshold of MES and picrotoxininduced convulsions with no neurotoxic effects, in a dose-dependent manner. Extract might be mediating its effect via modulating serotonin-dependent GABAergic and/or glutamatergic neurotransmission²¹.

Antioxidant Activity

Oxidative stress in diabetes may be due to a reduction in the antioxidant status, that further increase the deleterious effects of free radicals. The aqueous extract of *F. religiosa* reduces oxidative stress in experimentally induced type 2 diabetes rats gained relatively less weight during the course of development as compared to normal rats. Decrease in uptake of glucose, free fatty acids from circulation, and accelerated β -oxidation in adipose tissue lead to weight loss in diabetes. It was found that the aqueous extract of *F. religiosa* improved the body weight of diabetic rats. Aqueous extract of *F. religiosa* enhanced

the superoxide dismutase (SOD) activity in the diabetic rats dose dependently and decreased catalase (CAT) activity. It could be possible due to less availability of NADPH or gradual decrease in erythrocyte CAT concentration by excessive generation of O_2^{++} inactivates the enzyme. Since the activity of an enzyme depends upon its substrate, depletion of glutathione (GSH) may be the reason for decreased glutathione peroxidase (GSHPx) activity. Drug at higher dose (200 mg/kg) was better effective in modulating the enzyme²².

Shankpushpi

Synonym

Sanghpushpam, Aparajit

Taxonomic Classification

Kingdom : Plantae

Sub-kingdom: Trachoeobionta

Super-division: Spermatophyta

Division: Mangnoliophyta

Class: Mangnoliopsida

Sub-class: Asteridae

Order: Solanales

Family: Convolvulaceae

Genus: Convolvulus

Species: pluricaulies

Description

Shankpushpi consist of the whole part of the plant *Convolvulus pluricaulis* of the family Convolvulaceae. The flowers are blue in color and the leaves, which are elliptic in shape, are located at alternate positions with branches or flowers.

Chemical Constituents

It mainly consist of carbohydratemaltose, rhamnose, sucrose. Other constituents include glacial acetic acid, kaempferol, Palmiticacid, Scopoletin ,Myristicacid, Sitosterol, Convolvine²³.

Anticonvulsant activity

The water soluble portion of an alcoholic extract abolished spontaneous motor activity and the fighting reaction, but did not affect the escape response; electrically induced convulsive seizures and tremorine induced tremors were antagonised by the extract. It was observed that the animals treated with the methanolic extracts of stem callus, leaf callus and entire plant (200 mg/ kg oral) showed noteworthy protection against tonic convulsion induced by transcorneal electroshock, which was also similar with that of the standard drug phenytoin. It has also been shown to possess a potent anticonvulsant activity²⁴.

Antioxidant activity

The methanolic extract of whole plant on *Convolvulus pluricaulis* exhibited considerable antioxidant activity. Another study with ethanolic extract of *Convolvulus pluricaulis* when tested in vitro showed antioxidant activity²⁵.

Jatamansi

Synonym

Musk root, Indian spikenard

Taxonomical Classification

Kingdom: Planate

Division: Mangnoliophyta

Class: Mangnoliopsida

Order: Dipsacales

Family: Valerianaceae

Genus: Nardostachys

Species: jatamansi

Description

Jatamansi consist of the roots and rhizomes of the *Nardostachysjatamansi*. It is found in Alpine Himalayas, Sikkim, Bhutan. The leaves are rosy,slightly pink or blue in color, highly agreeable and aromatic adour. Shape is elongated and cylindrical.

Chemical Constituents

It consist of sesquiterpenes and coumarins. Others are jatamansin, jatamansone, angelicin, nardostachone, volatile oil, resin, sugar, ketone, jatamansic acid, gum, semicarbazone, lupelol, Malliene, Calaren, terpenic, coumarin-jatamansin, propionate, cyclohexanalester, heptacosanyl pentanoate, diethaniod bicyclic-ketone-nardostachone are isolated from rhizomes²⁶.

Antiepileptic Activity

The roots of Jatamansi showed a significant increase in the seizure threshold against the maximal electroshock model as indicated by a decrease in the extension/flexion ratio²⁷.

Antioxidant Activity

The antiperoxidative property of jatamansi was investigated as iron-induced lipid peroxidant model in rat

liver, quantified by thiobarbituric acid reactive substance content. They have observed in their study that the extract provide protection against lipid peroxidation²⁸

Calamus

Synonym

Calamus root, sweet grass, beewort, sweet cane,

Taxonomical Classification

Kingdom: Plantae

Sub-kingdom: Tracheobionta

Super-division: Spermatophyta

Division: Magnoliophyta

Class: Liliopsida

Sub-class: Arecidae

Order: Arales

Family: Araceae

Genus: Acorus

Species: Acorus calamus

Description

It consists of the seeds and rhizomes of *Acorus calamus* of the family Araceae. It possesses grass-like or sword-shaped, long slender leaves. Cut or bruised leaves produces a sweet, tangerine-like scent. The flower stem, arises from the base of the outer leaves. The plant bears green, angular, 1 to 3seeded berries. The rhizomes of the plant are the most important part. They possess strong, characteristics and aromatic odor and a bitter in taste.

Chemical Constituents

Active constituents include flavanoids, lecetins, phenols and saponins, glycosides, sterols, terpinoids. Calamenone (a tricyclic sesquiterpene) as well as calamendiol and isocalamendiol (both sesquiterpenes) also occur in the roots. The oil's constituents include acoramone and phenylpropane derivatives like α -asarone, β -asarone, γ -asarone, elimicine, isoeugenol, spathulenol and methyl ether²⁹.

Antiepileptic Activity

The aqueous and alcohol extracts were found to reduce the severity of maximum electro shock –induced seizures in rats. The essential oils showed a protective effect against electro shock seizures in rats.

Antioxidant Activity

The ethyl extract was found to be a potent antioxidant by inhibition of 1,1-Diphenyl-2-picrylhydrazyl(DPPH) free radical. In vitro antioxidant activity by DPPH scavenging at three different concentrations showed a maximum activity of 86.43% at 0.2g/ml³⁰.

CONCLUSION

Medicinal plants are the oldest form of healthcare known to mankind. They have been used by all cultures throughout history. Plants are valuable sources of secondary metabolites, which exerts a wide range of pharmacological effects. This review has focused on the plant drugs with both antioxidant and antiepileptic property. Antioxidants are considered to be important in fighting against the damages done by the free radicals produced due to oxidative stress. Antiepileptic drugs help to minimize or to irradiate the convulsive shocks and seizures as a result of abnormal and excessive nerve cell activity. Standardized, well established in vitro and in vivo

methods are available for experimental evaluation of antioxidant and antiepileptic agents. A step wise procedure from in vitro and in vivo seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing. Further studies have to be conducted to find out the mechanism of action and the molecules responsible for the antioxidant and antiepileptic activity of these drugs. This study will help in the formulation of potent antiepileptic drugs with minimum side effects.

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