



Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb



Document heading doi:10.1016/S2221-1691(13)60028-3 © 2013 by the Asian Pacific Journal of Tropical Biomedicine. All rights reserved.

Pharmacognosy of *Enicostemma littorale*: A reviewRajamani Saranya¹, Thirunavukkarasu Thirumalai², Munisami Hemalatha¹, Ranganathan Balaji¹, Ernest David^{1*}¹Department of Biotechnology, Thiruvalluvar University, Serkadu, Vellore-632115, Tamilnadu, India²Post graduate and Research Department of Zoology, Physiology Wing, Voorhees College, Vellore-632001, Tamilnadu, India

ARTICLE INFO

Peer reviewer

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Comments

The article is well presented with sufficient study results and imbibing traditional value of *E. littorale*.

(Details on Page 83)

ABSTRACT

Traditional medicine system of India comprised varieties of plants which are playing a significant role in curing diseases from ancient times. Among them, *Enicostemma littorale* blume (*E. littorale*) a perennial herb of the family Gentianaceae is cosmopolitan in occurrence in India. The bitter natured plant acts as a laxative, helps in curing fever, rheumatism, skin diseases, abdominal disorders, snake bite, obesity and helps to regulate blood sugar levels. The plant constituents have been reported for possessing antimicrobial, antioxidant, antiulcer, antiinflammatory, hypolipidaemic, hepatoprotective and hypoglycemic properties. This review provides a bird's eye view about geographical distribution, physicochemical parameters, phytoconstituents and pharmacological properties of *E. littorale*.

KEYWORDS

Enicostemma littorale, Folklore, Hypoglycemic, Medicinal plant

1. Introduction

The use of different parts of the medicinal plant in traditional medicinal system *viz.*, Ayurveda, Siddha and Unani to treat various ailments is in vogue for several centuries. Medicinal plants act as an alternative source for treating several ailments since their usage is increasing day by day^[1]. Approximately 72 000 plant species were estimated for having medicinal properties. Of which, India recognizes 3000 plant species for having medicinal values. *Enicostemma littorale* Blume (*E. littorale*) plays a vital role in human healthcare. The plant parts of *E. littorale* such as leaves, roots were used in traditional practice for treating several ailments like malaria, skin diseases, leprosy, diabetes *etc.* The leaf possesses hypoglycemic, antioxidant, hepatoprotective and hepatomodulatory properties and helps in reducing obesity^[2]. Medicinal compounds derived from this plant were considered to be very effective since these were less toxic, eco-friendly, palatable, long shelf

life and free from side effects^[3]. *E. littorale* is a good source of iron, potassium, sodium, calcium, magnesium, silica, chloride, sulphate, phosphate and vitamins B and C^[4]. According to the World Health Organization (WHO), herbal medicines serve the health needs of about 80% of the world's population, especially for millions of people in the vast rural areas of developing countries^[5].

2. Uses in folklore medicine

E. littorale is traditionally used in India as a stomachic, bitter tonic, carminative to reduce fever^[6] and as a tonic for appetite loss^[7]. In Indian ayurvedic medicine, *E. littorale* is taken in combination with other herbs, especially for diabetes. *E. littorale* is administered in ayurvedic pill form for treating type 2 diabetes since it plays a major role in reducing blood glucose and increases serum insulin level and significantly improves kidney function, lipid profile,

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Article history:

Received 18 Oct 2012

Received in revised form 23 Oct, 2nd revised form 27 Oct, 3rd revised form 3 Dec 2012

Accepted 31 Dec 2012

Available online 28 Jan 2013

systolic and diastolic blood pressure and pulse rate^[8]. *E. littorale* has demonstrated its anti-inflammatory activity, and tumour inhibition in rats^[9,10], and the plant possesses a secondary compound namely swertiamarin which shows central nervous system (CNS) depressant effects in rats^[11]. Nampalliwar and Godatwar observed that *E. littorale* enhances glucose-dependent insulin release^[12]. The hot aqueous extract of *E. littorale* has also been used by the traditional healers for the treatment of dyspepsia and malaria^[3].

3. Taxonomy

Kingdom:	Plantae
Subdivision:	Angiospermae
Class:	Dicotyledonae
Subclass:	Gamapetalae
Serius:	Bicarpellatae
Order:	Gentianales
Family:	Gentianaceae
Genus:	Enicostemma
Species:	Littorale

Nomenclature: The word *Enicostemma* is probably formed from the three words, “en” means inside, “icos” means 20 and “stemma” means wreath or circle due to the many flowers arranged in circles in the leaf axils along the stem.

4. Vernacular names

The ayurvedic name of *E. littorale* is Nahi, Maja–Makka booti, Vellarugu in Tamil, Vallari in Malayalam, White head in English, Chikka chiraayuta in Kanada, Mamajjakah in Sanskrit, Mamejavo in Gujarati, Nagajivha in Bengal, Chota chirayata in Hindi, Kaviyatu in Hindustani, Nela–guli in Telugu.

5. Geographical distribution

This tropical genus is widely distributed in South America, Africa, and Asia. *E. littorale* grows in many diverse habitats from savannas, grasslands, forests to beaches, from wet to very dry and also survives in a very saline environment.

6. Morphology of *E. littorale*

E. littorale is an erect, perennial herb, 5–30 cm tall, simple or branched at the base. Stem cylindrical, glabrous with a decurrent ridge below each leaf. Leaves are sessile sometimes narrowed into a petiole-like base, longer than the internodes; lamina (5.0–8.0×0.3–1.0)cm, linear to lanceolate or narrowly oblong, entire, obtuse and mucronate at the apex, somewhat narrowing towards the base, 3-nerved from the base, glabrous. Inflorescence in many flowered auxiliary clusters, numerous in the axils of each pair of leaves. Flowers are white with green lines, drying yellowish, sessile or subsessile; bracts long, shorter than the calyx, lanceolate–acuminate, carinate.

Calyx tube 1–2 mm long; lobes usually unequal, (0.7–1.5×0.4–0.7)mm, triangular to lanceolate, acute at the apex and narrowly scarious at the margin, or obovate to subcircular,

obtuse and mucronate at the apex, with wide scarious margin. Corolla tube 3.5–6.0 mm long; lobes (1.5–2.0×0.7–1.0)mm, ovate and abruptly narrowing to an acute or mucronate apex. Stamens inserted below the sinuses, just above the middle of the tube; filaments 1.5–2.3 mm long, with a double hood at the insertion point^[13].

7. Nutritional information

Daily uptake of 2 g of *E. littorale* fresh leaves is recommended for diabetic patients since its highly nutritious^[8]. The nutritional analysis report of Indian Council of Medical Research suggests that 100 g of fresh *E. littorale* contains 140 kcal energy, 7 g of protein, 0.7 g of fat, 26.5 g of carbohydrate, 4.2 g of fibre, 8.4 g of minerals, 49.9 mg of iron, 1.641 mg of calcium, 81 mg of phosphorus^[4].

8. Physicochemical properties of *E. littorale*

The physicochemical properties of powdered leaves of *E. littorale* were evaluated and summarised in Table 1. The values were expressed in w/w^[14].

Table 1

Physicochemical parameters obtained by using the leaves of *E. littorale*.

Parameters	Values (%w/w)
Loss on drying	0.198
Ash value	11.960
Water soluble extractive	27.650
Alcohol soluble extractive	24.570

9. Phytoconstituents of *E. littorale*

This plant comprises of different chemical compounds. Many compounds have been isolated from the plant, *E. littorale*. Tanna *et al.* reported that the aerial part of the plant gave 34% of dry alcoholic extract and 15.7% of ash^[15]. The presence of minerals like iron, potassium, sodium, calcium, magnesium, silica, phosphate, chloride, sulphate and carbonate were estimated in the qualitative analysis of ash. Natarajan and Prasad reported the presence of five alkaloids, two sterols and volatile oil^[7]. Betulin, a triterpene saponin was also isolated by earlier workers^[16]. Monoterpene alkaloids like enicoflavin, gentiocrucine and seven different flavonoids were isolated from the alcoholic extract and the structures were identified as apigenin, genkwanin, isovitexin, swertisin, saponarin, 5–o glucosylswertisin and 5–o glucosylisoswertisin were also isolated by Goshal *et al.*^[17]. The presence of catechins, saponins, steroids, saponin, triterpenoids, flavonoids and xanthenes and a new flavone C–glucoside named as Verticilliside was isolated for the first time this species was reported by Jahan *et al.*^[18]. Swertiamarin compound was isolated from *E. littorale* by using alcoholic extract^[19]. Six phenolic acids like vanillic acid, syringic acid, p–hydroxy benzoic acid, protocatechuic acid, p–coumaric acid and ferulic acid were also found by Desai *et al.*^[20]. Methanol extract of *E. littorale* was found to be containing different aminoacids like L–glutamic acid, tryptophane, alanine, serine, aspartic acid, L–proline, L–tyrosine, threonine, phenyl alanine,

L-histidine monohydrochloride, methionine, iso leucine, L-arginine monohydrochloride, DOPA, L-Glycine, 2-amino butyric acid and valine^[21].

Swertiamarin is a representative constituent of many crude drugs, which are marketed in Japan and other countries and these crude drugs are normally evaluated by their high swertiamarin content^[22,23].

10. Pharmacological properties of *E. littorale*

10.1. Antimicrobial activity of *E. littorale*

Tanna *et al.* reported the antifungal activity of *E. littorale* blume^[15]. The chloroform extract shows pronounced activity against *Aspergillus niger* (*A. niger*) and negligible activity against *Candida albicans* (*C. albicans*) at the concentration of 100, 200 μ g/mL. The ethyl acetate extract shows slight activity against *A. niger* and moderate activity against *C. albicans*. The ethanol extract shows pronounced activity against *A. niger* and *C. albicans*.

Praveena *et al.* observed that the antimicrobial activity of *E. littorale* against many pathogenic microorganisms by using different solvents like chloroform, ethyl acetate, methanol, petroleum ether^[24]. Among that methanolic and ethyl acetate extract of *E. littorale* showed a prominent antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella sonnei* and antifungal activity against *Aeromonas hydrophila*, *C. albicans*.

10.2. Anthelmintic activity of *E. littorale*

Mishra and Shukla reported that *E. littorale* exhibits anthelmintic effects. Petroleum ether and ethanolic extracts of aerial parts of *E. littorale* Blume were prepared and evaluated separately for finding an anthelmintic effect on adult Indian earthworm, *Pheretima posthuma*^[25]. Five different concentrations of each extracts were used in this anthelmintic activity, in which the time of paralysis and death of the worm were determined. The results indicated that an ethanolic extract of *E. littorale* was more potent than the petroleum ether extract.

10.3. Antinociceptive effect of *E. littorale*

Many traditional Indian medicinal plants which contain large quantity of secoiridoid, swertiamarin are being used to relieve pain. Iridoids present in a wide variety of medicinal plants possess a large number of medicinal properties. In the study by Jaishree V, *in vivo* anti-nociceptive activity of swertiamarin isolated from *E. axillare* was carried out using three different methods in mice^[26]. In the hot plate method, a significant increase in the latency period was observed for the treatment with swertiamarin at 100 and 200 mg/kg body weight after 30 and 45 min. The percent protection observed after 45 min was 109.42, 147.42 and 157.14, respectively, for the standard paracetamol and swertiamarin at 100 and 200 mg/kg body weight treatments. A significant increase in the tail withdrawal reflex was observed for the swertiamarin treatment at both the doses with percent protections of 150 and 200, respectively. In both these methods, swertiamarin showed potent activity than standard paracetamol. In the acetic acid induced writhing,

swertiamarin at 100 and 200 mg/kg body weight reduced the number of writhes significantly. Dose dependent results were observed in all the three methods and among the two doses, swertiamarin at 200 mg/kg body weight showed potent activity. These results proved that swertiamarin from *E. axillare* possess both peripheral and central antinociceptive activity^[26].

10.4. Antioxidant activity of *E. littorale*

Hyperlipidaemia is an important complication of alcohol induced liver injury since it accumulates cholesterol and triglycerides in the liver as well as in the blood leads to several complications^[27]. Thirumalai *et al.* investigated the hyperlipidaemic condition and antioxidant effects on hepatically injured male albino rats (ethanol induced) by treating with aqueous leaf extract of *E. littorale* at a dosage of 250 mg/kg body weight. After administration of aqueous leaf extract of *E. littorale*, levels of cholesterol, triglycerides and free fatty acids were decreased in serum and the activity levels of TBARS and lipid peroxidation levels were decreased and SOD, CAT, GPx were increased in liver tissue. He reports that an aqueous leaf extract of *E. littorale* blume has potent restorative effect on hyperlipidaemic and oxidative stress.

Clinically the usages of aminoglycosidic antibiotics were limited since it induces the nephrotoxicity. Oxidative stress is the main reason for this complication. Mukundray *et al.* investigated the role of *E. littorale* Blume as a promising antioxidant therapy in gentamicin induced nephrotoxicity in rats^[28]. Gentamicin treated animals showed high oxidative stress in mitochondrial as well as post-mitochondrial fractions of renal tissues as evidenced by increased lipid peroxidation levels, activities of antioxidant enzymes, SOD and GPx. Treatment with *E. littorale* ameliorates antioxidant defense system of mitochondrial as well as postmitochondrial fraction, with better improvement seen in mitochondrial fraction. *E. littorale* extract was used in antioxidant therapy to counteract mitochondrial and post-mitochondrial oxidative stress generated in kidney upon gentamicin treatment, thus prevented nephrotoxicity.

10.5. Antiulcer and anti-inflammatory activity of *E. littorale*

The aerial parts of *E. littorale* against aspirin, ethanol and pyloric ligation induced ulcers in rats and bovine serum albumin (BSA) denaturation were examined for antiulcer and anti-inflammatory effects by Roy *et al.*^[29]. The extract was administered to the overnight fasted rats, one hour prior to aspirin or alcohol or pyloric ligation challenge. The ulcer index, tissue GSH levels and lipid peroxidation levels in all the models of ulcers and the volume of gastric secretion, acidity and pH were estimated in the pyloric ligation model of ulcers. Pre-treatment with the aqueous extract of *E. littorale* showed a dose-dependent decrease in the ulcer index against aspirin, ethanol challenge and pyloric ligation. The prior administration of the aqueous extract also reduces the total acidity, free acidity, volume of gastric secretion and elevated the gastric pH. In addition, it was also observed that the aqueous extract inhibits the serum albumin denaturation in a dose-dependent manner. It was reported that the methanolic extract of *E. littorale* possesses antiulcer activity. And its anti-inflammatory activity may be attributed to the antioxidant potential.

10.6. Antitumour activity of *E. littorale*

The antitumour activity of methanolic extract of *E. littorale* has been evaluated against Dalton's ascitic lymphoma (DAL) in Swiss albino mice by Kavimani *et al.* A significant enhancement of mean survival time of methanolic extract of *E. littorale* treated tumour bearing mice was found with respect to control group. Treating with methanolic extract of *E. littorale* enhances peritoneal cell counts. When these methanolic extract of *E. littorale* treated animals underwent intraperitoneal inoculation with DAL cells, tumour cell growth was found to be inhibited. After 14 days of inoculation, methanolic extract of *E. littorale* is able to reverse the changes in the haematological parameters, protein and PCV consequent to tumour inoculation^[11].

10.7. Hepatoprotective activity of *E. littorale*

Paracetamol induced hepatic injury is commonly used as an experimental model for the study of hepatoprotective effects of medicinal plant extracts and drugs. The histological evaluation and the level of various biochemical parameters in circulation indicated the level of hepatic injury. Highly reactive trichloro free radical formation, which attacks polyunsaturated fatty acids of the endoplasmic reticulum, is responsible for the hepatotoxicity of paracetamol. It produces hepatotoxicity by altering liver microsomal membranes in experimental animals. The study by Gite *et al.*^[30] revealed that the extract was able to reduce all the elevated biochemical parameters since it has hepatotoxin detoxication property. *E. littorale* possesses a chemical compound called swertiamarin which has antioxidant and hepatoprotective properties against D-GalN induced hepatotoxicity given at 100 and 200 mg/kg body weight orally for 8 days, which might be due to its *in vitro* antioxidant activity^[31]. The present investigation indicates that the ethanolic extract of *E. littorale* exhibits significant hepatomodulation against oxidative stress induced liver injury by CCl₄ in rats through antioxidant potential and free radical scavenging activities along with reduction of fat metabolism^[13]. These attributes provide the rationale for the use of *E. littorale* in liver disorders by traditional healers in India^[32].

10.8. Hepatomodulatory activity of *E. littorale*

The hepatomodulatory response of ethanol extract of *E. littorale* Blume were examined for oxidative stress induced liver injury by carbon tetrachloride (CCl₄) in albino wistar male rats. The rats were administered with an extract, orally at the doses of 125, 250 and 500 mg/kg bodyweight per day for 21 consecutive days along with CCl₄ at the dose of 0.2 mL/kg body weight twice a week with intraperitoneal administration of olive oil, in the ratio of 1:1 treatment. The rats subjected only CCl₄ with olive oil, showed remarkable oxidative stress induced liver injury. Supplementation of *E. littorale* extract significantly increases glutathione, GPx, SOD, CAT, and vitamin-C in the liver, with a dose-dependent reduction of the TBARS as evidenced by reduced lipid peroxidation, total cholesterol and triglycerides levels in hepatic cells and it was significantly depleted in the treated group when compared to that of control group. Further, the hepatic marker levels aspartate transaminase

and alanine transaminase, alkaline phosphatase, acid phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase, sorbitol dehydrogenase, total bilirubin, total protein and albumin in serum were also restored to normal level dose-dependently after the supplementation of *E. littorale* extract in comparison to respective controls. Gupta *et al.* suggested that hepatomodulation by *E. littorale* Blume against oxidative stress mediated through interference with free radical generation and reduction in fat metabolism^[13].

10.9. Antihyperlipidaemic activity of *E. littorale*

The aerial part of the *E. littorale* reduces the serum cholesterol level in hepatoma bearing rats which induces hypercholesterolaemia. A component of plant enhances cholesterol acyltransferase by esterification of free cholesterol in the HDL^[33]. A new study demonstrates a new property of swertiamarin as a potent lipid lowering agent when compared to atorvastatin and it may also contributes cardioprotective and antiatherosclerotic effects. The swertiamarin and atorvastatin when orally fed also lowered the total serum cholesterol and triglycerides^[34]. Hypolipidaemic and antioxidant effects were evaluated by administering an aqueous extract of *E. littorale* to rats (1.5 g/100 g body weight/day) along with hypercholesterolaemic diet for 6 weeks. The treatment with this extract decreases the activities of erythrocyte CAT, SOD and LPO levels, with an increase in reduced glutathione levels, liver and kidney cholesterol levels were also decreased in *E. littorale* treated rats when compared to cholesterol fed untreated rats^[35].

10.10. Hypoglycemic activity of *E. littorale*

The effect of an aqueous *E. littorale* whole plant extract on antioxidant defense in alloxan-induced diabetic rats was observed by Prince and Srinivasan^[36]. A significant increase in blood glucose, TBARS and hydroperoxides in liver, kidney and pancreas, with an decreased concentration of reduced glutathione and suppressed activities of SOD, CAT and GPx were also observed in alloxan induced diabetic rats. Treating diabetic rats with oral administration of aqueous *E. littorale* whole plant extract daily for 45 days significantly decreases the blood glucose, TBARS, SOD, CAT and GPx. The effectiveness of *E. littorale* extract was compared with standard drug insulin. It was observed that an administration of insulin (6 units/kg) to alloxan induced diabetic rats for 45 days brought back all the parameters to near normal status. *E. littorale* extract at the dose of 2 g/kg was more effective. Hence it can be tried in clinical purpose to overcome these complications.

Vishwakarma *et al.* standardized the dose dependent effect with hot and cold aqueous extracts of *E. littorale* for three weeks in STZ induced type 1 diabetic rats^[37]. Treatment of diabetic rats with STZ significantly produced the carnial signs of diabetes-mellitus like weight loss, polyuria and polydipsia, increased the fasting blood glucose level and AUC glucose associated with decrease in insulin level. Treatment of diabetic rats with hot aqueous extract of *E. littorale* reduced the food, water intake and glucose and AUC glucose levels and decreased the serum glucose, serum cholesterol and triglyceride levels. TLC finger-print profiles were established for the aqueous extract using high performance thin layer chromatography. Swertiamarin was found to be a major component in hot extract of *E. littorale*

while it was absent in cold extract. The result suggested that *E. littorale* possesses potential antidiabetic activity and improves lipid profile at a dose of 0.5 g/kg.

10.11. Antihyperinsulinemic activity of *E. littorale*

Insulin resistance is responsible for the development of hyperglycemia in NIIDM patients. Aqueous extracts of *Aegle marmelos* and *E. littorale* reduces hyperglycaemic conditions in diabetic animal. Insulin resistance was induced in wistar rats by fructose rich diet (60% for 15 days). Treated groups received fructose diet plus aqueous extracts *A. marmelos* (500 mg/kg/day) and *E. littorale* (2 g/kg/day). Body weight, serum glucose, insulin, C-reactive protein and triglycerides levels were estimated after treating with an extract. Gohil *et al.* reported that the fructose feeding for 15 days significantly increased the serum glucose, insulin, C-reactive protein and triglycerides levels compared to control^[38]. Administration of aqueous extracts of *A. marmelos* and *E. littorale* for 15 days prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose.

10.12. Diabetic neuropathy activity of *E. littorale*

Poor glycaemic control and oxidative stress is one of the main reasons for the development of diabetic neuropathy. The protective effects of *E. littorale* Blume was investigated for hypoglycemic and antioxidant effect in alloxan induced diabetic neuropathy in male Charles foster rats by Bhatt *et al.*^[39]. Nociceptive responses were compared by formalin and tail flick in hot immersion test in both diabetic and non diabetic rats. Treating with *E. littorale* extract for 45 days significantly improved nociception in diabetic rats. The changes in lipid peroxidation and antioxidant enzymes like SOD, GPx and CAT levels, decrease in Na–K⁺ ATPase activity were also restored by *E. littorale* treatment. This study provides an experimental evidence for the preventive effect of *E. littorale* on nerve function and oxidative stress in animal model of diabetic neuropathy. Hence, *E. littorale* may be clinically tried for treating diabetic neuropathy since it was used as a folklore medicine in diabetic patients.

10.13. *E. littorale* as a new target for islet neogenesis

Gupta *et al.* highlighted an islet neogenic property of one herbal plant *E. littorale* Blume^[40]. An active herbal compound SGL–1 was isolated and purified from extract of *E. littorale* and used to differentiate two model stem cell lines PANC–1 and NIH3T3 which showed tremendous islet neogenic potential and significant islet yield compared to control serum free medium. Morphological, molecular and immunological characterization of newly generated islet like cellular aggregates proved them differentiated and positive for islet hormones. Functional characterization of ICA's confirmed significant glucose responsive insulin release. This preliminary data does offer exciting possibility of alternate source for increasing islet mass which can be used for the treatment of diabetic patients.

11. Conclusions

This review furnishes the presence of several

phytochemical components in *E. littorale* and its pharmacological properties. The recent evidences shows an effective role of swertiamarin, a phytochemical compound derived from *E. littorale*. It also showed anti-inflammatory, antimalarial, hepatomodulatory, hepatoprotective, antihyperglycemic, hypoglycemic, antioxidant, antitumor, hypolipidemic and antihelminthic activities of *E. littorale*. This review may focus scientists to develop clinical studies which might be of great scientific contribution for the society. The importance of medicinal plants in traditional healthcare practices provides clues to new areas of research and in biodiversity conservation.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

Authors are thankful to Department of Biotechnology, Thiruvalluvar University, Vellore, Tamilnadu for providing facilities during preparation of this article.

Comments

Background

E. littorale Blume has been used in traditional medicine system for various ailments. Several workers conducted systematic scientific study on the usage of different parts of the plant in curing diseases.

Research frontiers

E. littorale usage in traditional medicine and the systematic study of various plant parts and their active ingredients against various ailments are well documented.

Related reports

The article is well documented with folklore medicinal properties which lead to a systematic study on their efficacy and isolation of active ingredients.

Innovations and breakthroughs

The various medicinal uses against various ailments of the parts of *E. littorale* were recorded consistently for reference and for further probe.

Applications

This article could help to lead to the discovery of new plant based drugs.

Peer review

The article is well written and presented with sufficient study results.

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