Pharmacological screening of *Eryngium foetidum* Linn – A Review

**Abstract**

*Eryngium foetidum* L. (Family Apiaceae) is a biennial herb, and it is used as a culinary herb and spice across the different countries of the world, including Sri Lanka, India, Bangladesh, Malaysia, Singapore, etc. due to its high aroma quality. Also, it is used to treat several ailments, such as respiratory diseases, gastrointestinal ailments, and skin diseases among different indigenous populations for its medicinal properties. Based on ethnomedical evidence, many studies have been conducted to identify the phytoconstituents, underlying mechanisms, and related pharmacological effects of different parts of this plant. This study reviewed the current state of findings related to the Pharmacological activities of *E. foetidum*. Based on this review, this plant is widely used for ethnomedical and culinary purposes. Pharmacological screening of the plant revealed that it had different activities such as anti-inflammatory, antioxidant, antimicrobial, anthelmintic, anticonvulsant, anticancer, anti-diabetic, antimalarial, larvicidal, and hepatoprotective activities. This review further promised that potential new chemical entities could be elicited from the phytoconstituents of *E. foetidum*.

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**INTRODUCTION**

*Eryngium* is the largest and most complex genus in the Apiaceae family, and it includes more than 250 flowering species worldwide. Under this genus, the most studied species have been *Eryngium foetidum* L., cultivated in Asian countries such as Iran, Turkey, Europe, Tropical Africa, and Pacific islands. *Eryngium foetidum* is native to Tropical America and the West Indies. It is used as a culinary herb and spice globally, including in Sri Lanka, India, Bangladesh, Malaysia, Singapore, and others. *Eryngium foetidum* is also considered a general edible food component in Nigeria. *Eryngium foetidum* is commonly known as ‘spiny coriander’, ‘spirit weed’ or ‘saw-tooth coriander’ and is also called in different countries as *langer koriander* (German), *ketumbar java* (Malay); *pak chi funang* (Thai); *ngo gai* (Vietnamese); *cilantro, naco, reco* (Spanish); *Bahākhaur* (India) and *andu kola* (Sri Lanka). The leaves of this plant are frequently used interchangeably with *Coriandrum sativum* L. due to their similar pungent aroma character. It treats several ailments, such as respiratory diseases, gastrointestinal ailments, and skin diseases, by different indigenous systems.

A review study stated that the technology for mass production is available for this plant, cultivated for commercial purposes. Simultaneously, it is easily propagated by seeds (germinate in 20–25 days) in spring or suckers during monsoon. The seedlings are ready to transplant in 45–50 days after seed sowing. In Bangladesh, a research study provides a baseline of...
information concerning this plant’s cultivation techniques, market potential, and climate resilience. Based on ethnomedical evidence, many studies have been explored phytoconstituents, underlying mechanisms, and related pharmacological effects of the different parts of this plant. Still, many compounds actively responsible for different pharmacological effects of this plant are yet to be detected. Even though some therapeutic effects have been elicited using in vitro models, further studies will be needed to correlate these activities using in vivo models. This study reviews the current state of findings related to the Pharmacological screening of *E. foetidum*.

**PLANT CLASSIFICATION**

Classification and local names of *E. foetidum* are presented in Table I. This plant also has several synonyms, with many local names from various parts of the world. However, in general, this plant is better known as long coriander.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Identity</th>
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<tbody>
<tr>
<td>Domain</td>
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<td>Tracheophyta</td>
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<td>Magnoliopsida</td>
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<tr>
<td>Genus</td>
<td>Eryngium</td>
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<td>Species</td>
<td><em>Eryngium foetidum</em> L.</td>
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<tr>
<td>Synonyms</td>
<td><em>Eryngium antihystericum</em> Rottler, <em>Eryngium molleri</em> Gand</td>
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<tr>
<td>Common name</td>
<td>Long coriander, wild coriander, fitweed, culantro, Mexican coriander</td>
</tr>
<tr>
<td>English name</td>
<td>Long coriander/Sea Holly</td>
</tr>
</tbody>
</table>

**BOTANICAL DESCRIPTION**

*Eryngium foetidum* is a leafy herb and distributed in the tropical zone of the world. It is indigenous to tropical zones such as America and Caribbean islands, from southern Mexico to Panama via Brazil and from Cuba to Trinidad. It is generally grown in tropical areas like Africa, South Asia, Southern Europe, and the Pacific islands. It is extensively cultivated in Costa Rica and Puerto Rico for its usage and exporting to the US.

A biennial pungently smelling herb and *E. foetidum* (Figure 1) consists of fleshy waxy in nature, oblanceolate shape, 30 cm long and 4 cm broad serrated or dentate margin with dark green leaves; each tooth of the margin has a slight yellow spine spirally arranged around a short thick stem from a basal rosette. Flowers white, sessile and bisexual, white, narrow, oblonged and notched petals; corolla-creamy white with green calyx, sepals are tubular, acute, persistent, longer than petals and forming an umbel inflorescence on a long stalk, which arises from the leaf rosette at the bottom; fruits are globose to ovoid and evenly branched fibrous roots.

![Figure 1. Eryngium foetidum plant](image)

**TRADITIONAL-ETHNOMEDICAL USE**

*Eryngium foetidum* has been widely used in Southeast Asian countries, Caribbean islands, and Latin America, where its harvested leaves are commonly used in foods. In traditional medicine, the leaves and roots have been used to treat insanity, skin diseases, mucosal diseases, pulmonary ailments, diabetes mellitus, stomach disorders, and conditions related to the nervous system, such as convulsions, paralysis, spasms, and pains. Moreover, it is used as a vermifuge and febrifuge.
Eryngium foetidum has been used to treat colds and fever, burns, earache⁵¹, pneumonia, flu, convulsions in children, malaria⁵², hypertension, constipation, worm infections, and infertility complications⁵³. The roots have stomachic, sudorific, and diuretic effects⁵³⁴, where leaf juice/decoction stimulates the gut as a laxative⁶. It was also reported to treat several poisons, including the treatment of snake bites and scorpion-sting venom⁴⁵. In West Africa, aerial parts of this plant were used to treat respiratory diseases (asthma, cough, cold, and sinusitis), gastrointestinal ailments such as diarrhea, and crushed leaves in heated palm oil to treat rheumatism¹⁵. Tea or infusions prepared from the leaves of this plant were used as an inhalation to alleviate respiratory disorders¹². In traditional Chinese medicine, E. foetidum is widely used for the treatment of inflammation².

PHYTOCHEMICAL ANALYSIS

Phytochemical screening of this plant found several secondary metabolites such as flavonoids, phenols, tannins, saponins, ascorbic acid, and terpenoids⁶⁶. Leaves are an excellent source of vitamin A¹⁸. Mabeku et al.¹⁹ found that the methanol extracts of leaves of E. foetidum contained alkaloids, phenols, flavonoids, anthraquinones, and sterol. However, another study explored the presence of flavonoids, tannins, saponin, coumarins, and triterpenoid and the absence of alkaloids in the plant’s leaves¹⁴. The chloroform extracts of dried aerial parts by soxhlet extraction followed by chromatographic fractionation yielded a pentacyclic triterpenoid saponin and O-glycoside¹⁷. Some free triterpenoids were too identified from leaves’ hexane extract, including stigmasterol-the main phytosterol¹². Eryngium foetidum is a rich source of phenolic compounds⁵,⁵⁴,⁵⁵. Leitão et al.⁵⁶ found that the E. foetidum leaves showed major carotenoids as all-trans-lutein and all-trans-β-carotene and major phenolic compounds as chlorogenic acid and ferulic acid. The major constituent (E)-2-dodecenal with 14 compounds was identified in chloroform and methanol leaf extracts of E. foetidum via HPLC analysis. Moreover, another study found that the ethanolic extracts E. foetidum shows higher flavonoid contents²⁷.

Dried leaves yielded 0.1 to 0.95% of essential oil³⁸. Gas chromatography-mass spectroscopy (GC-MS) analysis of essential oil identified 63 different compounds²⁴. The linear unsaturated aldehyde, (E)-2-dodecenal was reported as the main constituent in the aldehydes, which were identified as the major constituents of the essential oil of E. foetidum⁶,¹²,¹³,²⁵,²⁶,²⁸,²⁹,³⁰. A study showed that the (E)-2-dodecenal was responsible for the fruity, sweet, sour, and characteristic “cilantro” aroma of this plant with the highest flavor dilution factor³³. The monoterpane hydrocarbons⁵ and positional isomers of trimethylbenzaldehyde²⁹ were present as the highest constituents from the stem and root essential oil of E. foetidum, respectively.

Seeds of E. foetidum yielded 0.2% of essential oil in which carotol (19.3%) was identified as the main constituent³⁴. Acharya et al.³⁵ investigated the phytochemical analysis of E. foetidum found in coastal Odisha, India, and revealed that leaves and branches of E. foetidum consisted of chiefly 10-undecenal followed by 2,4,6-trimethylbenzaldehyde, (Z)-9-tetradecenal, and (Z)-7-tetradecenal. This study further suggested that the chemo profile of E. foetidum and seasonal C. sativum were the same, and E. foetidum can be used as an alternative to seasonal C. sativum. Structures of different chemical constituents of the leaves, stem, and root of E. foetidum were given in the appendix³²⁴,³⁵⁴.

PHARMACOLOGICAL ACTIVITIES

Some compounds like (E)-2-dodecenal or ‘Eryngial,’ which present abundantly in E. foetidum, revealed to have
multiple bio-activities, and numerous studies revealed that the *E. foetidum* has anti-inflammatory, antioxidant, antimicrobial, antifungal, anti-helminthic, anti-tumor, anti-diabetic, antimalarial larvicidal and anticonvulsant activities. These activities are summarized in Table II.

**Anti-inflammatory activity**

Several studies explored the anti-inflammatory activity of the plant with pathways of mechanisms responsible for the activity\(^3\). The hexane extract from the leaves of *E. foetidum* has shown possible anti-inflammatory activity\(^4\). Prior treatment with ethanol extract of *E. foetidum* leaf inhibited the elevation of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX-2), together with their cognate messenger ribonucleic acid (mRNAs) in a dose-dependent manner. Nitric oxide (NO) and intracellular reactive oxygen species (ROS) contents were similarly reduced. This result suggested that *E. foetidum* leaf extract possesses suppressive effects on pro-inflammatory mediators, and the plant has the potential to reduce the risk of cancer associated with inflammation\(^7\). Leaf extract of *E. foetidum* consisted of lutein, β-carotene, chlorogenic acid, kaempferol, and caffeic acid, which had bioactive properties\(^8\). The aqueous bioaccessible fraction of leaves of *E. foetidum*, prepared from simulated digestion, has inhibited IL-8 and MCP-1 levels in the human intestinal Caco-2 cells, which were stimulated with interleukin-1β (IL-1β). Here, lipophilic constituents such as lutein and beta-carotene had a major role in the anti-inflammatory activity. Further study suggested that the consumption of *E. foetidum* could prevent intestinal inflammation\(^6,36\).

The topical anti-inflammatory activity of *E. foetidum* was studied in the TPA-induced mice; it was evident with the inhibition of myeloperoxidase (MPO) enzyme activity by hexane extract of *E. foetidum*\(^8\). Oral administration of decoction of *E. foetidum* inhibited carrageenan-induced edema in rat paws and TPA-induced edema in the ears of mice. Further, this extract potently inhibited the abdominal writhing induced by acetic acid\(^4\). In India, the North East Institute of Science and Technology developed a drug formulation for treating arthritis and skin disease in which the essential oil of *E. foetidum* is one of the main components\(^4\).

**Antioxidant activity**

Numerous studies have been conducted to evaluate the antioxidant activity of the plant. A study revealed that pretreatment with *E. foetidum* leaf extract (35-140 µg/ml) inhibited ROS generation mediated by NADPH oxidase in lipopolysaccharide (LPS)-induced mice\(^7\). Ethanol extract of the *E. foetidum* leaves exhibited 51.44% radical scavenging activity, correlated with a high level of phenolic and flavonoid contents\(^9\). Amazonian *E. foetidum* has shown that the scavenging capacity of methanol leaves extract against ABTS and DPPH\(^5\). Another study also proved the remarkable scavenging activity of methanol leaf extract against DPPH and FRAP assay\(^27\). The oxygenated compounds like 2,4,6-trimethylphenol, linear saturated aliphatic alcohols, unsaturated aliphatic alcohols, and aliphatic aldehyde compounds of essential oil from the stem were identified as enhancers of antioxidant activity\(^4\), and 78.08% of radical scavenging activity was observed with the essential oil extracted from the stem of *E. foetidum*, which were comparable with the activity of standard ascorbic acid\(^5\). The active polar principles such as chlorogenic acid, caffeic acid, and kaempferol-phenolics in a bioaccessible fraction of *E. foetidum* extract have reduced intracellular ROS accumulation in the IL-1β stimulated Caco-2 cells\(^8\). Methanol extract of *E. foetidum* shows the highest antioxidant activity compare to aqueous and chloroform extracts\(^4\). The DPPH assay revealed that the methanol extract has higher antioxidant activity than saponin and
essential oils from leaves of *E. foetidum*, and also, the saponin of this plant has been shown to have antioxidant activity. According to these results, the leaf and stem of *E. foetidum* have significant antioxidant properties, which vary due to the different methods of the extraction process. The Nigerian *E. foetidum* volatile oils have shown that the potential source of natural antioxidants is the high acyclic aldehydes and aromatic compounds. Moreover, a study found that these essential oil compounds from Colombian *E. foetidum* have antioxidant capacity against DPPH assay. The methanolic extract of leaves of *E. foetidum* showed high antimicrobial activity, which could be related to the high concentration of polyphenols and flavonoids.

**Antibacterial activity**

Methanol and chloroform extracts from *E. foetidum* leaves highly inhibited *Streptococcus pneumoniae, Staphylococcus aureus,* and *Listeria monocytogenes* (Gram positives bacteria), while aqueous extract highly inhibited *Salmonella typhimurium* (Gram-negative bacteria). Methanol extract showed a dose-dependent, mild to moderate antibacterial activity against *S. aureus*, while it was ineffective against any tested Gram-negative organisms (*Escherichia coli* and *Pseudomonas aeruginosa*). Another study was done with methanol, ethanol, and aqueous extracts from leaves of *E. foetidum*, *S. aureus*, *Pseudomonas oleovorans*, *Klebsiella pneumoniae*, *Salmonella enteric*, and *E. coli* were sensitive to at least one extract. At the same time, *Bacillus megaterium, Bacillus subtilis,* and *Bacillus flexus* were sensitive to all three extracts. Another study reported that the blanched *E. foetidum* leaf suspension (10% w/v) with 100% growth inhibition in tested *S. aureus* and *B. subtilis*. The methanol and ethanol extracts of the *E. foetidum* have shown a quite similar and good antibacterial potential to the aqueous extracts. Pre-treatment with essential oil of *E. foetidum* as an antimicrobial agent at 15 mg/L concentrations reduced the pasteurization temperatures of pineapple juice to 60°C, where customarily conducted at 80 to 95°C for 15 to 30 seconds. Due to the antibacterial effect of *E. foetidum* essential oil, there is inactivation of *L. monocytogenes*. Ndip et al. found that the methanol extract from *E. foetidum* leaves showed moderate antibacterial activity against six clinical strains of *Helicobacter pylori* out of 15 tested strains, using the disk diffusion method. Another study has shown that the methanol extract of *E. foetidum* has anti-helicobacter activity in vitro and in vivo compared to ciprofloxacin. The ZnO nanoparticles prepared by incorporating leaf extracts of *E. foetidum* showed broad-spectrum antibacterial activity. The polyacetylenes of this plant also demonstrated antibacterial abilities. Most of the studies evaluate the antibacterial activity of extracts only. Further studies need to evaluate the antibacterial activity of isolated phytoconstituents.

**Antifungal activity**

Leaf and stem extracts of *E. foetidum* inhibited some fungi including *Candida albicans, Candida guilliermondii,* and *Cryptococcus neoformans* with minimum inhibitory concentrations of 256, 1024, and 52 µg/mL, respectively. Additionally, this extract showed a significant inhibitory effect towards strains of *C. neoformans*. However, relatively few tests were carried out on fungi compared to bacteria.

**Anti-helminthic activity**

The methanol extract of *E. foetidum* exhibited a dose-dependent helminthicidal activity against *Panamphistomum sp*. In another in vitro study using the infective larvae at the 3rd stage of *Strongyloides stercoralis*, *E. foetidum* showed the most effectiveness at a 50 mg/mL concentration among 25 Jamaican herbal extracts. Eryngial (trans-2-dodecenal) possessed anti-helminthic activity against infective larvae of *S. stercoralis* and was significantly more effective than ivermectin as a comparison drug.
**Anti-tumor activity**

Extracts from *E. foetidum* can reduce the risk factors of cancer development associated with different inflammatory mediators. Inhibition of TNF-α expression by *E. foetidum* leaf extract would be helpful in cancer prevention involving reducing invasiveness of cancer cells. This plant can also inhibit cell division, which is another significant controlling factor in tumor development. The essential oil and methanol extract of leaves had selective inhibition towards the proliferation of PC-3 and A-549 cell lines. Another study revealed no clastogenicity associated with freeze-dried leaves of *E. foetidum* and has anticlastogenic potential in mice using erythrocyte micronucleus assay. This study further suggested the potential health benefit of *E. foetidum* leaves.

**Anti-diabetic activity**

*Eryngium foetidum* leaf extracts showed α amylase inhibitory activity in vitro. Further, *in vivo* studies reported the reduced blood glucose levels (comparable to glibenclamide) in streptozotocin-induced diabetic rat models at doses of 250 and 500 mg/kg of the extract. A study reported 52.2% inhibition of α-amylase activity using *E. foetidum* ethanol extract, where the slightest inhibition was observed with an aqueous extract. Kusirisin et al. revealed that *E. foetidum* potentially prevents glycation associated with diabetes subjects. However, another study found that the aqueous extract *E. foetidum* was ineffective as an anti-hyperglycaemic agent on STZ induced rat models subjected to oral glucose tolerance test. Another study mentioned that the *E. foetidum* plants of Manipur, India, could be used as herbal remedies for the treatment of diabetes mellitus.

**Antimalarial activity**

A survey on the use of herbal remedies for malaria and leishmaniasis in Loreto of Peru reported that boiled plant material from *E. foetidum* had been used to treat malaria/leishmaniasis. Nevertheless, *in vitro* study was unable to confirm such activity. However, another study identified that *E. foetidum* had an *in vitro* antiplasmodial activity with IC₅₀ more than 25 µg/mL when traditionally using antimalarial herbal medications among Quechua and Mestizo populations native to Loreto in Peru were tested against parasite cultures. Ruiz et al. found *in vitro* study that this plant has an antimalarial potential with IC₅₀ of more than 10 µg/ml, where 59 locally using plants to treat malaria in Nanay river banks of Peru.

Aqueous extracts of the whole plant of *E. foetidum* have shown an anti-plasmodial activity against *Plasmodium gallinaceum in vivo*, in chicken models, where 476 plants from the American continent were reviewed. Activity against different strains of plasmodium. Both n-hexane and ethyl acetate fractions from extracts of aerial parts of *E. foetidum* showed anti-leishmanial activity against *Leishmania tarentolae* and *Leishmania donovani*. An extract rich in eryngial was patented for the treatment of parasites in humans and other mammals.

**Larvicidal activity**

As much as 3% of brine shrimp larvae mortality was identified with aqueous and methanol extracts of *E. foetidum*, showed no mortality; 226 amazonian plants were tested to determine their lethal effect on brine shrimp larvae (nauplii) in an *in vitro* assay. An *in vitro* study reported that the crude extract of this plant achieved 100% mortality against mosquito larva after 24 hours. Further, this study suggested that terpenes present in these plants could be the reason for this mosquito larvicidal activity. Sumitha et al. reported that the essential oil from aerial parts of this plant could be effectively used against fourth-instar *Aedes albopictus* larvae, in which 90% of larvicidal activity was exhibited. Further, this study emphasizes using this plant’s essential oil as a natural insecticide with minimum side effects on
humans. Crude extract of *E. foetidum* showed the most toxic activity against the mosquito larvae. This plant can be used as a substitute for mosquito repellent coils.

**Anti-convulsant activity**

This plant has been extensively used in traditional medicine to treat fits in Jamaica\(^6\). In an *in vivo* study, intraperitoneal administration of the extract of *E. foetidum* with the concentration of 110 g/250 mL showed antiepileptic activity against picrotoxin-induced convulsions in rats\(^7,8\). The aqueous extract of chopped *E. foetidum* leaves, when given orally at a dose of 100 mg/kg, was effective against picrotoxin-induced convulsions in rats\(^7,9\). The aqueous extract of leaves of *E. foetidum*, in rat models, exhibited anticonvulsant effects equal to phenobarbital.

### Table II. Pharmacological activities of different parts of *E. foetidum*

<table>
<thead>
<tr>
<th>Parts</th>
<th>Preparation / extract</th>
<th>Activities</th>
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<tr>
<td>Leaves</td>
<td>n-hexane</td>
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</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td>Anti-inflammatory(^{37})</td>
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<td></td>
<td>Bioaccessible fraction</td>
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<td>Methanol, water &amp; chloroform</td>
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<td>Antibacterial(^{46})</td>
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<tr>
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<tr>
<td>Methanol, ethanol &amp; aqueous</td>
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<td>Methanol &amp; ethanol</td>
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<td>Anti-fungal(^{44})</td>
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<tr>
<td>Essential oil</td>
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<td>Anti-diabetic(^{37})</td>
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<tr>
<td>Whole plant</td>
<td>Methanol</td>
<td>Anti-helminthic(^{33,34})</td>
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<td></td>
<td>Essential oil &amp; methanol</td>
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<td></td>
<td>Aqueous</td>
<td>Anti-tumor(^{43})</td>
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<tr>
<td></td>
<td>ethanol</td>
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<td></td>
<td>Freeze dried leaves</td>
<td>Anti-convulsant(^{47,73,74})</td>
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<td>Aerial parts</td>
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<td>Extract</td>
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<td>Essential oil &amp; n-hexane and ethyl acetate fractions</td>
<td>Anti-plasmodial(^{63})</td>
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### TOXICITY STUDIES

The acute toxicity study of hydro-alcoholic extracts of *E. foetidum* did not show any morbidity, mortality, or post toxicity signs in albino mice, even at a dose of 2000 mg/kg\(^{74}\). Chandira *et al.*\(^{57}\) reported that the oral dose at 2500 mg/kg of aqueous extract of *E. foetidum* was lethal for healthy, adult, and young rodents. Acute oral toxicity of methanolic extract of leaves of *E. foetidum* was studied using rats to which extract was fed. This study revealed that LD\(_{50}\) of the extract showed 2000 mg/kg, and toxicity of the plant was extremely low upon oral administration\(^{48}\). Further genotoxicity of the methanolic extract of the plant revealed that plants protect damages to DNA induced by some substances. Also, the even higher concentration of extract did not produce DNA damages. It could be related to the higher antioxidant potential of the plant\(^{59}\).

Consumption of *E. foetidum* above 0.8%, which is more than 35 times human consumption, resulted in weight loss, kidney and spleen damage, as demonstrated through chronic toxicity animal studies. Further elevation of blood urea nitrogen was observed due to kidney damage by renal tubular-nephrosis, interstitial nephritis, and spleen hemosiderosis due to toxic metabolites of *E. foetidum*. *Eryngium foetidum* was influential in the amelioration of carbon tetrachloride-induced hepatotoxicity in mice\(^{75}\). This study demonstrated the hepatoprotective potential of this plant. Furthermore, the compound 'eryngial' as the main constituent of essential oil of *E. foetidum* showed significant inhibition on enzyme cytochrome P450 2E1\(^{66}\).

### CONCLUSION

*Eryngium foetidum* L is a potential aromatic crop and is widely used for ethnomedical and culinary purposes. Furthermore, it exhibited many pharmacological applications such as anti-inflammatory, antioxidant,
antimicrobial, anticonvulsant, antimalarial, anthelminthic, larvicidal, anticancer, anti-diabetic, and hepatoprotective activities with no cytotoxic effects. Even though several research studies were done to screen pharmacological activities, limited studies have been conducted to isolate and screen phytoconstituents of the plant. Studies should be focused on identifying the bio-actives with potential activities. This review promised that potential new chemical entities could be elicited from phytoconstituents of E. foetidum, and also this plant can also be used as a substitute for mosquito repellent coils. Therefore, further studies should be done to prove this effect in the future.

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None.

AUTHORS’ CONTRIBUTION

Galamula Hewage Tharuca Kanchana Hemachandra: conceived and design the analysis, writing of the paper.

Sinnadurai Thuvaragan: conceived and design the analysis.

Vinotha Sanmugarajah: collected data, contributed data or analysis tools.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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