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INTRODUCTION Eryngium is the largest and most complex genus in the Apiaceae family1, 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 Nigeria2.

Eryngium foetidum is commonly known as 'spiny coriander'3, 'spirit weed' or 'saw-tooth coriander' and is also called in different countries as langer koriander (German); ketumbar java (Malay); pak chi farang (Thai); ngo gai (Vietnamese); culantro, racao, recao (Spanish); Bahkhawr' (India) and andu kola (Sri Lanka)4. The leaves of this plant are frequently used interchangeably with Coriandrum sativum L. due to their similar pungent aroma character5. It treats several ailments, such as respiratory diseases, gastrointestinal ailments, and skin diseases, by different indigenous systems6.

A review study stated that the technology for mass production is available for this plant, cultivated for commercial purposes6. 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 sowing4. In Bangladesh, a research study provides a baseline of information concerning this plant's cultivation techniques, market potential, and climate resilience3. Based on ethnomedical evidence, many studies have been explored phytoconstituents, underlying mechanisms, and related pharmacological effects of the different parts of this plant7.

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 I. Classification of E. foetidum8 Classification _Identity _ _Domain _Eukaryote _ _Kingdom _Plantae _ _Phylum _Tracheophyta _ _Class _Magnoliopsida _ _Order _Apiales _ _Family _Apiaceae _ _Genus _Eryngium _ _Species _Eryngium foetidum L _ _Synonyms _Eryngium antihystericum Rottler, Eryngium molleri Gand _ _Common name _Long coriander, wild coriander, fitweed, culantro, Mexican coriander _ _English name _Long coriander/Sea Holly _ _ 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 US4. 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 roots6. // Figure 1. Eryngium foetidum plant 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 foods7.

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 pains9. Moreover, it is used as a vermifuge and febrifuge10. Eryngium foetidum has been used to treat colds and fever, burns, earache11, pneumonia, flu, convulsions in children, malaria12, hypertension, constipation, worm infections, and infertility complications13.

The roots have stomachic, sudorific, and diuretic effects13,14, where leaf juice/decoction stimulates the gut as a laxative7. It was also reported to treat several poisons, including the treatment of snake bites and scorpion-sting venom4,13. 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 terpenoids16,17. 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 leaves1,6,20.

The chloroform extracts of dried aerial parts by soxhlet extraction followed by chromatographic fractionation yielded a pentacyclic triterpenoid saponin and O-glycoside21. Some free triterpenoids were too identified from leaves' hexane extract, including stigmasterol-the main phytosterol22,23. Eryngium foetidum is a rich source of phenolic compounds5,24,25. Leitão et al.26 found that the E. foetidum leaves showed major carotenoids as all-trans-lutein and all-trans-ß-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 ethanol extracts E. foetidum shows higher flavonoid contents27. Dried leaves yielded 0.1 to 0.95% of essential oil18. 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. foetidum6,12,14,24-25,28-32.

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 monoterpene 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 appendix5,24-25,34. 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 activity36. The hexane extract from the leaves of E. foetidum has shown possible anti-inflammatory activity3. Prior treatment with ethanol extract of E.

foetidum leaf inhibited the elevation of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-a), 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 inflammation37. Leaf extract of E.

foetidum consisted of lutein, ß-carotene, chlorogenic acid, kaempferol, and caffeic acid, which had bioactive properties38. 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-1ß (IL-1ß). 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 inflammation38,39.

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. foetidum40. 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 acid41. 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 components4.

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 mice37. Ethanol extract of the E. foetidum leaves exhibited 51.44% radical scavenging activity, correlated with a high level of phenolic and flavonoid contents42. Amazonian E. foetidum has shown that the scavenging capacity of methanol leaves extract against ABTS and DPPH26.

Another study also proved the remarkable scavenging activity of methanol leaf extract

against DPPH and FRAP assay27. 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 activity43, 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 acid5.

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-1ß stimulated Caco-2 cells38. Methanol extract of E. foetidum shows the highest antioxidant activity compare to aqueous and chloroform extracts44. 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 activity45. 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 process46. The Nigerian E. foetidum volatile oils have shown that the potential source of natural antioxidants is the high acyclic aldehydes and aromatic compounds47. Moreover, a study found that these essential oil compounds from Colombian E. foetidum have antioxidant capacity against DPPH assay25. The methanolic extract of leaves of E. foetidum showed high antimicrobial activity, which could be related to the high concentration of polyphenols and flavonoids48.

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)44. 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)49.

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 extracts50. Another study reported that the blanched E. foetidum leaf suspension (10% w/v) with 100% growth inhibition in tested S. aureus and B. subtilis51. The methanol and ethanol extracts of the E. foetidum have shown a quite similar and good antibacterial potential to the aqueous extracts42. 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. monocytogenes28. Ndip et al.22 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 ciprofloxacin19. The ZnO nanoparticles prepared by incorporating leaf extracts of E. foetidum showed broad-spectrum antibacterial activity52. The polyacetylenes of this plant also demonstrated antibacterial abilities1. Most of the studies evaluate the antibacterial activity of extracts only. Further studies need to evaluate the antibacterial activity of isolated phytoconstituents53. Antifungal activity Leaf and stem extracts of E. foetidum inhibited some fungi including Candida albicans, Candida guilliermondi, and Cryptococcus neoformans with minimum inhibitory concentrations of 256, 1024, and 32 µg/mL, respectively.

Additionally, this extract showed a significant inhibitory effect towards strains of C. neoformans54. 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 Paramphistomum sp13. 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 drug50. Anti-tumor activity Extracts from E. foetidum can reduce the risk factors of cancer development associated with different inflammatory mediators. Inhibition of TNF-a expression by E. foetidum leaf extract would be helpful in cancer prevention involving reducing invasiveness of cancer cells37. This plant can also inhibit cell division, which is another significant controlling factor in tumor development39. The essential oil and methanol extract of leaves had selective inhibition towards the proliferation of PC-3 and A-549 cell lines45. 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 leaves55.

Anti-diabetic activity Eryngium foetidum leaf extracts showed a amylase inhibitory activity in vitro56. 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 extract57. A study reported 52.2% inhibition of a-amylase activity using E. foetidum ethanol extract, where the slightest inhibition was observed with an aqueous extract42. Kusirisin et al.58 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 test59. Another study mentioned that the E. foetidum plants of Manipur, India, could be used as herbal remedies for the treatment of diabetes mellitus42. 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 activity60. 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 cultures61. Ruiz et al.62 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 plasmodium63. Both n-hexane and ethyl acetate fractions from extracts of aerial parts of E. foetidum showed anti-leishmanial activity against Leishmania tarentolae and Leishmania donovani64. An extract rich in eryngial was patented for the treatment of parasites in humans and other mammals65,66. 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 assay67. 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 activity68. Sumitha et al.69 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 coils70. Anti-convulsant activity This plant has been extensively used in traditional medicine to treat fits in Jamaica71,72. 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 rats73,74. 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 albino rats71. Furthermore, Nsour et al. 73 reported that intraperitoneal injection of aqueous extracts of leaves and stem of E. foetidum, in rat models, exhibited anticonvulsant effects equal to phenobarbital. Table II. Pharmacological activities of different parts of E. foetidum Parts _Preparation / extract _Activities _ _Leaves _n-hexane _Anti–inflammatory40 _ _ _Ethanol _Anti–inflammatory37 _ _ _Aqueous bioaccessible fraction _Anti–inflammatory38 _ _ _Methanol _Antioxidant26,27,44,45,52 _ _ _Methanol, water & chloroform _Antibacterial44 _ _ _Methanol _Antibacterial19,22,49 _ _ _Methanol, ethanol & aqueous _Antibacterial42 _ _ _Methanol & ethanol _Antibacterial42 _ _ _Essential oil _Antibacterial28 _ _ _Aqueous extract in ZnO nanoparticles _Antibacterial52 _ _ _Methanol _Antifungal54 _ _ _Methanol _Anti-helminthic13,50 _ _ _Essential oil & methanol _Anti-tumor45 _ _ _Aqueous _Antidiabetic57 _ _ _Ethanol _Antidiabetic42 _ _ _Aqueous _Antidiabetic58 _ _ _Aqueous _Anti-convulsant71,73,74 _ _ _Freeze dried leaves _Anticlastogenic55 _ _ _Aqueous bioaccessible fraction _Anti–inflammatory38 _ _Leaves and stem _Essential oil _Antioxidant5,25,45 _ _Whole plant _Methanol _Antifungal & antioxidant54 _ _ _Aqueous _Antiplasmodial63 _ _ _Extract _Larvicidal67,70 _ _ _Essential oil _Larvicidal69 _ _Aerial parts _n-hexane and ethyl acetate fractions _Antiplasmodial63 _ _ 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/kg74. 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 LD50 of the extract showed 2000 mg/kg, and toxicity of the plant was extremely low upon oral administration48.

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 plant75. 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. foetidum76. Eryngium foetidum was influential in the amelioration of carbon tetrachloride-induced hepatotoxicity in mice75. 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 2E16.

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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