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Review Article

A Comprehensive View Of Kaffir Lime (*Citrus Hystrix*)

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ABSTRACT

The Rutaceae family includes kaffir lime (Citrus hystrix). Citrus hystrix is referred to as "kaffir lime" internationally. Citrus hystrix DC, sometimes known as kaffir lime, is a tropical plant that is native to Southeast Asia, India, Malaysia, and China. It is extensively utilized in the Netherlands, Germany, France, Italy, and Spain. From C. hystrix, 78 components have been described thus far. It mostly consists of phenolic chemicals and essential oils. The chemicals in kaffir lemon that have the strongest scents are á-Terpeneol, ä-Cadinene, 1,8-Cineole, L-Linalool, and citronellal. Makrut lime contains non-volatile substances such alkaloids and glyceroglycolipids in addition to chemicals like Citrusosides-A and furanocoumarines. Citrus hystrix DC has been used in traditional medicine to treat a variety of ailments, most notably stomach disorders and cold pain, because of its numerous biological actions resulting from its volatile and nonvolatile components. It can also be used as a spice for its aromatic leaves or as a juice for its fruit. This article discusses the chemical makeup and medicinal properties of kaffir lime (Citrus hystrix), with a focus on the latter's pharmacological properties, which include antimicrobial, anti-inflammatory, antioxidant, antitumor, antifertility, antidiabetic, hepatoprotective, neural protective, and anticholineastarase activity. It also discusses the use of kaffir lime (Citrus hystrix) in conventional medicine

INTRODUCTION

A member of the Rutaceae family, Citrus hystrix is frequently grown in Thailand and is sometimes referred to as kaffir lime. Its leaves are widely used in folk medicine. The leaf extracts were discovered to possess antioxidant, anti-inflammatory, and anti-cancer qualities. Meanwhile, the juice is utilized to eliminate gas, cleanse the blood, increase hunger, and keep the scalp and hair healthy. Citrus hystrix DC, with its volatile and nonvolatile components, has been used for centuries to treat a variety of diseases, including stomach problems and cold pain, because of its many biological effects. Citrus belongs to the subfamily Aurantioidea and order Sapindale of the

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Rutaceae family, which collectively comprise over 140 genera and over 1,300 species distributed over 7 subfamilies. Originating in Southeast Asia, India, Malaysia, China, Thailand, and Indonesia, kaffir lime flourishes in tropical climates. In the Netherlands and Germany, the lime is commonly referred to as Mauritius papeda, or Kaffir lime, whereas in France, Italy, and Spain, it is sometimes called "combova." After bringing the seeds from Mauritius to his botanical garden in Montpellier, southern France, De Candolle (DC) later in 1824 gave the Kaffir lime the name "Mauritius papeda." De Candolle had previously investigated and categorized C. hystrix as the initial species of the papeda sub-genus. The fruit has received a lot of attention for its potential as a natural antioxidant supplement. It is added to teas like Citrus Hystrix Flavonoid-Rich Sachet and used as a flavoring. The fruits are used to stimulate the digestive system, reduce hypertension, and cleanse the blood. The components of C. hystrix exhibit a wide range of pharmacological actions, including anti-microbial, anti-mosquito, anti-tumor, neuroprotective, antioxidant, anticholinesterase, anti-inflammatory, hepatoprotective activity, antifertility, tyrosinase inhibitory activity, cardioprotective, anti-diabetic, antiviral, and antilarval properties, as demonstrated by current pharmacological research. The majority of these activities match those observed in conventional applications for C. hystrix. Traditionally, C. hystrix seems to have been primarily used as an insecticide to treat the feet and wash the head in order to eradicate terrestrial leeches.

BOTANY & TAXONOMY

Citrus hystrix, commonly known as kaffir lime, typically grows as a small tree reaching heights of 3-6 meters and widths of 2.5-3 meters. The tree often has a crooked, irregular form with glabrous, spiny branches. The leaves are notable for their unique structure among citrus varieties: they are alternate, unifoliolate, and broadly ovate to ovate-oblong, measuring 7.5-10 cm in length. They are dark green on the upper surface and lighter underneath, with a strong fragrance. Each leaf has a long petiole that expands into prominent wings (15 cm long and 5 cm wide), giving the appearance of a "pinched" double leaf. The leaf base is either cuneate or rounded, and the apex can be obtuse, slightly acuminate, or notched. The flowers are small, fragrant, and white, with a calyx that is cuspidate and 4-lobed, featuring a white color with a violet fringe. The petals are 4-5 in number, ovate-oblong, yellowish-white with a pink tinge, and the stamens number 24-30 and are free. The fruit is large, with a verrucose, warty, or bumpy texture, and is globose to ovoid or elliptic in shape. It is green when unripe and turns yellowish-green when mature, with a thick rind and very acidic, bitter, yellowish pulp. The fruit measures approximately 5-7 cm in diameter and has a wrinkled surface. The seeds are numerous, ridged, ovoid-oblong, measuring 1.5-1.8 cm by 1-1.2 cm, and are monoembryonic with white cotyledons.

Figure 1: Kaffir lime fruit

PRODUCTION AND POST HARVEST

Kaffir lime grows best in warm subtropical or tropical areas, and it also requires a good growing season. Citrus hybrids' primary components are flavonoids and phenolic acids, which have been demonstrated to have a variety of possible

medicinal uses. The culinary, fragrance, sanitary, cosmetic, pharmaceutical, and agronomic industries all use citrus hystrix oil as a feedstock. It is also a necessary ingredient in a lot of cosmetics and beauty items, and aromatherapy uses it a lot.To facilitate transportation, the harvested leaves are gathered into 10 kg bundles and kept in pink polypropylene weaved sacks. Because kaffir lime trees don't require regular fertilizer applications, flowering schedule regulation, or irrigation to maintain fruit loading, maintenance on them is comparatively easier. Rain-fed fields contain the majority of the kaffir lime in the region. Farmers do not use a uniform fertilizer. Balitjestro (2009) recommends applying 20g N, 10g P2O5, and 5g K2O of fertilizer per tree. Regular hand weeding takes place once a month.

Figure 2: Fresh and processed products from kaffir lime at Tulungagung market: fresh leaves (A); essential oil (B); fruits (C); stems after stripping the leaves (D).

CHEMICAL COMPOSITION

Based on chemical analysis C. hystrix DC, is rich on bioactive molecules such as essential oils, phenolic compounds glycerolipids, flavonoids, terpenoids, coumarins, carbohydrate, phytosterols, saponins, tannins and alkaloids.

Figure 3: Kaffir lime plant. A. Kaffir lime tree. B. Lime leaves. C. Kaffir lime fruit. D. Kaffir lime flower. E. Kaffir lime seeds.

S. No	PLANT	PARTS	PHYTOCONSTITUENTS
1.	Kaffir lime	Essential oil in leaves	Citronellal, p-cimene and 1.8-cineole
2.		Essential oil in peel	Sabinene, α-citronellol, terpinolone α-terpinene
3.		Pulp	Carbohydrates, crude protein, crude fibre, coarse ash and crude fat
4.		Leaf	Elementol, δ-cadinene, L-linalool, α-humulene
5.		Peel	Terpinen-4-ol, α-pinene, limonene

ESSENTIAL OIL

Essential oils are intricate blends of volatile to semi-volatile substances that are insoluble in water, seldom colored, and typically have a strong smell. C. hystrix essential oil is utilized in aromatherapy and is a necessary component of many cosmetic and beauty products. Numerous bioactivities, including antibacterial, antitussive, antileukemic, and antioxidant properties, have been documented. The primary ingredient in the essential oils extracted from the peels of Malaysian citrus species is limonene, a monoterpene hydrocarbon. Citronellal, citronellol, and limonene were determined to be the main constituents of the essential oil recovered from fresh C. hystrix leaves using steam distillation and the Likens-Nikerson extraction method. The extracted essential oils showed high levels of á-terpineol (7.6%), p-cimene (5.6%), citronellol (6.0%), terpinen-4-ol (13.0%), and â-pinene (10.9%), but low levels of limonene (4.7%). However, the main constituents of the kaffir lime peels (from Masjid Tanah, Melaka, Malaysia) were found to be â-pinene (39.3%), limonene (14.2%), citronellal (11.7%), and terpinen-4-ol (8.9%). Subsequently, Nor (1999) showed that the primary constituents in C. hystrix peel were â-pinene (23.5%), sabinene (20.1%), citronellal (12.6%), limonene (11.8%), and â-citronellol (3.3%). Recent studies by Aumeeruddy-Elalfi et al. (2016)40 identified á-pinene (3.02%), limonene (83.89%), â-pinene (0.78%), and â-myrcene (0.89%) as the primary constituents of the essential oils extracted from C. hystrix leaves, with traces of methyl-eugenol (0.21%).

Figure 4: Essential oil of kaffir lime

PHENOLIC AND FLAVONOID COMPOUNDS

Phenolic compounds have an aromatic ring at least, to which one or more hydroxyl groups are attached to form aliphatic or aromatic structures. Simple phenolic molecules and highly polymerized compounds are both examples of phenolic compounds. The majority of these phenolic chemicals were extracted using ethanol. It has been proposed that citrus fruits' polyphenolic contents, such as naringin, hesperidin, and gallic acid, are what give them their anti-diabetic properties. The widely dispersed class of plant phenolics that includes isoflavones, flavonols, flavones, and anthocyanin pigments is known as flavonoids. Condensed tannins are produced by the polymerization of flavanols. The most prevalent and widely dispersed classes of phenolic chemicals found in plants, flavonoids are found in fruits and vegetables and are distinguished by their

benzopyrene structure; and can be analyzed using calorimetric method.

OTHER EXTRACTS

Two glyceroglycolipids were extracted from C. hystrix leaves by Murakami et al. (1995): l,2-di-O-a-linolenoyl-3-O-beta-galactopyranosyl-sn-glycerol (DLGG) and a mixture of two substances, l-O-a-linolenoyl-2-O-palmitoyl-3-O-beta-galactopyranosyl-sn-glycerol and its counterpart (LPGG). These compounds inhibit the growth-promoting properties of 12-O-Tetradecanoylphorbol 13-Acetate on mouse skin tumors. However, two coumarins (hystrixarin and hopeyhopin), a benzenoid derivative (hystroxene-I), and a quinolinone alkaloid (hystrolinone) were also isolated from the crude acetone extract of the C. hystrix root. The antibacterial activity of isolated coumarins (hystrixarin and hopeyhopin), namely benzenoid derivatives (hystroxene) and quinolinone alkaloids (hystrolinone), obtained from kaffir lime root acetone extract, was found to be effective against Acinetobacter baumannii. β-pinene, citronellal sabinene, and limonene the main components of kaffir lime compounds have antibacterial qualities.

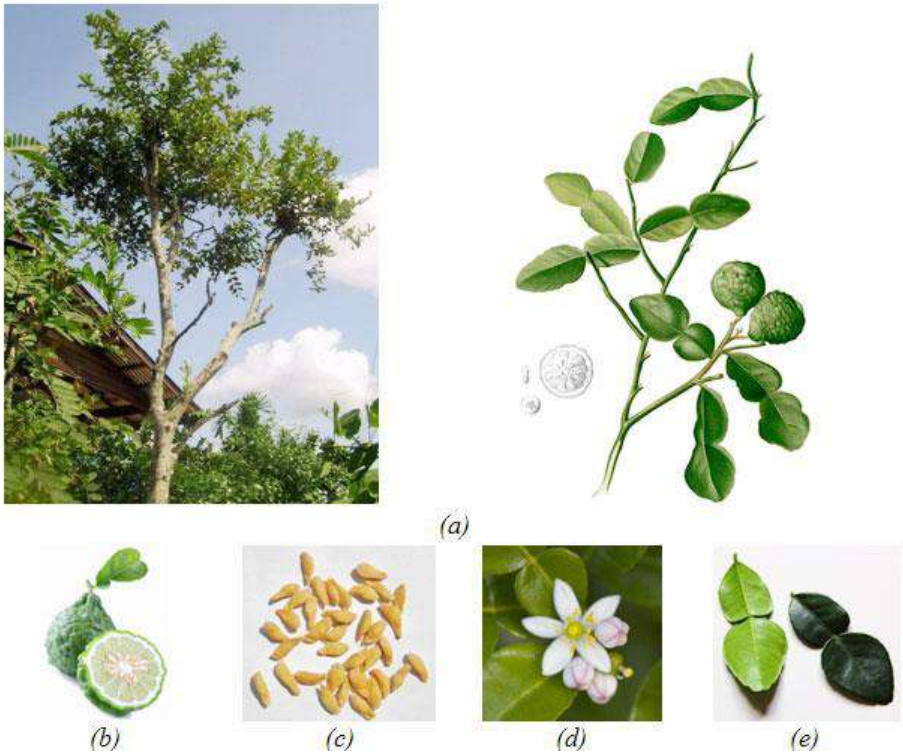

Figure 5: Tree (a), Fruit (b), Seeds (c), Flowers (d) and Leaves (e) of citrus hystrix.

PHARMACOLOGICAL ACTIVITY

1. ANTIOXIDANT ACTIVITY

The methanolic extracts of C. hystrix leaves and peel, when evaluated for antioxidant activity using the DPPH radical scavenging capacity method, show promisingly high levels of antioxidant activity, with IC50 values for the leaves and peel of 24.6 and 66.3 microg/ml, respectively. Several in vitro tests were used to assess the antioxidant activity of fresh C. hystrix juice. 30504.40 mmol of ferrous equivalents/L of juice are shown by FRAP assays; corresponding values for DPPH and ABTS + scavenging are around 10903.28mmol of trolox equivalents/L of juice. These findings suggest that C. hystrix fresh juice may have applications as a source of antioxidant agents. The ORAC test yields 10.51 mmol TE per g, the kaffir lime leaf extract displays FRAP values (781 mM TE per g), and the bleaching activity of β-carotene (35.67%).

2. ANTI- INFLAMMATORY

According to reports, a number of components extracted from C. hystrix have anti-inflammatory properties in various models (Murakami et al., 1999). From C. hystrix, a cluster of coumarins with notable anti-inflammatory properties was isolated and described. Bergamottin (8, IC50: 14 lM) had an inhibitory effect that was comparable to that of the reference standard, N-(iminoethyl)-ornithine (IC50: 7.9 lM).

3. ANTI- TUMOUR ACTIVITY

The components of Agrostophillinol, 1,2-Di-O-linolenoyl-3-O-b-β-galactopyranosyl-sn-glycerol, amottin, citronellal, citronellol, phytol and lupeol. Extraction of C.hystrix compounds of citronellal and citronellol were evaluated in vitro against the MDA-MB-231 cells through multiple molecular biology methods. Results revealed that C. hystrix extracts, citronellal and citronellol decreased cell proliferation, colony formation and cell migration by inducing cell cycle arrest, as well as inducing apoptosis in MDA-MB-231 cells via inhibition of the expression of anti-apoptotic Bcl-2, activating the caspase-3 dependent pathway. Constituents from extracts of C. hystrix leaves have been shown to display antileukamic Cell proliferation. Phytol and lupeol isolated from the extracts were Anti-proliferative agents for decreasing the proliferation of leukemic cells tested by the bioassay. Essential oils extracted from the peel of C. hystrix exhibited strong anticancer action, according to Borusiewicz et al. (2017). The authors of the study first demonstrate the cytotoxic and anti-proliferative properties of C. hystrix essential oils against fibroblasts from normal human skin and human melanoma cells (WM793 and A375). Furthermore, the obtained results demonstrate that the oil exhibits inhibitory effects at the studied dosages (0.05, 0.1, and 0.15 mg/mL). The discovery that both melanoma cell lines (WM793 and A375) were more susceptible to the effects of C. hystrix peel essential oil than normal cells like fibroblasts from human skin was very intriguing.

3. ANTI- BACTERIAL ACTIVITY

Anti-microbial activity can be attributed to the main constituents of kaffir lime compounds, including limonene, citronellal sabinene, and β-pinene. Samples were tested for their antibacterial activity using thin layer chromatography. When exposed to visible light and after being sprayed with vanillin sulfate, elute exhibits a distinct separation effect. Compared to other samples, Kaffir lime leaf essential oil (KLLEOs), which was derived from powdered brown and green leaves, exhibited a higher level of antioxidant activity. Less stains were seen in E. coli glass plates than in S. aereus ones, suggesting that KLLEOs E. coli was less sensitive than S. aereus.

4. ANTI-FUNGAL ACTIVITY

Studies on phytochemicals have revealed that the primary component of KLL is citronellal. A-pinene, camphene, b-pinene, limonene, copaene, linalool, b-cubebene, isopulegol, caryophyllene, citronellyl acetate, and other chemical compounds are examples of other compounds. Citronellal has been found to have potent antifungal properties. By demonstrating the presence of a zone of inhibition for the growth of both fungi in both extracts, KLL demonstrated that the leaf extracts possessed remarkable anti-fungal activity against all tested fungi. Aspergillus niger exhibits stronger antifungal activity in aqueous KLL extract compared to alcohol extract. On the other hand, alcohol KLL extract of Candida albicans exhibits greater antifungal activity than aqueous extract. We propose that KLL has the potential to be used medicinally as an ototopical antifungal with a low ototoxicity risk. Additionally, since KLL is easily accessible in Malaysia, it can be cheap and environmental friendly source of medication..

6. ANTI-LARVAL ACTIVITY

After 24 and 48 hours of treatment, the essential oil of fresh kaffir lime leaves shown substantial

anti-larval activity against tobacco armyworm larvae, with IC50 values of 29.25 µg/ml and 26.75 µg/ml, respectively. The three instar larvae of A were exposed to doses of 500 ppm, 1375 ppm, 250 ppm, 3125 ppm, and 4000 ppm of kaffir lime leaf extract (methanol and n-hexane) according to Ansori et al. (2015). When compared to the methanol extract, which had LC90=3180 ppm, the n-hexane extract of kaffir lime leaves was more toxic and an effective biolarvicidal at LC90=2885 ppm.

7. ANTI-DIABETIC ACTIVITY

Worldwide use of citrus makes it a significant source of phenolic compounds and vitamin C. It has been suggested that the chemicals found in citrus fruits protect the liver, reduce the synthesis of glucose, delay the passage of glucose through the intestines and liver, prevent intestinal glucose absorption, and stimulate beta cells to secrete more insulin and have an action similar to that of insulin.The chemicals isolated from Citrus hystrix peel have the potential to block starch breakdown into sugars, hence decreasing postprandial blood glucose levels. This is related to the samples' ability to inhibit the carbohydrate-digesting enzymes α-amylase and α-glucosidase.

8. ANTI-FERTILITY ACTIVITY

In a study conducted by Piyachaturawat et al. (1985), the antifertility activity of kaffir lime peel chloroform and alcohol extract was administered orally to pregnant adult female Wistar rats at various stages of gestation. Research has indicated that the combined administration of both extracts enhances the uterotrophic effect of estradiol. Furthermore, uterine contractions are stimulated by kaffir lime extract. Pregnancy problems may be related to one or both of these impacts. It was also shown that kaffir lime chloroform and alcoholic extracts, when administered consecutively from the second to the fifth day, the eighth to the twelfth day, and the fifteenth day till delivery, might prevent implantation, cause an abortion, and slightly speed up the delivery process. Remarkably, terpenoids have also been discovered to be present in kaffir lime leaf extract. Certain terpenoids were shown to have a pattern of coincident occurrence with mammalian hormones based on their structural makeup. However, some terpenoid kinds were found to be very effective when used as an active ingredient in antifertility treatments. This claim is made in reference to earlier research on Piper betle and Jatropha gossypifolia that identified terpenoid as one of the secondary metabolites causing antifertility. Consequently, it is recommended that future study include additional evaluations that highlight the various terpenoids found in kaffir lime leaf extract and their impact on folliculogenesis. It has been demonstrated that kaffir lime leaf extract works well to increase the number of follicles in female white rats.At the primary, secondary, tertiary, and de Graaf follicles, there was a notable rise. Though there was a negligible difference between the two treatments (one at a dose of 500 mg/kg and the other at 750 mg/kg), the therapy with the higher follicular number was produced.

9. INHIBITORS OF NITRIC OXIDE GENERATION:

In RAW 264.7 cells, coumarins (oxypeucedanin, bergamottin, and 5-[(6', 7;-dihydroxy-3', 7'-dimethyl-2-octenyl) oxy-]-psoralen) from the fruit methanolic extract were shown to be inhibitors of interferon-induced nitric oxide production and lipopolysaccharide. Out of the three coumarins, bergamottin had the most inhibitory action, with an IC50 value of 14 µM. This value was similar to that of an artificial L-arginine analogue inhibitor of iNOS (N-(iminoethyl)-L-ornithine), which had an IC50 value of 7.9 µM. Bergamottin may be able to suppress the iNOS enzyme activity and the pathways that are initiated by LPS and IFN-γ.

10. NEURAL PROTECTIVE ACTIVITY

When furanocoumarin derivatives were separated from C. hystrix in 2010 and tested for

cholinesterase inhibitory activity, compound (R)-(+)-6γ –Hydroxy-7γ-methoxybergamottin demonstrated the strongest AChE inhibition, with an ICs0 Value of 11.2 uM, suggesting a promising potency in the treatment of Alzheimer's disease (Youkwan et al., 2010). Since the existence of a deoxygenated geranyl chain in the separated constituents was discovered to be necessary for the inhibitory effect, the initial structure-activity relationship can be generalized.

11. CHOLINESTRASE INHIBITION ACTIVITY

The juices of C. hystrix possess strong anti-cholinesterase activity of 79.74% against 86.89% of the used reference compound (Eserine: From the hexanes and dichloromethane extracts of the peels of C. hystrix fruits, Youkwan et al. (2010,^% have isolated 4 new citrusosides A-D. six furanocoumarins, a sesquiterpene (eudesmane-4b, 1 |-diol), 5 monoterpenes, and 1- The 0-fractions was investigated and 62 - hydroxy-72 methoxyberganmottin was found as a compound to possess the highest potency, showing an IC value of l1.2+/-0.1 iM against 3.2+0.2 iM of galanthamine (a positive control). However, β-sitosterol, -dihydroxybergamottin and isomperatorin showed IC50., values of154+/-0.3 and 23+/-0.2 iM, respectively. The butyrylcholinesterase inhibitory capabilities of the separated Citrusosides A-D and furanocoumarins compounds from the hexane and methanolic peel extract were reported, and their measured IC50 values of 11.2, 15.4, and 23 µM were equivalent to that of the standard Galanthamine (3.2 µM). Anticholinesterase activity is compared to the positive control serine, the substances neohesperidine and oxypeucedanin showed the strongest activity, with IC50 values of 0.16 mM toward AChE and 0.26 mM BChE

12. HEPATOPROTECTIVE ACTIVITY

However, the recent study conducted by Abirami et al. (2015), shows that methanolic extracts of C. hystrix leaf possess hepatoprotective action against murine paracetamol induced hepatotoxicity; The level of enzyme markers (alanine transanminase, aspartate transaminase and alkaline phosphatase) in experimental rats were significantly restored the interventions C. hystrix leaves extract to the comparable level of normal control.

13. OTHER ACTIVITIES

In 2017, Nararak and colleagues conducted a study. C. hystrix leaf oil demonstrated the greatest spatial repellent activity at 1% and 2%, and significant combined irritant and repellent activity responses at 1-5% concentrations. C. hystrix oils were confirmed to show more inhibition against A. minimus mosquitoes than A. aegypti mosquitoes Apart from the activities introduced above, other activities of C. hystrix have also been explored. In 2015, Ali et al. (2015) evaluated the thrombolytic and membrane-stabilizing activities of C. hystrix leaf extracts using human erythrocytes, and the results were compared with those of standard streptokinase (SK) and acetyl salicylic acid (ASA), respectively. In 2007 C. hystrix oil was demonstrated to promote the blood pressure and reduce the skin temperature.

CONCLUSION

Kaffir lime (Citrus hystrix) is a small, bushy plant renowned for its fruit and leaves, which are used as seasoning in various cuisines. Belonging to the Rutaceae family, kaffir lime is native to the tropics and originates from Southeast Asia, India, Malaysia, and China. It is commonly used in countries such as the Netherlands, Germany, France, Italy, and Spain. C. hystrix an important medicinal herb which are being utilized in the field of Ayurveda, Siddha and other medical systems. C. hystrix contains a number of phytoconstituents, which are the key factors in the nutritional and medicinal value of this plant. Almost all parts of this plant such as leaf, fruit, seed and root are used to cure a variety of diseases. Crude extracts and

phytochemicals extracted from different portions of C. hystrix have been discovered to possess a wide range of pharmacological actions, including antimicrobial, antifungal, antioxidant, anti-inflammatory, and anticancer properties. The underappreciated fruit of C. hystrix is crucial to biodiversity and the sustainable usage of the plant for coming generations. A substantial amount of research has been conducted on the biological activity and potential applications of these compounds; however, further pharmacological analysis and clinical studies are required to fully realize their therapeutic potential in the treatment of a variety of illnesses. Through in vivo research, the nutraceuticals potential of dietary fiber made from the peel and pulp of the C. hystrix fruit may be further explored for broader application.

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