Review for *Citrus hystrix* DC.

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ABSTRACT
Herbal medicines have played a critical role in the treatment and prevention of some diseases. Among a diversity of natural medicinal sources, Citrus hystrix DC. is an outstanding plant broadly distributed in tropical regions. Citrus hystrix DC. has many biological activities, and it has been used in traditional medicine for treating various illnesses, particularly cold pain and stomach disorder. This review article focuses to enhance and prepare a comprehensive review on phytochemical and pharmacological studies of Citrus hystrix DC., and aims to lay the foundation for further study on the extraction enhancement of these biomolecules and more useful formulations. Based on published scientific data, these plants may suggest a gigantic biological potential of an abundant source of chemical constituents and a variety of bioactivities contributing to therapeutic values.

Keywords: *phytochemical, biological activities*, *Citrus hystrix*

1. INTRODUCTION

Citrus hystrix (*C. hystrix*) is known as a wild lime, medicinal lime and kaffir lime in English [1], and is also known as "Trúc", "Chúc", "Trấp" and "Chanh xác" in Vietnam. The plant is cultivated in several Southeast Asian countries [2], including Vietnam. *C. hystrix* belonging to the family *Rutaceae* is an underutilized tropical fruit and its fruits are locally used for spices and essential oils [3]. All parts of *C. hystrix* plant (leaves, fruits, seeds) contain essential oils. *C. hystrix* fruits are the main material for the essential oils production. However, the plant leaves also contain valuable volatile com-pounds such as β-citronellol, citronellyl acetate, linalool, and caryophyllene, beside the main compounds such as α-pinene, eucalyptol, camphene, bicyclo hept-3-en-2-one, caryophyllene, endo-borneol, and bornyl acetate [1]. Oils usually varies considerably because of intrinsic (sexual, seasonal, ontogenetic, and genetic variations) and extrinsic (ecological and environmental aspects) factors [4, 5].

C. hystrix is known to have a distinct citrusy aroma and spicy flavor, its leaves and fruits are widely used as an additive to improve the organoleptic properties of food [6, 7]. Besides, the oils from the leaves and the fruits of *C. hystrix* are commercially used as flavors and fragrances, as well as in cooking, perfumery and medical treatments, especially in aromatherapy [8]. Many kinds of organic compounds have been detected in *C. hystrix* leaves. Flavonoids, tannin, saponin, glycoside, coumarine, bergamottin, pinene, phenolic acids, limonoids, glycerolipids and α-tocopherol have been identified in kaffir lime leaf extracts [9, 10]. Preclinical studies have shown that some of its phytochemicals possess antibacterial, anti-fungal, anticancer, chemopreventive, anti-oxidant, anticholinesterase, cardio and hepa-toprotective effects.

2. BOTANY

C. hystrix belongs to a small tree with a width of 2.5 - 3 m and a height of 3 - 6 m, it often does not have a straight one, branched, with spiny and glabrous branches (Figure 1A). *C. hystrix* leaves

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are distinctive among the varieties of citrus species, they are alternate, unifoliolate. The leaves grow into two sections, apparently by a double leaf. The leaf is roughly ovate-oblong to ovate shape, which is 7.5 - 10 cm long, has a dark green top with lighter bottom, and is immensely aromatic. The long petiole is prolonged into notable wings, about 15 cm long and 5 cm wide. Leaf and expanded petiole appear to be a single "pinched" leaf. Leaf base is cuneate, or rounded, apex obtuse or slightly acuminate or notched (Figure 1B). Flowers grow at the tips of branches. The flower (Figure 1C) is small, strong aromatic, white in colour, with a four-lobed calyx cuspidation, and has an ovate-oblong shape with a long violet fringe, petals 4 - 5, ovate-oblong, yellowish-white tinged with pink; stamens 24 - 30 free; ovule attachment: axile placentation. The *C. hystrix* fruit has a large size (approximately 5 - 7 cm diameter), globose, verrucose, ovoid to elliptic and colour may turn from green to yellowish-green when ripe. It has a thick rind, bumpy or warty with yellowish pulp, which has bitter and acidic tastes (Figure 1D). The *C. hystrix* fruit produces numerous seeds that are numerous, ridged, ovoid-oblong, 1.5 - 1.8 cm by 1 - 1.2 cm, mono-embryonic with white cotyledons (Figure 1E) [11].

C. hystrix grows well in a tropical or warm subtropical climate; plants grow in well-ventilated conditions and prefer well-drained, neutral to slightly acid soil and direct sunlight with ample moisture during the growing season [12]. The leaves of *C. hystrix* are falling in winter, producing young leaves and flowers in mid-spring. Some biological features of the *C. hystrix* are often similar to other species of the *Citrus* genus. However, the growing area of *C. hystrix* is lower than that of oranges, lemons, tangerines and pomelos. In Vietnam, flowers of *C. hystrix* appear during February to April, and fruits are harvested from May to August [13].

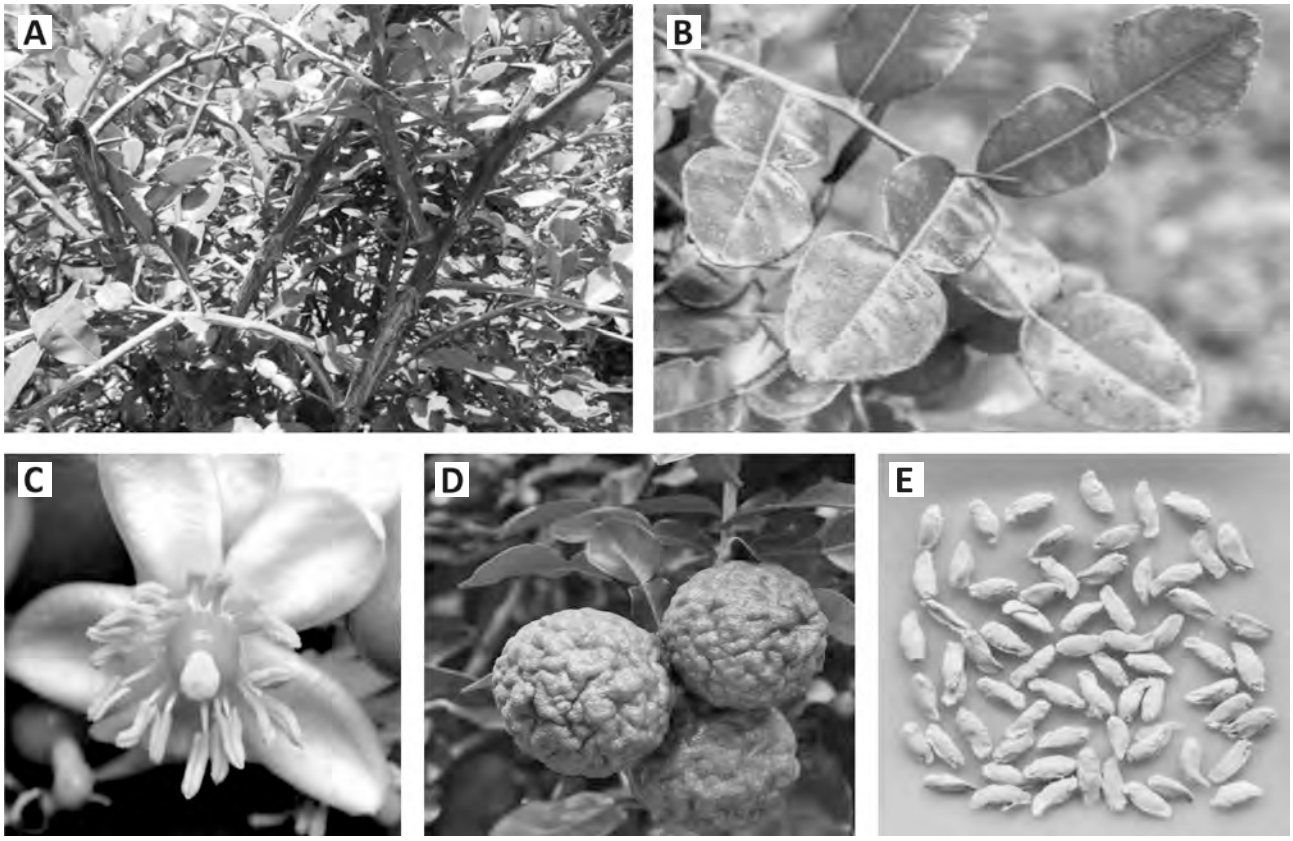

Figure 1. Morphology of *Citrus hystrix DC.* plant
A - Tree; B - Leaves; C - Flowers; D - Fruits; E - Seeds

3. CHEMICAL COMPOSITION

All parts of C. *hystrix* contain different bioactive molecules, insluding: essential oils, phenolic compounds, flavonoids and others. The main compounds of *C. hystrix* will be described in this review.

3.1. Essential oil

3.1.1. C. hystrix leaf essential oil

Essential oil of *C. hystrix* has been claimed to have many different bioactivities. *C. hystrix* leaves' essential oils were subjected to a GC-MS (gas chromatography-mass spectrometry) analysis for the identification of its constituents. There are 56 identified compounds in *C. hystrix* leaves' essential oils. In this literature, principal constituents of essential oils obtained have majorly consisted of monoterpenes, monoterpenoids, sesquiterpenes and sesquiterpenoids [14]. However, the yield of essential oils is affected by many different factors such as the plant's growth phases (vegetative, fruiting, and flowering), material, climate, soil... [15-18]. On the other study, *C. hystrix* leaves' essential oils contains 15 volatile compounds such as β-citronellal (85.436%, as the main component), β-citronellol (6.808%), citronellyl acetate (1.705%), sabinene (0.744%), β- pinene (0.311%), D-limonene (0.34%), β-linalool (1.891%), cyclohexanol (0.657%), α-copaene (0.211%), β-cubebene (0.133%), β-elemene (0.092%), α-caryophyllene (1.012%), cyclohexane (0.191%), naphthalene (0.283%), and elemol (0.185%) [19]. Besides, Othman et al. (2016) identified that the main volatile compounds present in the *C. hystrix* leaves were citronellal (72.4%), β-citronellol (6.7%), α-citronellyl acetate (4.1%) and pinene (1.9%) [20].

However, all studies show that the main component of essential oils is β-citronellal (a member of monoterpenoids). The monoterpenoids in *C. hystrix* leaves' essential oils account for 78.21% to 90.36% of the total essential oil content, depending on different isolation methods. There are 5 functional group monoterpenoids consisting of alcohol (linalool, isopulegol, 4-terpineol, α-terpineol, α-citronellol, citronellol, geraniol, and thujol), aldehydes (citronellal and hydroxycitronellal), carboxylic esters (citronellyl acetate, citronellyl butyrate, and geranyl acetate), oxides (linalool oxides and ascaridole), and diols (terpin and isopulegol hydrate) [14]. In other research, hydrocarbon and oxygenated monoterpene group of the essential oil of C. hystrix were observed. The hydrocarbon monoterpene group consist of sabinene (2.79%), β-pinene (0.33%), β-myrcene (1.04%), limonene (0.13%), β-ocimene (0.44%), cyclo-germacrene (0.3%), caryophyllene (1.77%) and cadinene (0.22%); and the oxygenated monoterpene group: linalool (3.46%), citronellal (85.07%), citronellyl acetate (2.77%) and geranyl acetate (0.61%) [21].

3.1.2. C. hystrix fruit essential oil

There are 21 identified constituents in *C. hystrix* fruit peel essential oils, with 3 major constituents: l-limonene (40.65%), terpinene-4-ol (13.71%), α-terpineol (13.20%). However, the major constituent of C. hystrix leaf essential oils were citronellal (80.04%) and 18 other constituents [22]. This result is similar to the results in the study of Hongratanaworakit and Buchbauer, the main compounds of fruit peel oil consist of limonene (30.73%), β-pinene (18.76%), terpinene-4-ol (10.63%), α-terpineol (8.35%), γ-terpinene (6.18%), α-terpinene (5.09%) and terpinolene (4.33%) [23]. In other studies, *C. hystrix* fruit peel essential oils contained 54 constituents. The major constituents were limonene (20.39%), α-terpineol (15.32%), 2-β-pinene (10.62%), terpinene-4-ol (7.69%), γ-terpinene (6.29%), α-terpinene (5.92%), and α-terpinolene (5.06%) [24].

The main constituents of *C. hystrix* peel and leaf oil were citronellal (about 23.85-23.41%),

elemol (6.59-4.17%), δ-cadinene (5.96-4.74), geranylacetate (5.12-4.45%), α-terpineol (5.15-5.40%), L-linalool (4.22-4.36%), β-pinene (1.82%), limonene (1.13%) and α-humulene (1.09-0.94%) [1].

C. hystrix juices were investigated to determine the composition of terpene group. Concentration of terpenes in the volatile fraction of C. hystrix juices were identified, including of α-pinene (3.07%), limonene (10.78%), aromadendrene (1%), camphene (4.86%), linalool (20.13%), terpinen-4-ol (44.79%), myrcene (22.36%), ϒ-Terpinene (25.01%) and α-terpineol (1.5%) [25].

3.1.3. C. hystrix twig essential oil

The essential oils content in different parts of the plant varies, including the roots, stems, leaves, flowers, fruits, and seeds [20]. In the research of Warsito et al., constituents hydrocarbon and oxygenated monoterpene group of the essential oil of *C. hystrix* twigs were observed. The hydrocarbon monoterpene group consists of sabinene (5.91%), β-pinene (1.24%), β-myrcene (1.27%) and cymene (0.80%); and the oxygenated monoterpene group contains linalool (13.111%), citronellal (46.40%), isopulegol (1.57%), terpinen-4-olb 1.52%), α- erpineol (0.93%), rhodinol (0.59%), citronellol (11.03%), citronellyl acetate (6.76%), geranyl acetate (0.77%) and nerodinol (1.11%). The *C. hystrix* twig oil has a higher content of constituents' hydrocarbon monoterpene group than the *C. hystrix* leaf oil. Conversely, the *C. hystrix* leaf oil has a higher content of constituents oxy-genated monoterpene group than the *C. hystrix* twig oil [21].

3.2. Phenolic and flavonoid compounds

Polyphenols are secondary metabolites, and are producted to protect themselves and interact with other plants. Polyphenols were found in all vegetative organs, fruits and flowers. Also, polyphenols have an effect on the formation of bitter taste in plants [26]. Polyphenols contain at least one aromatic ring and one or more hydroxyl groups, in addition to other components of them [27, 28]. There are 4 classifieds of polyphenols as follows: flavanoid, lignan, stilbene and phenolic acids [29].

Phenolic acids are divided into 2 types: (1) Benzoic acid and derivates, and (2) Cinnamic acid and derivates. Phenolic acids have many different roles in human health care [29]. Phenolic compounds of *C. hystrix* scavenge radical activities, so that phenolic compounds which have beneficial implications in human health. Phenolic compounds are widely distributed in fruits and vegetables [30]. Phenolic compounds include simple phenolic molecules to highly polymerized compounds. However, these phenolic compounds were obtained mainly in ethanolic extracts [31]. Six compounds of phenolic acids have been detected in *C. hystrix* leaves, including of vanillic acid, r-coumaric acid, sinapic acid, m-coumaric acid, benzoic acid and cinnamic acid [32].

Flavonoids represent the widely distributed group of plant phenolics. There are 6 flavonoid subspecies: flavonol, flavanol, isoflavone, flavone, flavanone and anthocyanin [33]. The peels of *C. hystrix* fruit have been reported to contain 3 main phenolic compounds, consisting of flavanone, flavone and flavonol. The fruit peels of *C. hystrix* have been reported to contain 3 main phenolic compounds, consist of flavanone, flavone and flavonol [34]. Besides, hesperidine was found in the peel of *C. hystrix* fruit. Hesperidine is a member of the flavanone group, and has been reported to have antioxidant, anticarcinogenic, anti-hypotensive and ntimicrobial properties. Also, hesperidine is responsible for radical scavenging activity [35 - 37]. The types and amounts of flavonoids were analyzed by HPLC

(High-performance liquid chromatography). There are 22 flavonoids monitored at 210 nm. Eight flavonoids were identified in *C. hystrix* leaves (100 g dry weight), including of cyanidin (123 mg), myricetin (179 mg), peonidin (206 mg), quercetin (43 mg), luteolin (25 mg), hesperetine (365 mg), apigenin (50 mg) and isorhamnetin (113 mg) [9].

3.3. Other extracts

Two glycerolipids (1,2-di-O-a-linolenoyl-3-O-ß-galactopyranosyl-sn-glycerol and 1-O-a-linllenoyl-2-O-palmitoyl-3-O-ß-galactopyranosyl-sn-glycerol) from methanolic extract of leaves of *C. hystrix* were evaluated [38]. Coumarins (bergamottin, oxypeucedanin and 5-[(6', 7;-dihydroxy-3', 7'-dimethyl-2-octenyl) oxy-]-psoralen) were exhibited from the methanolic extract of *C. hystrix* fruits [39]. Besides, 2 coumarins (hystrixarin and hopeyhopin) and hystrolinone (an quinoli-none alkaloid) were isolated from the crude acetone extract of root of *C. hystrix* [40]. Shaha et al. reported that pectin yields varied from 10.4% to 59.30% for sun-dried peel while for microwave dried peel of *C. hystrix* fruit was 25.9% to 61.80%. The best extraction condition is using citric acid at 90°C using microwave-dried peels [41]. There is 21.58 mg to 37.24 mg vitamin C in 100 g of *C. hystrix* fruit [42].

4. BIOLOGYCAL AND PHARMACOLOGICAL ACTIVITIES

4.1. Antioxidant

Most of the metabolism pathways in living organisms can relate to reactive oxygen species. Reactive oxygen species are chemically derived from oxygen such as superoxide anion, hydroxyl radicals and hydrogen peroxide, while the anti-oxidant system is able to defend against it to keep balance [43]. Reactive oxygen species play a critical role in the pathogenesis of many diseases such as aging, arthritis, cancer, inflammation, and heart disease, and cause oxidative stress [44]. *C. hystrix* leaf and fruit extracts were found to have potential anti-oxidant bioactivity [1, 9, 20, 21, 31]. Phenolic acids, flavonoids and their derivatives of *Citrus* fruits are reported to have a good antioxidant ability [44, 45]. The role of these compounds are listed: (1) Direct absorption and neutralization of free radicals [46], (2) Inhibition of enzymes associated with ROS pathways: NADPH oxidase, xanthine oxidase and myeloperoxidase [47, 48], and (3) Enhancement of the activities of human anti-oxidant enzymes: superoxide dismutase, catalase, ... [49].

The essential oils antioxidant activities of parts *C. hystrix* (twigs, twigs-leaves, leaves, fruit peel) were evaluated by the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay and expressed as IC_{50} (the 50% inhibition concentration) values. Fruit peel oil was the highest DPPH inhibition in four types of *C. hystrix* oil, with an IC_{50} value of 6.43 µL/mL, followed by twigs-leaves oil, twigs oil, and leaves oil. The reason for the different antioxidant activities of *C. hystrix* oils was due to the different chemical compounds containing and amounting of hydrocarbon monoterpene and oxygenated monoterpene groups [21]. Abirami et al. practiced experiments to compare the antioxidant activity of *Citrus* juices. The result showed that the *C. hystrix* juice was able to reduce the DPPH radical. However, *C. hystrix* juice had the lowest DPPH radical dot scavenging ability [50]. Besides that, ethanolic extracts of *C. hystrix* peels and leaves were investigated to the free radical scavenging capacities by DPPH assay and ABTS (2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid)) assay. *C. hystrix* peels extracts had ABTS radical scavenging ability higher than *C. hystrix* leaves extracts, while the DPPH radical scavenging ability of *C. hystrix* leaves and peels extracts were similar [51].

4.2. Antimicrobial: Antibacterial and anti-fungal activities

Chanthaphon et al. investigatied on the antimicrobial activities of ethyl acetate extracts and hydrodistillated-essential oils from *C. hystrix* peels. The ethyl acetate extracts from *C. hystrix* peels showed stronger antimicrobial activities than their essential oils obtained from hydrodistillation. The ethyl acetate extract of *C. hystrix* peels showed broad spectrum of inhibition, and it inhibited all Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Listeria mono-cytogenes*), yeast (*Saccharomyces cerevisiae* var. sake) and molds (*Aspergillus fumigatus* TISTR 3180). The major components of the ethyl acetate extract from *C. hystrix* peels were limonene (31.64%), citronellal (25.96%) and β-pinene (6.83%) [52]. However, the volatile oils and methanol extracts of *C. hystrix* (peel and leaf) did not show any antimicrobial activity (including of Gram-positive bacteria: *Bacillus subtilis* (ATCC6051), *Staphylococcus epidermidis* (ATCC12228), *S. aureus* (ATCC25923); Gram-negative bacteria: *Escherichia coli* (ATCC25922), *Enterococcus faecalis* (ATCC1406), *Proteus mirabilis* (ATCC14153), *Pseudomonas aeruginosa* (ATCC27853) and fungi: *Candida albicans* (ATCC10231), *C. parasilosis* (ATCC90018) and *C. tropicalis* (ATCC13803)). Except for *Mycobacterium phlei* (ATCC 11758), this bacteria was inhibited by the volatile oils of *C. hystrix* peel [53]. On the other hand, the *C. hystrix* leaves essential oil was tested against three Gram-positive bacteria (*S. aureus, S. epidermidis* and *Bacillus subtilis*), two Gram-negative bacteria (*Klebsiella pneumonia* and *Escherichia coli*), and five fungal strains (*Aspergillus fumigates, Candida albicans, Cryptococcus neoformans, Saccharomyces cerevisiae* and *Trichophyton entagrophytes*). The result showed that the *C. hystrix* leaves essential oil was only effective on *Cryptococcus neoformans* and *Saccharomyces cerevisiae* with MIC of (50 mg/mL) [54]. By the sensitivity test method of the diffusion disk method, the anti-fungal activity of *C. hystrix* leaves oil was demonstrated. The growth of *Pityrosporum ovale* was inhibited at a high level, with an inhibition zone diameter being 16.20 mm [55]. It is hypothesized that the antimicrobial active ingredient of *C. hystrix* (peel and leaf) is probably absent from the volatile oils and methanol extracts [53], and from the above data, it showed that the anti-fungal ability of essential oils is very strong with types of fungi.

Contrary to the above hypothesis, the methanol extract of *C. hystrix* fruit peel has high degree antibacterial activities, especially against *S. aureus* and *Salmonella typhi* [56]. Besides that, Srisukh et al. has tested the antibacterial activities of *C. hystrix* oils (leaves and fruit peels). The *C. hystrix* oils were prepared by steam distillation. The result showed that the antibacterial activity of *C. hystrix* oils were both effective against all the pathogens with minimal inhibitory concentration ranges of 0.06-68 mg/mL and 0.03-17.40 mg/mL, respectively. In this study, groups A, B, C, F, G *Streptococci*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus* (methicillin-resistant and -sensitive *S. aureus*) and *Acinetobacter baumannii*, obtained from patients with respiratory tract infections, were tested. On the other hands, the emulsion of *C. hystrix* peel oil, consisting of 40% w/v kaffir lime oil, 8% w/v gelatin, and 3% w/v lecithin, was diluted with water into a soaking solution. The soaking solution which contained 0.75% w/v of *C. hystrix* peel oil reduced the natural bacterial population on chinese cabbag. Five strains of the bacteria (*Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Salmonella typhimurium* (ATCC 13311),

and *Pseudomonas aeruginosa* (ATCC 9027)) were tested by agar dilution method [57].

4.3. Anti-inflammation

The expression of inflammation is swelling, heat, redness, fever and pain. Inflammation is a normal reaction of living tissue to injury [58] or a response of the body to infection diseases [59]. Chemical mediators from immune cells is released to the damaged area. Prostaglandin E2 and nitric oxide (NO), two interesting chemical mediators, are produced to induce symptoms of inflammation (pain, fever, redness and swelling) [60]. Kidarn et al. have tested the anti-inflammatory ability of two furanocoumarins (6′, 7′-dihydroxy-bergamottin and oxypeu-cedanin hydrate) which were isolated from *C. hystrix* fruit peel. The anti-inflammatory ability was proceeded by using an assay of nitric oxide scavenging effect- guided fractionation. The results demonstrated that two furano-coumarins inhibited lipopolysaccharide interferon gamma - induced NO and nitric oxide synthase production in RAW264.7 cells and cyclooxygenase-2 production in HT-29 and HCT116 cells. The inhibitory effect of 6′, 7′-dihydroxybergamottin on the production of nitric oxide synthase and cyclooxygenase-2 was significantly stronger than that of oxypeu-cedanin hydrate [61].

During inflammation, the acute phase response includes changes in the concentrations of many plasma proteins, which are known as the acute phase proteins. Interleukin-6 is the chief stimulator of the production of most acute phase proteins [62]. Agrostophillinol, a compound was isolated from a hexane fractional extract of *C. hystrix* leaves, exhibited potent anti-inflammatory activity, significantly inhibiting interleukin-6 secretion [63]. Besides, lupeol, a compound fractionated from the ethanolic extract of *C. hystrix* leaves, was investigated on NLRP3 and NF-κB signaling pathways. The result showed that lupeol significantly reduced the release of pro-inflammatory cytokines and sup-pressed the expression of both in flammasome genes and NF-κB proteins. Lupeol showed potent anti-inflammatory activities by targeting NF-κB and NLRP3 sig-naling pathways [64].

4.4. Anti-cancer

C. hystrix has been reported to possess many biological activities, including anti-cancer. *C. hystrix* has also been reported to exert potency against many types of cancers. Anti-cancer of *C. hystrix* leaf extract has a cytotoxic effect on cervical cancer and neuroblastoma cell lines [65]. The anti-cancer activity of *C. hystrix* leaves was caused by the action of bioactive compounds in the extract. These compounds may cause changes in metabolism. The expression of this change can be detected by protein profile. Tunjung et al. were to determine the protein profile of T47D and Vero cell after being treated *C. hystrix* lime leaf. The results showed that different solvents in extraction led to different protein profiles in T47D and Vero. The dose of ethyl acetate extract and chloroform extract were 283 µg/mL and 129 µg/mL respectively. Different protein profiles possibly caused by changes of cell metabolism [66].

A previous research showed that two glycerolipids (1,2-di-O-a-linolenoyl-3-O-ß-galactopyranosyl-sn-glycerol and 1-O-a-linllenoyl-2-O-palmitoyl-3-O-ß-galactopyranosyl-sn-glycerol) from methanolic extract of *C. hystrix* leaves were demonstrated to inhibit the tumor promoting activity of 12-O-tetradecanoyl-phorbol-13-acetate in mouse skin with dimethylbenz anthracene and 12-O-tetradecanoylphorbol-13-acetate. Both lipids were potent inhibitors of tumor promoter-

induced Epstein-Barr virus activation [67]. The extracts of *C. hystrix* induced cell cycle arrest in lymphoma cells [68], and also suppressed cell migration and induced cell shrinkage in human pancreatic cancer cells (PANC-1, MIA PaCa-2, and PSN-1) [69]. Two acyclic monoterpenoids (citronellol and citronellal that have been identified in *C. hystrix*) have been reported to exert many varied biological activities [70]. Citronellal exhibited toxicity against cancer cells (MCF-7 breast) [71] and reduced proliferation hepatocellular carcinoma (Huh7) by inducing apoptosis [72]. While citronellol induced necroptosis of lung cancer cell [73]. Both citronellol and citronellal against the triple negative breast cancer MDA-MB-231 cell line [74].

However, some of chemical compounds in the metanolic extract of *C. hystrix* could significantly enhance the hepatocarcinogenic effect. Hepatocarcinogenesis was induced by 2-amino-3,8 dimethylimidazo (4,5-f) quinoxaline. Methonolic extract of *C. hystrix* leaves were exerted strong promotive potential on induced hepatocarcinogenesis which was demonstrated in the rat model [75].

4.5. Anticholinesterase

Increasing communication between nerve cells that use acetylcholine as a chemical messenger produce a therapeutic effect in patients with Alzheimer's disease, glaucoma, myasthenia gravis, and for the recovery of neuromuscular block in surgery, then, acetylcholine breakdown in the brain can be prevented by the inhibition of acetyl-cholinesterase activity, which subsequently increases the concentration of acetylcholine [76]. Anti-cholinesterase activity due to the presence of active compounds, such as limonene, l-camphor, citronellol, o-cymene and 1,8-cineole. The juices of *C. hystrix* possess strong anti-cholinesterase activity of 79.74% against 86.89% of the used reference compound (Eserine) [50].

Several furanocoumarins, compounds were isolated from the hexanes and CH_2Cl_2 extracts of the peels of *C. hystrix* fruits, were evaluated for their cholinesterase inhibitory activity. 6′-hydroxy-7′-methoxybergamottin; 6′,7′-dihydroxybergamottin, and isoimparatorin showed IC_{50} values of 11.2 ± 0.1, 15.4 ± 0.3, and 23 ± 0.2 μM, respectively [77]. Besides, 3-O-β-d-glucopyranosyl-3,5,7,4′-tetrahydroxy-6,8,3′-trimethoxy flavonol nucleus in the prenylfuranocoumarin-HMGA conjugate (A compound was isolated from the ethyl acetate extract of the fruit peels of *C. hystrix*) showed very potent butyryl-cholinesterase inhibitory activity with IC_{50} value of 10.12 ± 0.22 μM, against galanthamine, a positive control compound with IC_{50} value of 11.2 ± 0.09 μM [78]. The tested essential oil of *C. hystrix* exhibited inhibitory activity on butyryl-cholinesterase higher than on acetylcholi-nesterase [79].

4.6. Diabetes

Diabetes is characterized by high concentrations of blood sugar which can cause serious complications in the kidneys, eyes and cardiovascularsystem [50]. One of the effective managements of diabetes mellitus, in particular, noninsulin-dependent diabetes mellitus, is to retard the absorption of glucose by inhibition of carbohydrate hydrolyzing enzymes, such as α-glucosidase and α-amylase, in the digestive organs [80]. Therefore, the α-amylase and α-glucosidase inhibitors are currently used for diabetic treatment as oral hypoglycemic agents. The α-amylase and α-glucosidase inhibition activities of *C. hystrix* were 75.55% and 70.68%, respectively [50]. Irawaty et al. optimize the extraction conditions of antioxidant, presented as total phenolic compounds, from *C. hystrix* peel using response surface methodology. The optimum conditions of polyphenolic compounds extraction from

C. hystrix peel were obtained at 7.8 h of extraction time by employing ethanol 41% as the solvent. In addition, *in vitro* study to investigate the antidiabetic effect of the extract was also performed. The results showed that the extract also exhibited the anti-diabetic activity [81]. The flavonoids of *C. hystrix* leaf effectively attenuated diabetes (fasting blood glucose) and mitigated diabetic cataracts on rats. It helps reduce diabetes-related hyperglycaemia, oxidative stress, inflammation, and vascular leakage. The evidence was that flavonoids consumption reduced the serum biomarkers tumor necrosis factor-alpha TNF-α; prostaglandin E2 PGE2, vascular endothelial growth factor, and malondial-dehyde. The *C. hystrix* leaf contains hesperidin, apiin, diosmin, saponarin, api-getrin, rutin and xanthotoxol, and other flavonoid glucosides [82].

4.7. Hepatoprotective

Swiss albino mice have evaluated the hepatoprotective effects of *C. hystrix* methanolic leaf extracts on paracetamol induced toxicity. Leaf extracts were administrated at the dose of 200 mg/kg bodyweight for 7 days and toxicity was induced by paracetamol (2 g/kg) on the 5th day, liver function markers (ALT, AST, ALP), total bilirubin and total protein in blood serums and hepatic antioxidants (SOD, CAT, GSH and GPx) in liver homogenate were estimated after those animals were sacrificed on the 7th day. The level of enzyme markers (alanine transaminase, aspartate transaminase and alkaline phosphatase) in experimental rats were significantly restorated of by the interventions *C. hystrix* leaves extract to the comparable level of normal control [10].

5. CONCLUSION

C. hystrix is a versatile, nutritious fruit with a great variety of uses. *C. hystrix* contains a number of phytochemical constituents, which are the key factors in the nutritional and medicinal value of this plant. The chemical structures of bioactive molecules explain their traditional uses and their potential to be used in cosmetical and pharmaceuticals.

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 isolated from various parts of *C. hystrix*, as reviewed here have been found to have many pharmacological activities such as antibacterial, antifungal, antioxidant, anti-inflammatory, anticancer and antioxidant activity.

Quite a significant amount of work has been done on the biological activity and possible application of these compounds and hence extensive investigation on its pharmacology and clinical trials is needed to exploit their therapeutic utility to cure various diseases.

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Tổng quan về cây Trúc

Lê Văn Út

TÓM TẮT

Cây thuốc đóng một vai trò quan trọng trong điều trị và phòng ngừa bệnh tật. Trong đó, cây Trúc (Citrus hystrix DC.) là một dược liệu phân bố rộng rãi ở khu vực nhiệt đới. Citrus hystrix DC. có nhiều hoạt tính sinh học và nó được sử dụng trong y học cổ truyền để điều trị các bệnh khác nhau, đặc biệt là cảm lạnh và rối loạn tiêu hóa. Bài viết tổng quan này tập trung vào việc tổng hợp thông tin các nghiên cứu về thành phần hóa học và tác dụng sinh học của cây Trúc nhằm đặt nền tảng cho các nghiên cứu sâu hơn về việc chiết xuất và ứng dụng các hoạt chất một cách hiệu quả hơn. Dựa trên

các dữ liệu khoa học được công bố, cây Trúc thực sự là một dược liệu đầy tiềm năng vì sự đa dạng các thành phần hóa học và các hoạt tính sinh học mà dược liệu này mang lại.

Từ khóa: *thành phần hóa học, hoạt tính sinh học, cây Trúc*

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