Egypt. J. Chem. **Vol. 66**, No. SI: 13 pp. 437 - 459(2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

An Overview on Botanical Characteristics, Phytochemical Constituents and Pharmacological Effects of *CordiaDichotoma* (G. Forst.) and *Cordia Sebestena* (L.) (*Boraginaceae*)

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Abstract

Genus *Cordia* has been well acknowledged in tropical and subtropical regions worldwide as traditional medicine, where its folk applications include uses in numerous disorders. The current review considers the geographical distribution, macromorphological characters, nutritional properties, phytochemical profile and biological prospective survey of *Cordia dichotoma* (G. Forst.) and *Cordia sebestena* (L.), aiming to highlight the pharmacological significance of the two species. Considering their nutritional value, fruits and leaves of *C. dichotoma* are rich in nutritional constituents, while limited data described the nutritional importance of *C. sebestena*. A chemical analysis of both species revealed many metabolites as coumarins, phenolic acids, flavonoids, sterols, terpenoids, volatile oils, carbohydrates, amino acids, fatty acids and others. The bioactivity studies of both species have been focused to possess potential antioxidant, antidiabetic, anticancer, anti-inflammatory, anti-pyretic, analgesic, anti-microbial, hypoglycemic, hypolipidemic and antiulcer activities. Meanwhile, antidepressant, antifertility, antiaging, anti-atherosclerotic, anti-anemic and diuretic activities were limited to *C. dichotoma*. On the other hand, anti-Alzheimer and larvicidal activities were limited to *C. sebestena*. There are fewer reported studies on *C. sebestena*, in spite of its important folk uses. Thus, this overview draws attention to further biological study on*C. sebestena* to discover its medicinal activities.

Keywords:*Cordia dichotoma*; *Cordia sebestena*; active constituents; folk uses, pharmacological activities

1. Introduction

Over the previous decades, plants possessing biologically active metabolites, which have been proven to be powerful natural medicines.The utilization of natural products, to prevent diseases is an old custom that resulted in discovery of many of pharmaceuticals used today. There is increasing interest in utilizing phytopharmaceuticals as alternative medicine in many diseases [1]. Genus *Cordia*contains approximately 300 species of trees and shrubs, distributed across the world's warmer regions[2]. The majority of *Cordia* species have edible fruits. The different plant parts of a variety of *Cordia* species, like *C. dichotoma, C. myxa, C.*

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EJCHEM use only: Received date 04 February 2023 revised date 30 March 2023; accepted date10 April 2023
DOI: 10.21608/EJCHEM.2023.191642.7557

oblique, C. Verbenaceae and C. Africana, have long been used in traditional medicine as antimalarial, anthelminthic, astringent, cicatrizing, diuretic and febrifuge. In addition, genus *Cordia* is used in lung diseases, leprosy and urinary infections [3]. Also, many species were reported to be used for treating cardiac, vascular, blood and digestive system disorders [4] and as appetite suppressant [5]. The most important isolated secondary metabolites from this genus include prenylated hydroquinone, terpenoid hydroquinone, triterpenoids, meroterpenoid naphthoquinone, sesquiterpenes, aryl naphthalene type lignin, polysaccharides, fatty acids, flavonoid, phenolic compounds, pyrrolizidine alkaloids,lignans and hydrocarbons [2]. *Cordia dichotoma* G. Forstis a traditional important deciduous plant in this genus.The entire plant is edible and used as food [6,7].Its fruit is rich with polysaccharides and produces a sticky, jelly-like mass [8]. It is utilized in Indian traditional systems of medicine e.g. Siddha, Unani and Ayurveda [9]. Seeds were used to treat a variety of inflammatory conditions [10],while seed kernels were used as cattle food [11]. Its different organs are used as anti-anemic, laxative,antidyspepsia [8], larvicidal and immunomodulator [2,12].

C. dichotoma is used in treatment of kidney, spleen, heart and blood diseases.*C. dichotoma* flowers are used to protect skin from sunburns [13]. Pyrrolizidine alkaloids, Coumarins, flavonoids, sterols and terpenes are the main constituents in fruits and leaves of *C. dichotoma*. Besides,four flavonoid glycosides (datiscoside, rutin, robinin and hesperidin),one flavonoid aglycone (dihydrorobinetin) and two phenolic acids (chlorogenic acid and caffeic acid) were isolated from its leaves and fruits [14,15].*Cordia sebestena* L. is an evergreen, Bahamas native tree. It can grow up to 25 feet tall. It has beenused as an ornamental plant due to its attractive flower.*C. sebestena* fruit is small and edible but not usually eaten by public. *C. sebestena*is used in gastrointestinal disorders[16,17]. The plant is known in the Hawaiian region for its timber because it is durable, has light weight and easily workable nature [17,18]. Initial screening of phytochemicals in suitable solvent extracts indicated existence of alkaloids, flavonoids, sterols, saponin, steroids [19], terpenoids, tannins, proteins, amino acids, cardenolides, carbohydrates [20] and glycosides [19,21,22]. Caffeic acid and its methyl ester, rosmarinic acid, sebestenoids A-D (1-4) and netpetoidin A-B are examples of compounds isolated from *C. sebestena* fruit [18]. For our knowledge, green AgCuO bimetallic nanomaterial has been synthesis from *C. sebestena* leaf extract [23].Review studies were conducted on *C. dichotoma* concerning its nutritional value, phytochemical constituents and pharmacological activities[8,24].Another study focused the interest on its traditional uses [7]. In addition, a short review about previously isolated phytochemical and some pharmacological activity of *C. dichotoma* was recorded [25].Also,areview about three *Cordia* species from Caribbean regions was recorded [26].Finally, a review represented the different extraction techniques of some bioactive metabolites of *C. dichotoma* was recorded [27]. On the other hand, only one review article has been published about various phytoconstituents, pharmacological activities and folk uses of *C. sebestena*[28].The current review study took into consideration all the previously published data on *C. dichotoma* and*C. sebestena* from the last twenty years. So, it is considered as updated, well documented overview with traditional medicinal system, which is advantageous for evaluating the biological effectiveness and identifying biologically active metabolites of the two plant species under investigation. The detailed information on *C. dichotoma* and how it can be used to treat various illnesses could be furthermore beneficial for references and related research works. The findings of the current review may lead to the discovery of new plant-based medications and therapies. It is clear that there was little reported information considering biological activity and metabolites isolated from *C. sebestena*. So, researchers can use the information in this review as a starting point to conduct more studies on *C. sebestena*.

2. Taxonomical classification

***Cordia dichotoma*:**

Local names: English (Indian cherry, clammy cherry), Gujarati (gunda, vadgundo), Bangali (bahubara, buhal), Tamil (vidi, naruli, kalvirusu), Hindi (lasura, borla, bhokar), Lao (sino-Tibetan), Javanese (Kendal), Thai (phakmong, manma), Nepali (kalo, bohori),Sanskrit (bahuvarka, shelu ,shleshmatak) and Malay (sekendai, petekat) [7].

Kingdom	*Plantae*
Subkingdom	*Tracheobionta*
Super division	*Spermatophyta*
Division	*Magnoliophyta*
Class	*Magnoliopsida*
Subclass	*Asteridae*
Order	*Lamiales*
Family	*Boraginaceae*
Genus	*Cordia*
Species	*Cordia dichotoma* G. Forst.

Cordia sebestena

Vernacular names: Hindi: Lal lasora, bohar, Bengali: Kamla buhal, Tamil: Acchinaruvihli, Kannada: Challekendala , Telugu: Virigi.Also, it is commonly known orange Geiger tree, large leaf Geiger tree, aloe wood, sea trumpet, ziricote, scarlet *Cordia*, Texas olive, geranium tree, sebesten plum tree and Spanish *Cordia* [29].

Kingdom	*Plantae*
Subkingdom	*Viridiplantae*
Super division	*Embryophyta*
Division	*Tracheophyta*
Sub-division	*Spermatophytina*
Class	*Magnoliopsida*
Order	*Boraginales*
Family	*Boraginaceae*
Genus	*Cordia*
Species	*Cordia sebestena* L.

3. Geographical distribution

The genus *Cordia* was given its name by Valetrius Cordus,a German pharmacist and botanist. It is distributed in regions with warmer weather in Africa, Asia, Sri Lanka, China and India[4].

C. dichotoma is known as gundaor tentiis, it is a plant of warmer regions, grows as a wild tree in Sub-Himalayan and beyond regions or may be planted alongside road, but rarely cultivated for commercial uses [30]. It is found in many of tidal forests in Myanmar as in Rajasthan's dry deciduous forests and the Western Ghats humid forests. Besides, it is growing alone in moist protected valleys [31], in the region with less than 500 mm of annual rainfall and it also develops well sideways depression [32]. It is distributed extensively in countries such as Formosa, Polynesia [33], Central South America [30], Philippines, Cambodia, Thailand, Timor, Vietnam, Singapore, Malaysia, India, Southern China, Solomon, Islands, Taiwan, Japan, New Caledonia and north-eastern Australia [34]. *C. dichotoma* tree is cultivated in Egypt and called mokhate [8,35].

C. sebestena is a type of evergreen plant, which commonly called as Kou Haole, Geiger tree, which is translated to "Geiger" in Indonesia and "foreign plant" in Hawaiian. The treeis cultivated widely in tropical areas, where it is widely available as a result of its widespread use in landscape gardening [28,36]. Tree is distributed in Colombia, Indonesia, Jakarta, Jamaica, Brazil and Costa Rica .While, it is native to Cuba, northern west Indies, United States, South Florida and the Caribbean region[21,30].

4. Macromorphological characters

C. dichotoma is deciduous tree, 15 m tall, with a crooked short trunk and a wide crown [13]. The bark of its stem is brownish gray in color, longitudinally wrinkled or smooth, becomes fissured with age [37]. Correspondingly, the stem has glabrous, soft wood and gray branchlets [25]. Its buds are nearly globose. The fruit is 1–2.5 cm long [38], ovoid drupe or globose, pinkish-yellow or yellow, seated in an enlarged saucer-like calyx. Fruit, when ripe, turns black in color and the pulp becomes viscid [3,13,39]. The hard stone has 1-4 seeds. The seed is flattened, ovoid and reaches up to 6 mm long [25]. The flower is yellowish white, bisexual inflorescence subcorymbose to subthyrsoid, short stalked, dimorphic and sessile [38,39]. The flower is either axillary or terminal in position and opens only at night [3,37,40].

Finally, *C. dichotoma* leaf is simple, oblong-ovate to ovate or elliptic-ovate-lanceolate, having a spiral arrangement, entire, slightly dentate or undulate at margins. The apex of leaf is rounded or acuminate and base is rounded or cordate [37].

Leaf petiole length ranges from 1.5 to 5 cm and stipules are not present. Tree shows pseudo dichotomous branching [38].
C. sebestena is an evergreen thick medium-sized tree, [16], up to 7 - 10 m tall and it spreads 20 to 25 feet. Crown of plant is dense, round to vase-shaped and symmetrical.Trunk is straight, dark to light gray or brown in color, 12 inches thick. Bark is fissured [28]. Fruit is ovoid drupe, three inches long and it contains 2-4 seeds [41]. Fruit covering is dry and hard [16]. When the fruit is ripe, its color changes from green to white[28]. Flower is complete, perfect, slightly zygomorphic, arranged in corymbs or cymes, 2-5 cm long [29], dark orange to red, funnel-shaped and having 5-7 petals borne on a terminal panicle inflorescence [16]. Petals are irregular, wrinkly and aggregate as clusters at branch tips. While, calyx has 5 fused sepals. Stamen is short and yellow in color. Flowers are abundant in June and July [36].
*C. sebestena*leaf is ovate, 4.5-10 cm, green in color, covered with several hairs. Leaf has simple and alternate arrangement. The margin of leaf is entire or serrate with an acute apex. Characteristic features of leaves are that they are thick, deeply veined and upper surface is rough [42][29].

5. Nutritional properties:
Ripe fruit of *C. dichotoma* is eaten raw as well as it is pickled and used in vegetable dishes. *C. dichotoma* seed kernels have high concentration of proteins and fatty oils, as a result, seed has the potential to be used as cattle feed. Chromium content in the fruit has beneficial role in diabetes. Leaves contain 16%-27% crude fibers , 22%-4% total calcium, 12%-15% crude protein and 0.3% phosphorus [25].Thefruit contains seventy percent pulp. The pulp contains 6 g water, 37 g fats, 18 g carbohydrates, 35 g proteins, Mn (2 mg), P (275 mg), Zn (2 mg), Ca (55 mg), Fe (6 mg) and Cr (0.2 mg) per 100 g.The fruit also has some antinutritional contents *viz;*, oxalic acid (250 mg) , phosphorus (100 mg)and phytic acid (355 mg) per each100 g[43].Another study revealed that *C. dichotoma*fruit from Malkangiriregion contains acidity, protein, carbohydrate, non-reducing sugar, reducing sugar and maximum amount of moisture. While, contain least amount of saponin, phytate, oxalate and tannins [44]. As conclusion, fruits of *C. dichotoma* are important source of fibers and vitamins [7,45,46].Tree of *C. sebestena* is sometimes harvested from the wild for its edible fruit, which is eaten locally.*C. sebestena* seed is rich with oil and protein content. It may also provide macronutrients such as Mg, Ca Na and Zn. Besidesthe nutrient contents, the presence of antinutrients such as phytate, oxalateand tannins were high in concentration.So, it can be a drawback to use seed as food [47].

6. Phytochemical constituents:
Initial phytochemical screening of *C. dichotoma* different parts (**Figure 1**) showed existence of metabolites such as flavonoids, phenylpropanoids, phenolic acids, pyrrolizidine alkaloids, coumarins, terpenes, sterols, carbohydrates, amino acids, tannins and saponins [48].The fruit contained several phytoconstituents, including flavonoids, alkaloids, proteins, tannins, saponin, glycosides, phytosterols and carbohydrates [49]. Seventeen fatty acids were identified from stem bark by GC-MS [50]. Many phenolic compounds and lignans were identified in ethyl acetate extract of *C. dichotoma* fruit [35].The most important secondary metabolites identified in *C. sebestena* include prenylated hydroquinone, naphthoquinone, terpenoid hydroquinone, sesquiterpenes, triterpenoids, fatty acids, anthocyanins, steroids, phytosterols, polysaccharides, flavonoids, phenolic acids, glycosides and hydrocarbons [21,51]. These secondary metabolites were found massively in the flower than in leaves and bark. As well as, those metabolites can be extracted with polar solvent rather than non-polar one [52].Leaves of*C. sebestena* demonstrated the existence of, proteins, tannins, amino acids, alkaloids, saponins ,carbohydrates, volatile oil and fixed oil [28]. Oleic acid, is the main unsaturated fatty acid in seed oil, constituting 71.1% from all fatty acids content ofseed oil, which is very beneficial to be consumed by humans [53]. It's worth noting that extract of ethyl acetate from the leavescontains aromatic compounds and non-polar aliphatic compounds [17,19].GC–MS of essential oil obtained from *C. sebestena* by hydro distillation of stem bark revealed 19 compounds in total including cyclic hydrocarbons (13.89%) and aliphatic hydrocarbons (72.73%) [54]. The different isolated constituents from both *C. dichotoma* and *C. sebestena* are given in table (**1**) and figures (**1**) and (**2**).

7. Folk uses

Mucilage from *C. dichotoma* fruitis used to treat cough, chest disease, uterus and urethra disorders. Besides, fruits are used also as emollient, demulcent, expectorant, astringent[10], anthelmintic, diuretic, antiulcer, anti-inflammatory, wound healing agent, aphrodisiac, analgesic and as cosmetic agent [8,55]. The fruit kernel is used to heal tinea [14].Bark powder from *C. dichotoma* is utilizedto cure mouth ulcers, dental caries, abscesses, tumors and fever [34,56]. Bark is also used to treat dysentery when combined with pomegranate, while with coconut water is used to relieve colic. Goiter is treated with a decoction of stem bark [38]. The Unani medical system used *C. dichotoma*as antiviral, antibacterial and antitussive [43]. Since ancient time, stem bark as well as leaves of *C. dichotoma* were used to treat diarrhea, common cold, catarrh, dyspepsia, leprosy, gonorrhea and burning sensation[8]. Also, it was used to treat impotency, bronchitis, asthma, rheumatism and infection of urinary passage [43].*C. dichotoma* peel extracts were used to treat fever and externally to treat skin conditions like heat boils [12,38,56].*C. sebestena*has long been utilized in Ayurvedic medicine for treating several disorders such as urinary incontinence, rheumatism, inflammatory disorders, snake bite, influenza and cough. The decoctions of leaves, syrup of bark, flowers and fruit are used to treat gout, tumors, menstrual spasm, ulcer, wounds, fever, asthma, boils, diarrhea, dysentery and liver ailments [20,57,58]. Root decoction is employed to cure malaria ,oedema, bronchitis and tuberculosis [2,59]. Bark is used as a liver stimulant and astringent. The flowers' tea is used to cure venereal ailment and leaf poultice is used for headaches and sprains [60].Fruits and leaves of *C. sebestena* have emollient effect. While, only fruits are used as blood purifier and emetic[20,61].

Reported pharmacological activities for both *C. dichotoma* and *C. sebestena*:

The reported pharmacological activities for the two species are presented in figure (**3**) and summarized in the following part.

Acute toxicity study

Rats were not harmed by 2000 mg/kg of methanol extract of *C. dichotoma*[14]. The methanolic extract of its bark was subjected to acute toxicity study at doses of 10, 100 and 1000 mg/kg for 24 hours and at doses of 2000, 3000, and 5000 mg/kg for 48 hours. Up to 48 hours no toxicity whether mortality or behavioral changes were observed [60].In sub-acute research of *C. sebestena*, 200-400 mg/kg of the plant extract was given every day for 14 days to rats. The extract's LD_{50} was 4000 mg/kg. During the period of experiment, no rat died. Meanwhile, for acute toxicity experiment, the ethanolic leaf extract was given at doses ranging from 50 to 5000 mg/kg to rats. There were no obvious toxic symptoms or deaths were observed 24 hours after administration of the extract[62]. The ethanolic extract of *C. sebestena* leaf [63]androot extracts [64] up to 2000 mg/kg, showed no evidence of mortality in rats. Also, *C. sebestena* leaves ethyl acetate extract was not harmful to rat liver at the different examined dosages (50,100 and 200 mg/kg), renal function was normal, but the extract produced significant increase in urea levels [58]. Also, acute toxicity of fruit extract was assessed at different doses. Dosage of 2000 mg/kg was presented toxic symptoms to rats [57].

Analgesic activity

C. dichotoma ethanol leaf extract at oral dose of 500 mg/kg, has pain-relieving activity in acetic acid model in mice. This dose displayed 71.75% writhing prohibition in rat, in comparison to diclofenac sodium as reference drug [65]. Furthermore, in Eddy's hot plate model, leaf methanolic extract (400 mg/kg) showed remarkable dose dependent analgesic effect, comparing to indomethacin (10 mg/kg) [14].*C. sebestena* leaf ethyl alcohol extract (100, 200 and 400 mg/kg), showed strong analgesic effects activity by writhing method and hot plate method, using tramadol as reference drug. This effect was concentration independent [17].

Anti-inflammatory activity:

C. dichotoma seed ethanol and aqueous fractions have acute anti-inflammatory action in dextran and carrageenan-induced paw oedema in rats at 250 mg/kg and 500 mg/kg oral dose, comparing to diclofenac sodium (10 mg/kg) [66]. Such effect was attributed to phytochemicals such as α-amyrin and taxifolin [31]. Furthermore, transdermal films made from

C. dichotoma natural polymer (fruit gum), exhibited anti-inflammatory effect in carrageenan model compared with diclofenac sodium[67]. As well as, leaf methanol extract of *C. dichotoma*exerted anti-inflammatory activity in female albino rats at 200 and 400 mg/kgin carrageenan-model, comparing to

indomethacin (10 mg/kg) [14].Moreover , defatted methanol extract of bark (250 and 500 mg/kg) suppressed inflammation induced by carrageenan using indomethacin as standard drug. The phytochemical constituents in barksuch as phenolic compounds, saponins and alkaloids are responsible for this activity [60]. Finally, the ethylalcohol extract of *C. dichotoma* leaves displayed potent anti-arthritic activity by protein denaturation assay. Protein denaturation inhibition revealed to be 79.12% ,when concentration was 1000 µg/ml [68].*C. sebestena* leaf alcoholic extract exerted anti-inflammatory activity in carrageenan test [17,41]. *C.sebestena* (100, 200, 300, 400 and 500 µg/ml) ethanolic extract showed *in vitro* anti-inflammatoryactivity in proteinase inhibitory method (IC_{50} =169.53µg/ml). Diclofenac sodium was taken as standard drug[69].

Anti-ulcerative activity:

Different fractions of *C. dichotoma* fruit were examined for antiulcer activity using three distinct ulcer induced models (aspirin, pyloric ligation and indomethacin) in albino rat. Total acidity and gastric secretion volume were decreased with respect to reference group [70]. Methanol and aqueous extracts of *C. dichotoma* ripe fruit demonstrated an effective ulcer index reduction in rats in comparison to ranitidine (50 mg/kg) in two ulcer models (aspirin and pylorus ligation). It had been discovered that aqueous extract was more effective than methanol one [71]. The fruit has thick mucilage, because of this its form protective coat in stomach, which helps to heal ulcer. Moreover, apigenin from *C. dichotoma*bark methanol extract showed antiulcer activity on acetic acid model in male Swiss mice. Apigenin (5 mg/kg) displayed very good healing and less infiltration of inflammatory cells. The gross lesion scores and themyeloperoxidase levels in blood and tissue were decreasedcompared with prednisolone [72].

C. dichotoma fruit aqueous and methanol extracts reduced the damage effect caused by aspirin on rabbit gastric mucosa. Thevolume of gastric fluid , pH of stomach and acidity levels weredecreased[73]. Additionally, methanol extract of *C. dichotoma* leaf (50, 100 and 200 mg/kg), presented antiulcer effect in stress and indomethacin -induced gastric ulcer models in Wistar rats, in comparison to omeprazole (10 mg/kg). Gastric volume, pH, gastric acidity and other parameters were decreased in dose dependent manner [12].

Methanol, chloroform, and ethyl acetate extracts of *C. sebestena* root showed antiulcer activity in ethanol induced ulcer model, comparing to lansoprazole. It was found that methanol extract was the most potent tested extract [64].

Antioxidant activity

C. dichotoma seeds and leaves demonstrated antioxidant activity in a way that depends on dose using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and hydrogen peroxide models (H_2O_2). Leaf presented higher antioxidant potential than seed [37]. But another study demonstrated that the extract of seeds was more potent than leaves. The activity of seeds was related to taxifolin content [39,74]. *C. dichotoma* bark displayed antioxidant activity in DPPH model (IC_{50} = 62.46 µg/mL) [60]. Also, *C. dichotoma* bark butanolic and methanolic extracts demonstrated antioxidant potential in DPPH (IC_{50} =28 µg/mL) and ferric reducing power capacity methods [75]. Leaf, stem, fruit and fruit pulp exhibited antioxidant potential by methods of 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), lipid peroxidation and DPPH assays. All parts of plant tested showed good antioxidant potential, but fruit pulp was the most active [3].As well as, *C. dichotoma* fruit pulp aqueous extract has antioxidant activity by different methods such asDPPH(IC_{50}=41.92 µg/ml), metal chelator, reactive oxygen species scavenging agent and reductive power. It worth noting that fruit extract showed reducing power capability more than that documented with ascorbic acid or butylated hydroxytoluene. Metabolites in fruit *viz;* polyphenols, tannins, glucuronic acid, flavonoids and many volatile constituentsare responsible for this activity [76]. Furthermore,root extract presented forceful antioxidant activity in DPPH (IC_{50}= 30.15 µg/ml) and H_2O_2 (IC_{50}=55.97 µg/ml) methods [77]. *C. sebestena* essential oil obtained from the stem bark [54],ethanolic extract of whole plant (IC_{50} =30.5 µg/ml) [63] and methylated fatty acids of flower [41]showed antioxidant activity by DPPH assay, comparing to butylated hydroxyanisole as standard [54]. Aside, hesperetin from acetone extract of flower and acetone extract of flower exhibited antioxidant activity by numerous *in vitro* methods like DPPH,

hydroxyl free radical scavenging activity (IC_{50} =436 µg/mL), reducing power activity and nitric oxide radical scavenging activity [52].In addition, leaves extract of *C. sebestena* with different solvent systems displayed antioxidant activity by DPPH method. The more phenolic content was present in the 70% ethanol extract of leaves the more its antioxidant effect [22]. Moreover, leaves ethanolic extract demonstrated a dose dependent antioxidant activity by phosphomolybdenum ,DPPH and ferric reducing antioxidant power methods .This activity was related to vitamin C, polyphenolics and tannins content [78].

Hepatoprotective activity:

C. dichotoma leaf methyl alcohol extract (300 and 500 mg/kg) exerted hepatoprotective effect in carbon tetrachloride-induced liver damage model in Wistar rats. The leaf extract meaningfully decreased the activities of thiobarbituric acid reactive substances , and aspartate amino transferase (AST) and alanine aminotransferase (ALT)levels ,comparable with silymarin (100 mg/kg) [79]. In addition, methanol and aqueous extracts of fruits (300 mg/kg) exerted hepatoprotective effect in paracetamol caused hepatic damage in rabbits. The fruit extract caused significant reduction of serum liver enzymes and improvement of histopathological changes [80]. Ethanol extract of whole plantof *C. sebestena*[63] and methanol extract of its fruit [57] were examined for hepatoprotective effect in Wistar albino rats at 200 mg/kg and 400 mg/kg for 30 days, silymarin was used as reference drug. Results showed dose-dependent upturning of the simvastatin-induced change in levels of ALT, AST, urea, cholesterol and total bilirubin, as well as bringing back the total albumin and protein levels. This result was supported by histopathological improvement.

Cytotoxic activity

Ethyl alcohol extract of *C. dichotoma* showed cytotoxic action on brine shrimp lethality assay (LC_{50}=20 µg/mL) [65]. Cytotoxicity of *C. dichotoma* leaf methanolic extract on human cervical cancer cell line (HeLa) was evaluated using 4′,6-diamidino-2-phenylindole (DAPI) and (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) (MTT) staining tests .The results showed that extract with gotten IC_{50} of 202 µg/mL, prohibited *in vitro* proliferation and induced apoptosis of HeLa cell, which signified a powerful anticancer property in comparison to tamoxifen (IC_{50} =48 µg/mL) [81,82].

As well as, leaves methanolic extract exhibited cytotoxicity effect against a cell line from a human prostate carcinoma. It increased cell death significantly (IC_{50} = 74.5 µg/ml) [83]. Besides, methyl alcoholic extract of seed of *C. dichotoma* as well as itsdifferent fractions (ethyl acetate,chloroform and aqueous) exhibited antiproliferative activity against human lung carcinoma (A549) and HeLa cell lines at a range of concentration from 25 µg/mL to 250 µg/mL.This study offers proof of higher anticancer activity of the previous extracts towards HeLa cell lines than lung cancer cell lines [55]. As well as, *C.dichotoma* fruit pulp extract (500 mg/kg) revealed anti-tumor effect against Ehrlich ascites carcinoma (EAC) cells in mice, using fluorouracil as reference drug. The weight of solid tumor and numbers of viable Ehrlich cells were meaningfully reduced. The extract of fruit pulp also demonstrated *invivo* antitumor capability against EAC in mice [76]. Finally, anticancer activity of extract of fruit pulp, leaf, bark and seed of *C. dichotoma* was examined *in vitro* on ten different human carcinoma cell lines utilizing SulforhodamineB assay. The result displayed that bark had anticancer property and leaded to cell death against A-549 cell line, with IC_{50} :37.978 (µg/ml) [6].Pentane-2,4-dione, isolated from petroleum ether extract of leaf of *C. sebestena* showed anti-proliferative effect on HeLa cell line in MTT assay (IC_{50}=10µg/ml). In addition, molecular docking simulations showed that this compound, displayed a high affinity for Kras protein, with the least bindingenergy. This activity may be due to Kras protein inhibition [84]. Consequently, hesperetin from*C. sebestena* flower acetone extract showed cytotoxic activity (IC_{50} =2.86 µg/mL) against HeLa cell line in MTT assay [52].

Antibacterial activity

*C. dichotoma*leaf extractdisplayed antibacterial activity by method of agar well diffusion against two strains of *Escherichia coli*[85]. Ethanol and butanol extracts of bark were reported to have an antibacterial effect on *Streptococcus pyogenes,Pseudomonas aeruginosa* and *Staphylococcus aureus*[65,86]. Also, *C. dichotoma* leaf ethanolic extract showed antibacterialactivity against *Hafnia alvei, Streptococcusepidermis, Vibrio cholerae, Streptococcus aureus and Streptococcus epidermis)* [65]. Additionally, methyl alcohol and chloroform extracts of *C. dichotoma* displayed antibacterial effect on *P. aeruginosa, E. coli and Bacillus cereus,* while petroleum ether fraction presented no activity against the previous tested bacteria [87].

Moreover, methanolic extract of fruit pulp, stem and leaf of*C. dichotoma* demonstrated significant antibacterial actionagainst methicillin resistant, *Bacillus subtilis, B. cereus, S.aureus, Proteus vulgaris, Pseudomonas aeruginosa and E. coli* at dose levels of 50, 100 and 150 µg/ml. The fruit pulp was found to be more active than other parts tested [3]. Along with, a study described the anti-biofilm and photocatalytic activity of *C. dichotoma* fruit synthesized silver nanoparticles (Cd-AgNPs). Synthesized Cd-AgNPs displayed over 90% prohibition of biofilm activity which made by*S. aureus and E. coli*[88]. The various *C. dichotoma* root extracts showed antibacterial power by agar diffusion assay against bacteria *viz;Salmonella typhi, Klebsiella pneumonia,* Staphylococcus*epidermidis,P. vulgaris* and *B. subtills*. Also, root extract exhibited antimycobacterial activity towards *Mycobacterium tuberculosis* with minimum inhibitory concentration (MIC) of 30 mg/mL [77]. *C. sebestena* flower methanol extract displayed antibacterial potential by agar method against, *P. aeruginosa, S. aureus, E. coli,B. cereus and S. pyogenes*. The inhibition zone is ranging from 6 to 13 mm [19]. Ethyl acetate, hexane, and ethyl alcohol extracts of *C. sebestena* showed antibacterial action by method of agar dilution against, *S. aureus*, *B. subtilis, B. Cereus, E. coli* and *P. aeruginosa*. Ethyl acetate extract displayed the highest antibacterial activity.MIC of the extracts was varying from 8.94 to 18.97mg/ml[58].Also,*C.sebestena*demonstratedantim ycobacterial activity at doses of 20, 100 and 200 mg/mL, by agar cup diffusion assay [58]. Hesperetinfrom *C. sebestena* flower acetone extract and acetone extract of flower exhibited potent antibacterial action against*B. subtilis, S. aureus*,*E.coli* and *P. aeruginosa*[52]. Silver nanoparticles made from *C. sebestena* plant extract demonstrated antibacterial effect against *E. coli* with maximum zone of inhibition at 12.5mg/disc, in disc diffusion method[89].

Anthelmintic activity

C. dichotoma fruit Ethanolic and aqueous extracts ofwere tested for anthelmintic potential on*Eudrilids eugenia* earthworm at a dose of 10-100 mg/mL, piperazine citrates (10 mg/mL) was used as reference drug. The two extracts displayed dose dependent paralysis and mortality of worms, but aqueous one was more active [90]. In addition, the root extract (10, 25, 50 and 75 mg/mL) showed dose-dependent anthelmintic activity action*Pheretima posthuman* compared to standard drug albendazole. Plant constituents like caffeic acid, lupeol, octacosanol and hentriacontane may be responsible for this activity. Computersoftware was used also to confirm anthelmintic activity of constituents [91]. Chloroform, ethyl acetate, Petroleum ether and methyl alcohol extracts of leaves of *C. sebestena* presented anthelmintic action towards Indian earthworms *Pheretima posthuma* at concentration of 10 mg/mL to 50 mg/mL, but less than piperazine citrate [92].

Hypoglycemic activity:

C. dichotoma methanolic extract of fruit (200 mg/kg) displayed asignificant hypoglycaemiceffect in alloxan and glucose loaded models in male rats. However, this potency was less than metformin [93]. Another study demonstrated hypoglycaemic effect of leaf aqueous extract's effect in alloxan model and normoglycemic rats. Different doses of the extract (250,500 and 1000 mg/kg) were tested, only 500 and 1000 mg/kg dose levels exhibited strong antidiabetic activity [11]. Furthermore, *C. dichotoma* bark methanol extract (250 and 500 mg/kg) showed hypoglycaemic effect in alloxan model. Bark extract presented enhancement of biochemical parameters such as, antioxidant enzymes/biomarkers, serum lipid profile and body weight. Potency of extract (500 mg/kg) was somewhat comparable with glibenclamide (5 mg/kg)[9].Quercitrin and one other flavanol glycoside, from stem bark of *C. dichotoma* weretested to assess their antidiabetic potential by molecular docking and ADMETstudy (Chemical absorption, distribution, metabolism, excretion, and toxicity).ADMET and docking study showed that flavonoid molecules have a high affinity for binding to human pancreatic α-amylase and human lysosomal α-glucosidase [94]. Moreover, various *C. dichotoma* leaf extracts were tested for *in vitro*antidiabeticeffect.It was found that the methanol fraction possessed the strongest inhibitory action towards α-glucosidase (IC_{50} :295.38 µg/mL) and α-amylase (IC_{50} :278.95 µg/mL) [95].Ethyl alcohol extract of fruit of *C. sebestena* (100 and 200 mg/kg)presented hypoglycemic activity in streptozotocin induced diabetogenic rodents. Also, it showed improvement in body weight, biochemical

parameters, serum electrolytes and hematological indices, that are disturbed in diabetes [59]. *C.sebestena* ethyl alcohol extract (500 µg/ml) displayed alpha amylase inhibitory activity. The IC_{50} value of the hydroethanolic extract extraction was shown to be 270.67µg/ml[69].

Pharmacological activities reported for *C. dichotoma* rather than *C. sebestena*

Antipyretic activity

Methyl alcohol extract of *C. dichotoma* leaf (200 and 400 mg/kg) showed strong antipyretic effect in yeast-induced pyrexia model, comparing to paracetamol (100 mg/kg) [14].

Antifungal activity

Extracts of *C. dichotoma* bark and leaves presented dose dependent antifungal activity against three pathogenic fungi (*Aspergillus niger, Candida albicans* and *Aspergillus clavatus*). The zone of inhibition was 12–21 mm [40]. Besides, root extract displayed antifungal activity against different strains of fungiwith MIC recorded 10-40 µg/ml. In addition, the *in vitro* antifungal efficacy of root was confirmed by *in silico* docking study [77].

Wound healing activity

Different fractions of *C. dichotoma* fruit (300 mg/kg) revealed significant wound healing activity in rats of Wistar strain. This was related to flavonoid, saponin and amino acid content of fruit [10].

Antiaging activity

C. dichotoma extractenhancing skin biomechanical properties, mainly its firmness and elasticity. As well as, preventing wrinkles from appearing or reducing their depth. So, extractwas used in cosmetic preparation [31].

Antifertility activity

C. dichotoma bark methanol extract [96] and ethanol extract of leaf [97] showed anti-implantation effect at a dose of 100 mg/kg. Constituents, like saponins, glycosides and flavonoids, were related to activity. The previous extracts showed antifertility potential, when tested on male rat at the same previous dose level for 21 days. Also, the leaf extract exhibited complete anti-implantation effect when administered at dose of 800 mg/kgon female albino rats and also demonstrated powerful estrogenic effect. Luteolin and apigenin in leaf were responsible for this activity [97]. *C. dichotoma* leaf extract (200 and 400 mg/kg) was given to female albino rats (200-250 g) of proven fertility. The extract had a strong anti-implantation effect by 59.39% at dose of 200 mg/kg, meanwhile by 81.22% at dose of 400 mg/kg. Besides, extract showed estrogenic potential due to the existence of estrogenic plant constituents as steroidal glycosides and saponins [98].

Finally, the impact of a hydroethanolic extract of fresh fruits (500 mg/kg) concerning fertility was investigated. Fruit extract exhibited fully reduction in sperm total count. In addition, fruit extract exhibitedremarkable decrease on testosterone, luteinizing hormone and folliclestimulating hormone [99].

Antidepressant activity, behavioral changes and hypoperfusion effect

Ethyl alcohol and aqueous extracts of leaves of *C. dichotoma* (200 and 400 mg/kg) were investigated for antidepressant effect in behavioral animal model. Ethanolic extract showed more potent antidepressant effect than aqueous extract. Additionally, locomotor activity was also measured in open field test, but no change of motor dysfunction was observed [100].*C. dichotoma* long-term effects on the cerebral hypoperfusion in rats was assessed. A brief period of cerebral ischemia was caused by ketamine.*C. dichotoma* at dose of 250 mg/kg for 28 days, decreased cognitive, histopathological and behavioral changes [101].

Hypolipidemic activity:

Seed of *C. dichotoma* has hypolipidemic effect, so itis used for treatment of cardiovascular diseases.

C. dichotoma seed pulp was tested in two dose levels. Pathological study findings showed that seed pulp extract reduced fatty changes in rats' livers [45]. Moreover, aqueous extract from *C. dichotoma* fruits (0.5 and 1.0 g/kg) was tested for hypolipidemic effect in rats fed a high-fat diet. Fruit extract displayed enhancement in rat lipid metabolism relative to the control group. Furthermore , it lowered overall weight gain and increased the dry and fresh weight of feces [102].

Anti-atherosclerotic activity

Isorhamnetin from C. *dichotoma* bark showed a potent concentration dependent anti-atherosclerotic action in L-Nitro-Arginine Methyl Ester induced hypertension model. Total cholesterol, low density lipoprotein, triglyceride and very low-density

lipoprotein levels were decreased, while high-density lipoprotein level was increased. In addition, isorhamnetin decreased the high arterial pressure[103].

Inhibitory activity of angiotensin-converting enzyme

The ethyl alcohol extract of bark of *C. dichotoma* possessed a high inhibition ability towards this enzyme [27].

Diuretic activity

Different fractions from alcoholic extract of *C. dichotoma* fruits (300 mg/kg) showed a raise in urine volume as well as cations excretion in rats [27].

Anti-anemic effect

The extract of fruit of *C. dichotoma* (100, 200 and 300 mg/kg)presented a substantial concentration dependent increase in RBC count and hemoglobin content in anemic rats. The higher doses (200 and 300 mg/kg), also decreased the bleeding and clotting times [104].

Thrombolytic activity

C. dichotoma leaves ethyl alcohol extract displayed thrombolytic activity. Human blood volunteer was used to test the thrombolytic activity. The percentage of clot lysis was found to be 31.23% [68].

Pharmacological activities reported for *C. sebestena* rather than *C. dichotoma*

Anti-Alzheimer activity

Sebestenoids A–D isolated from *C. sebestena*fruit revealed activity against serine and aspartic protease, which are the primary cause to Alzheimer's ailment. This activity was dose-dependent [18].

Larvicidal activity

Different extracts of leaves of *C. sebestena* (100, 250, 500, 1000 and 2000 µg/mL) were assessed for larvicidal effect, against *Aedes aegypti* third and fourth instar larvae. They showed a weak larvicidal activity [28].

Conclusion

The current review provides an overview study of*C. dichotoma* and *C. sebestena* with respect to their macromorphological and taxonomical features, geographical distribution, nutritional values, phytochemical constituents, traditional usages and pharmacological activities. Whole of 92 compounds were reported to be isolated from different organs of the two plant species, these compounds were mostly related to terpenoids, phenolic acids,steroids and flavonoids. *C. dichotoma* fruit is a traditional delicious and nutritious fruit. Previous studies have shown that*C. dichotoma* fruit possesses good wound healing, antiulcer, hypoglycemic effects. So, C. *dichotoma* fruits have enormous potential for the development of functional foods. Existing pharmacological studies have revealed that extracts from both plants possess broad range of beneficial pharmacological effects on human health, especially for their cytotoxicity, anti-inflammatory and hypoglycemic activities. Some traditional uses of the two species have been demonstrated through the development of evidence from *in vitro* studies. However, extensive preclinical and clinical research will still be required for new drug discovery from those plants. In conclusion, it was found that fewer works were reported on *C. sebestena* considering its phytochemical constituents and pharmacological activities. As a result, more research should be conducted in the future to explore a more aboutabout its chemical composition and medicinal value.

Table (1)

Chemical constituents reported in *C. dichotoma* and *C. sebestena*

Class	**Compound**	**Species and part used**	**Reference**
Phenolic acids	Caffeic acid (1) Rosmarinic acid (2) Methyl rosmarinate (3)	Fruit of *C. dichotoma* and *C. sebestena*	[18] [51]
	Gallic acid (4) Catechin (5) *p*-Coumaric acid (6) Syringic acid (7) *p*-Hydroxy benzoic acid (8) Ferulic acid (9) Vanillic acid (10) Chlorogenic acid (11)	Fruit of*C. dichotoma*	[35]
Phenylpropanoids	Netpetoidin A–B (12) (13) Sebestenoids A–D (14-15-16-17)	Fruit of *C. sebestena*	[18]
Flavonoids	Hesperidin (18) Hesperetin (19) Hesperitin-7-rhamnoside	Fruit, leaf, bark and seed of *C. dichotoma*	[31,94]
	Luteolin (20) Apigenin (21)	Leaf of *C. dichotoma*	[97]
	Quercetin (22) Quercitrin (23) Quercetin-3-O -2Grhamnosylrutinoside (24)	Leaf of *C. dichotoma*	[2]

	Rutin (25) Isorhamnetin (26) Isorhamnetin-3-O-rutinoside (27)	Leaf and fruit of *C. dichotoma*	[2]
	Kaempferol (28) Kaempferol-3-O-robinoside (29) Kaempferol-3-rutinoside (30) Kaempferol-3-O-rhamnosylrutinoside (31)	Leaf of *C. dichotoma*	[38]
	Taxifolin (32) Taxifolin-3, dirhmnoside Robinin (33) Datiscoside (34) Dihydrorobinetin	Seed of *C. dichotoma*	[77,105]
	3',5-dihydroxy-4'-methoxy flavanone-7-*O*-L-rhamnopyranoside 7,3,5-trihydroxy-4-methoxyflavone-7-*O*-L-rhamnopyranoside	Bark of *C. dichotoma*	[94]
Carbohydrates	Arabinoglucan D-Glucose L-Arabinose	Fruit of *C. dichotoma*	[106]
	Glucuronic acid (35) Fructose Sucrose		[51]
Terpenoids	Betulin (36)	Bark of *C. dichotoma*	[39]
	Lupeol (37)	Flower of *C. sebestena* and	[107][29]

		Seed of *C. dichotoma*	
	Lupeol-3-rhamnoside (38) *α*-Amyrins (39) Oleanolic acid (40) Protoaescigenin(41)	Seed and bark of *C. dichotoma*	[39][2]
Sterols	Calcifediol (42) Ergosterol peroxide (43) Pregnanediol (44) Ethyl cholate	*C. dichotoma*	[108]
	β-sitosterol(45)	Flower of *C. sebestena* Bark of *C. dichotoma*	[21][13]
	β-Sitosterol-3-glucoside (46) *β*-Sitosteryl-3-*β*-glucopyranoside-6'-*O*-palmitate (47)	Twig of *C. dichotoma*	[48]
	Stigmasterol (48)	Flower of *C. sebestena,* bark of *C. dichotoma*	[38][29]
Fatty acids	Arachidic acid (49) Behenic acid	Seed of *C. dichotoma*	[7]
	Palmitic acid Stearic acid (50) Oleic acid *γ* -Linolenic acid Linoleic acid	Seed of *C. dichotoma* and *C. sebestena*	[25][47]
	Retinoic acid	Flower of *C. sebestena*	[29]

Volatile constituents	*α*-Phellandrene (51) Linalyl butyrate (52) Bornyl acetate *α*-Terpineol	Fruit of C. *dichotoma*	[76]
	Hemimellitene *β*-Myrcene (53) *γ*-Elemene *p* -Vinyl guaiacol Nerolidol (54)	Bark of *C. sebestena*	[16]
Miscellaneous compounds	Octacosanol Hentricontane Hentriacontanol Allantoin (55)	Seed, bark of *C. dichotoma*	[39]
	Chlorophyll 1,2-dilinoleoyl-3-linolenoylglycerol Nervonyl4-hydroxy-transcinnamateester (56) Squalene	Leaf, twig of *C. dichotoma*	[48]
	Acetyl acetone (57)	Leaf of *C. sebestena*	[84]

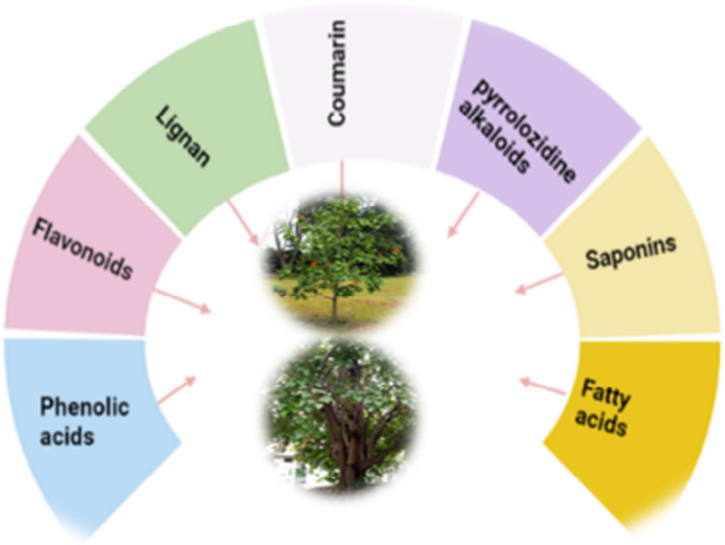


Figure 1: Major phytoconstituents in *C. dichotoma*and *C. sebestena*

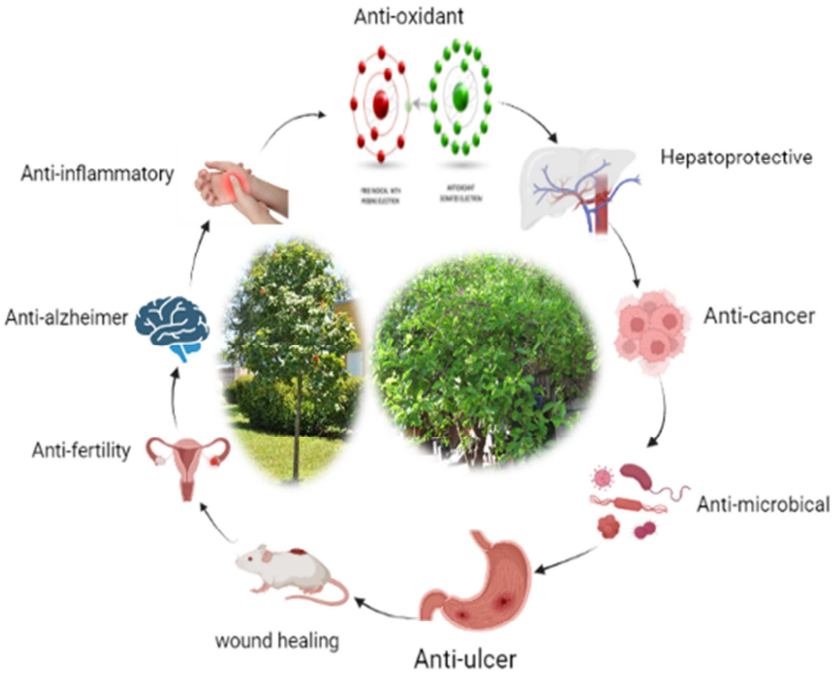
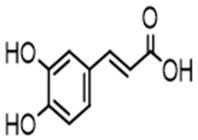


Figure 3: Common pharmacological activities of *Cordiadichotoma* and *Cordiasebestena*



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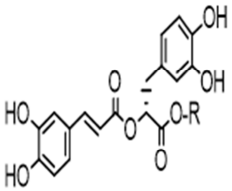
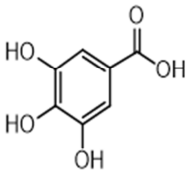


R=H 2

R=methyl group 3



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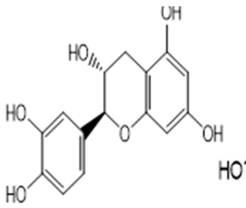

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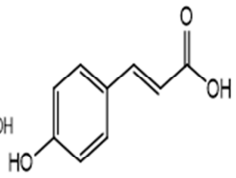

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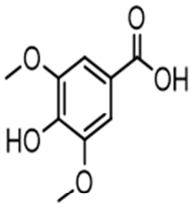

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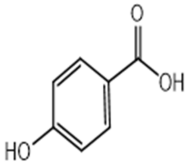

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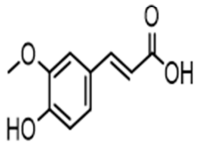

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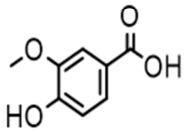

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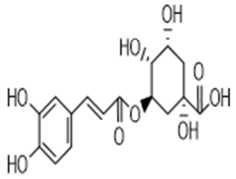

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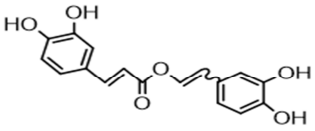
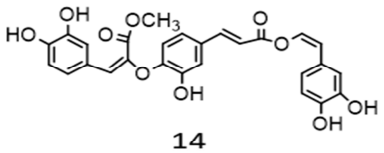


Δ7, 8 = E	12
Δ7, 8 = Z	13



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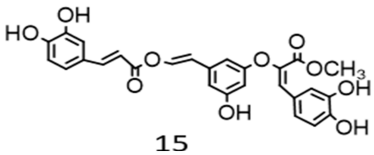

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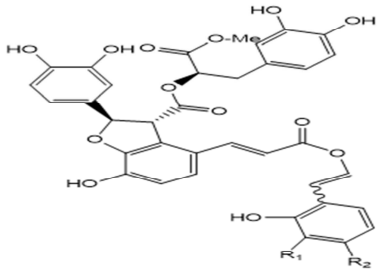
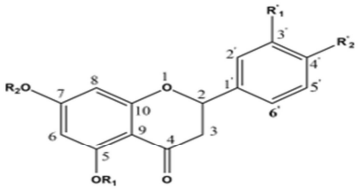
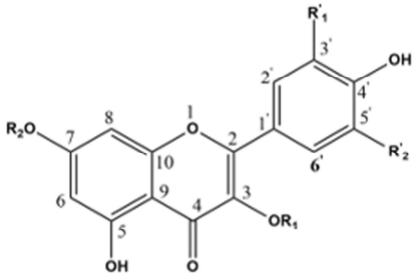


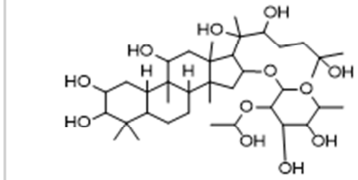
R_1=OH	R_2=H	16
R_1=H	R_2=OH	17



Compound	R_1	R_2	R`$_1$	R`$_2$
18	H	Rha1-6gluc	OH	OCH_3
19	H	H	OH	OCH_3
20	H	H	OH	OH
21	H	H	OH	H



Compound	R_1	R_2	R_1`	R_2`
22	H	H	H	OH
23	rhamnose	H	H	OH
24	2G-rhamnosylrutinose	H	H	OH
25	rutinose	H	OH	H
26	H	H	H	0-CH_3
27	rutinose	H	H	0-CH_3
28	H	H	H	H
29	robinose	H	H	H
30	rutinose	H	H	H
31	2G- rhamnosylrutinose	H	H	H
32	H	H	H	OH
33	gal-rham-	rham	H	H



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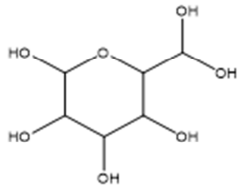

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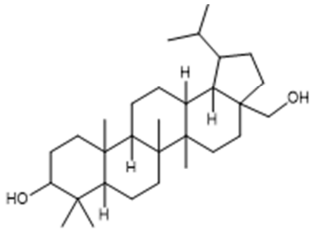

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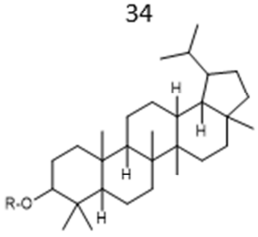
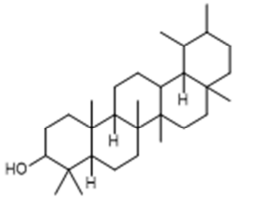


R=H 37

R=rhamnose 38



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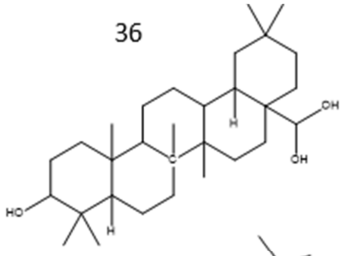

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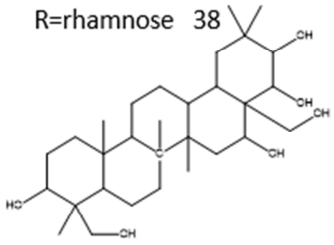

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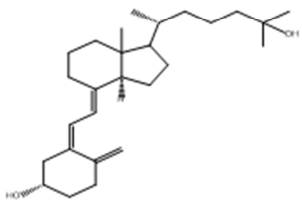
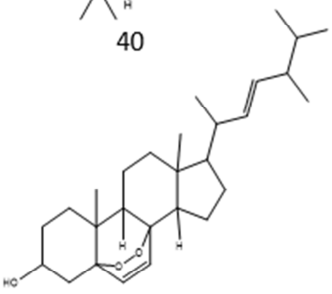


42



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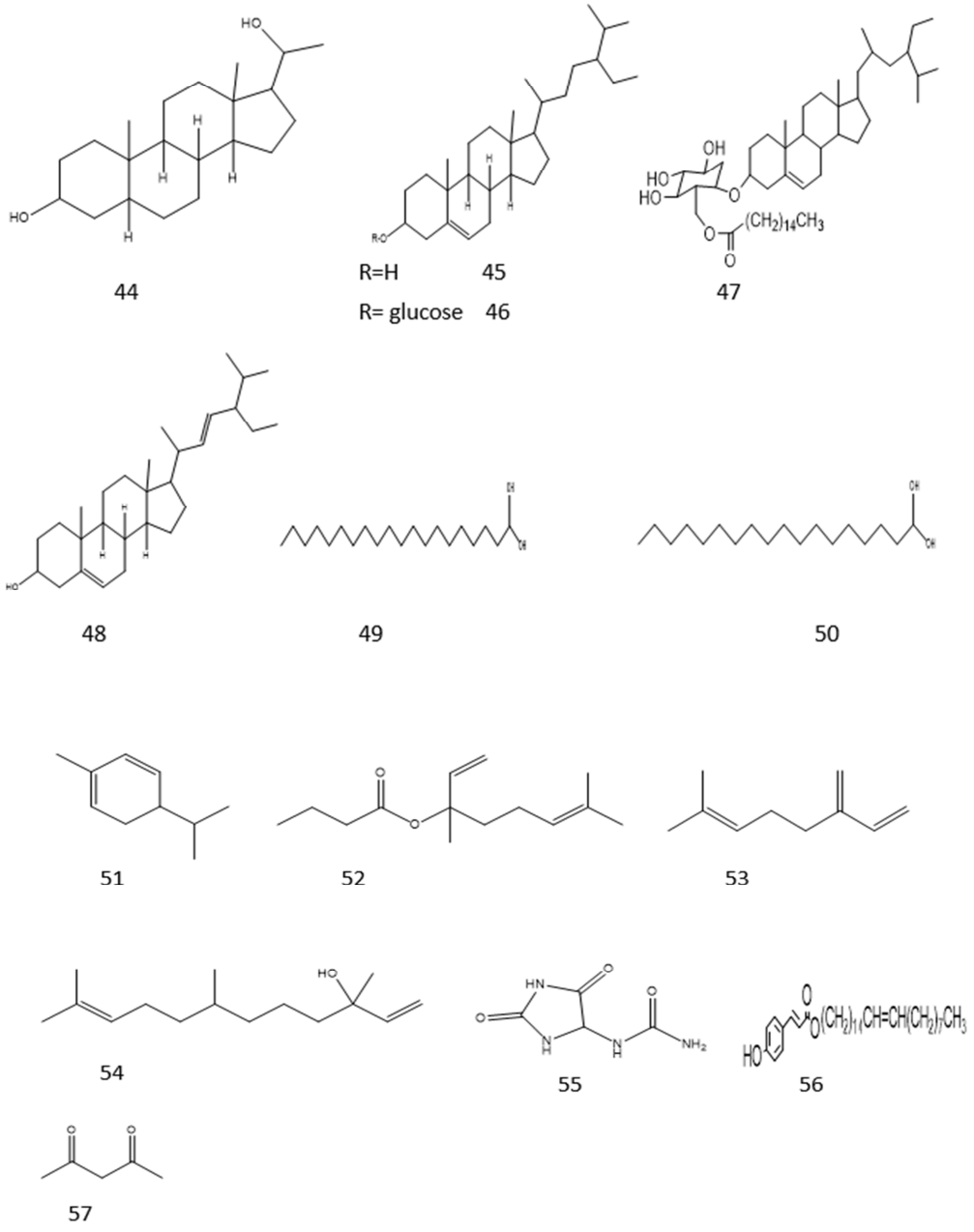

Figure 2: Chemical constituents isolated from *C. dichotoma* and *C. sebestena*

Statements and Declarations: The authors have no relevant financial or non-financial interests to disclose.

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