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Review

A review of traditional uses, phytochemical and pharmacological aspects of selected members of *Clausena* genus (Rutaceae)

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The present review describes the morphological, traditional, phytochemical and pharmacological aspects of the most medicinally important members of *Clausena* genus. *Clausena excavata*, *Clausena anisata, Clausena lansium*, *Clausena harmandiata, Clausena anisum*-olens and *Clausena dentata* are the targeted species for investigation in this review. The selected members of the genus *Clausena* which belongs to the Rutaceae family represent the most important sources of phytochemicals, particularly alkaloids, coumarins, limonoids and essential oils. The aim of this review paper is to investigate in a systematic way, the more recent developments in the phytochemical and pharmacological aspects of this genus as well as the traditional uses of its members. The species in which the largest numbers of secondary metabolites have been identified are *C. excavata* and *C. anisata*. Pharmacological investigations have also been made, however, of other species in this genus. Accordingly, anti-inflammatory, antiviral, antioxidant, cytotoxic and antibacterial activities of the two former mentioned species as well as the lesser known species of the genus is demonstrated here. This present paper enumerates an overview of its phytochemical and pharmacological properties, which may provide assistance to researchers to determine further, the efficacy and potency of *Clausena* genus members as medicinal plants.

Key words: Ethonpharmacology, secondary metabolites, coumarins, bioactivities, anticancer, phytomedicine.

INTRODUCTION

The discovery and identification of biologically active secondary metabolites from new promising drug species is one of the most effective ways in which the study of medicinal plants has clearly progressed. In this sense, the genus *Clausena* has been essential in providing us with so many natural products of interest to researchers in the field of pharmacology. *Clausena* is a genus of about 14 species of evergreen trees, occurring mostly in India and tropical Asia (Burkill, 1966). One of the most advantageous features of the species of this genus is their availability in the different parts of the world, mainly in India, Tropical Asia and South Africa. They are being easy to grow and free of pests and diseases as well as can withstand heavy pruning (Swarbrick, 1997). It was found

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that few species of *Clausena* genus (about 9 out of 23 known species) have been explored and identified for chemical and biological studies. The present study has been focused on six species which are considered as the most promising species of *Clausena* genus. According to the review of the literature of this genus, further investigations concerning ethnopharmacological aspects should be carried out on these selected species. The focus of this review is to study the traditional uses, chemical constituents and biological activities of the different species of *Clausena* genus. Therefore, the review includes all compounds (secondary metabolites) known to the selected species of Clausena genus. The work is planned to be a guide for future research. Thus, the overall body of the review involving Clausena plants has been ordered in a way that it could serve as easily accessible and comparable forms of knowledge Govindarajan et al., 2009).

OCCURRENCE AND BOTANICAL FEATURES

The geographical distribution of *Clausena* is of interest since it has the widest range of any genus included in the orange subfamily. The species are being found all the way from Northwestern India to China and Taiwan, south through the East Indian Archipelago to Timor, Northern Australia, and New Guinea. Moreover, there is a group of three species that covers a wide range in Africa, from Ethiopia (Abyssinia) to Cape Province and through Western Africa from Angola north to Serra Leone. There are wide differences in the character of the growth and the height of the species; they range all the way from shrubs of 20 to 40 cm high in Indo-China to trees reaching a height of 20 m (66 feet) in Africa. The most distinctive morphological character of the genus *Clausena* is the gynophore, which in the typical species is a large, well-developed, hourglass-shaped structure supporting the ovary (Ayisi and Nyadedzor 2003). Nevertheless, it is present in all species of *Clausena* and separates them from the species of other related genera. The numerous species of this genus, still only imperfectly studied with respect to the minute flower characters, cannot be arranged now in natural sections or subgenera.

TRADITIONAL USES OF *CLAUSENA* SPECIES

Many different traditional uses of about six species of *Clausena* genus have been reported in this review. Medicinal uses as well as food uses are the most observable ones. The different parts of the plant (leaves, stem bark, stem, fruit, flowers, twigs and roots) have been used for treatment of a large group of diseases. Sometimes a mixture of two parts or more of the plant in a form of powder or liquid doze is given to the patients to treat a certain disease. In some parts of Asia, the fruits of some species are eaten by human beings and also given to animals as food. More details are given subsequently for each species (Chokeprasert et al., 2007).

Clausena excavata (Burm. f, Rutaceae)

Description and distribution

C. excavate (Figure 1A and B) is a shrub with strong and rather objectionable smell, found from the Himalayas and China to and throughout Malaysia; particularly in the Peninsula. In Malaysia, it is locally known as “Cherek hitam”, “Chemama” and “Kemantu hitam”. The English name of this species is “Clausena” (Burkill, 1966). It is a slender tree to 10 m tall. Twigs are finely hairy. Leaves pinnate, to 60 cm long, with 10 to 15 pairs of dark green narrowly oval oblique leaflets 3.5 to 7 cm long with pointed tips. Leaflets have a characteristic curry-like smell when crushed. Small white flowers occur in terminal clusters, followed by translucent pink berries 7 to 10 mm across, each containing 1 to 2 seeds. *C. excavata* has a striking hourglass-shaped gynophore which is completely glabrous (Tanaka, 1937).

Morphology of the plant

For its traditional uses, Tamils introduced it as a potherb (Burkill, 1935); and among the Malays, it is a plant of some medicinal importance (Ridley, 1935). This plant is used traditionally as a medicine in the treatment of abdominal pain, snakebite and as a detoxification agent. The pounded root is used as a poultice for sores including ulceration of the nose and the leaves also used as a poultice. A decoction of the roots is drunk for bowel-complaints, chiefly colic. Gimlette was found to be used in Kelantan for yaws (He et al., 2006). The flowers and leaves may be boiled and the decoction taken for colic and a decoction of leaves is given after child birth. The leaves of this plant are used to cure cold, abdominal pain, malaria and dysentery. Decayed teeth can be treated using the drayed and powdered rootstock, whereas its stem is given in colic with or without diarrhea (Kirtikar and Basu, 1933). The expressed juice of the plant is used in Java for coughs, as vermifuge. The timber is used for handles of axes in Java (Wu et al., 1992).

Phytochemistry of C. excavata

A large number of secondary metabolites, mainly alkaloids, coumarins, limonoids and some essential oils have been isolated from different parts of this plant using different techniques of extraction and purification. The structures of these compounds have also been

Figure 1. *C. excavata* (Burm. f, Rutaceae); (A) the fruits and leaves; (B) the appearance of overall tree.
Source: (A) http://citrusvariety.ucr.edu/ ; (B) http://www.tradewindsfruit.com

elucidated using different spectroscopic methods. Details are given in Aoudou et al., (2010).

Alkaloids: Ten new carbazole alkaloids, clausine-M, -N, -O, -P, -Q, -R, -S, -U, -V and clausenatine-A, together with 39 known compounds were isolated and identified from the acetone extract of the root bark of *C. excavata* (Tian-Shung Wu et al., 1999). Also biscarbazole alkaloid known as Clausemine-A was isolated from the stem and root bark of *C. excavata* (Zhang et al., 2000). It is reported that a new carbazole alkaloid, 3-carbomethoxy-2-hydroxy-7-methoxycarbazole, Clausine-TY, together with two known carbazole alkaloids, Clausine-H and Clausine-B, were isolated from the ethyl acetate extract of the stem bark of the Malaysian *C. excavata* (Taufiq, 2007). Another six known carbazole derivatives, 3-formylcarbazole, mukonal, 3-methoxycarbonylcarbazole, murrayanine, 2-hydroxy-3-formyl-7-methoxycarbazole and clauszoline J were isolated from the rhizomes and roots of *C. excavata* (Sunthitikawinsakul et al., 2003). Extraction process on the stems of *C. excavata* led to isolation of a new carbazole alkaloid, sansoakamine, together with 11 known compounds (Wu et al., 1999). Pottert, O. reported that a new carbazole alkaloid, named clausine Z, has been isolated from the stems and leaves of *C. excavata* (Potterat et al., 2005).

Coumarins: Four natural pyranocoumarins clausenidin, nordentatin, clausarin, and xanthoxyletin were isolated from the medicinal plant *C. excavata* (Laphookhieo et al., 2009). Chemical investigation of the fruits and stems of *C. excavata* led to the isolation and identification of a new coumarin, namely clausenaexcavin (Kongkathip et al., 2010). A study of the chemical constituents of the leaves of *C. excavata* cultivated in a greenhouse led to the isolation and identification of 10 new furanone-coumarins named clauslactones A, B, C, D, E, F, G, H, I, and J, together with a known carbazole, clauszoline M, and a coumarin, umbelliferone (Ito et al., 2000). A new dimeric coumarin, diseselin B, and 3 new phenylpropanoids, lenisin A to C, together with 8 known O-terpenoidal coumarins, were isolated from the aerial part of *C. excavata* (Takemura et al., 2004).

Two new O-terpenoidal coumarins named excavacoumarin A and B, and a known one were isolated from the leaves of *C. excavata* collected in Xishuangbanna, Yunnan (He et al., 2000). Chemical investigation on an ethanol extract from the aerial part of *C. excavata* resulted in the isolation of two new O-diterpenoidal coumarins, excavacoumarins H and I (He et al., 2004). Six new O-terpenoidal coumarins, named excavacoumarins B to F and G, were isolated from the aerial part of *C. excavata* collected in Xishuangbanna, Yunnan. An epimer of excavatin D was found also. Three new coumarins containing a C10 terpenoid side chain, clauslactones R to T, together with 14 known coumarins and 11 known carbazole alkaloids, were isolated from the leaves and stems of *C. excavata* (Xin et al., 2008). In addition to a known alkaloid, some limonoids and coumarins, the new coumarins excavatins A to M (e.g. I, excavatin A) have been isolated from *C. excavata* (Thuy et al., 1999). Four new furanone-coumarins, clauslactones-N, -O, -P and -Q were isolated from the leaves and twigs of *C. excavata* (Takemura et al., 2000).

Limonoids: A limonoid, clausenolide-1-ehylether was isolated for the first time from the crude ethanol extract of the rhizomes and the roots of *C. excavata* (Sunthitikawinsakul et al., 2003). The stem bark of *C. excavata* collected from Jabi, Kedah yielded two limonoids, clausenarin and CEA. The stem bark of *C. excavata* collected from Jabi and Pendang, Kedah in December 2006 yielded a new limonoid, clausenolide-1-metylether. This was obtained from the methanol extract

Figure 2. *Clausena anisata* (Willd.) Hook. f. ex Benth; (A) the appearance of the overall tree; (B) the leaves and fruit of the plant.
Source: (A) www.findmeacure.com; (B) www.zimbabweflora.co.zw

together with a known limonoid, clausenarin (Trinh et al., 1999).

Essential oils: The essential oils of this plant were obtained by hydrodistillation using fresh leaves and analyzed using GC-MS spectrometry. It was reported that the main essential oil components from *C. excavata* (Jabi A) were safrole and α-terpinoline, while (Jabi B) gave safrole and β-sitosterol.

Clausena anisata (Willd.) Hook. f. ex Benth.

Description and distribution

This species of *Clausena* genus (Figure 2A and B) is slightly different in morphology compared to the two previously mentioned ones. The plant, a tropical shrub or tree up to 10 m high is growing in and on the margins of evergreen forests. The leaves are pinnately compound with 10 to 17 alternate or sub-opposite leaflets and a terminal leaflet. The leaves are densely dotted with glands and have a strong scent when crushed. The scent has been likened to aniseed and opinions vary on its pleasantness. Inflorescence, a branched axillary spray; flowers are small but attractive, white with orange-yellow stamens. The plant is native to Africa, mainly in West Africa and North Africa. In Mozambique, it is locally known as "Horse wood" (Burkill, 1966).

Morphology of the plant

The plant is traditionally used in different African countries for treatment of many illness cases. In Nigeria, a mixture of *C. anisata*, *Afraegle paniculata* and *Azadirachtha indica* is taken against gut disturbance and a concoction of the latter called "Agbo" is used as an antimalarial medicine. In Tanzania, traditional healers use *C. anisata* against oral candidiasis and fungal infections of the skin. In the Temeke district (Daressalam, Tanzania) traditional healers employ *C. anisata* against epilepsy and as an anticonvulsant. In South Africa, the leaves of *C. anisata* are applied against high blood pressure. In some parts of Africa and in the Philippines the burning of fresh leaves is utilized to repel mosquitoes.

Phytochemistry of C. anisata

Alkaloids: Carbazole alkaloids are the major constituents of this plant. They belong to the class of 1-oxygenated-3-methoxy-carbazoles having a prenyl side chain or an analogous moiety at C-4. From the alcoholic extract of the stem bark of *C. anisata*, two alkaloids clausenol and clausenine were isolated. From the combined stem bark and root extracts of *C. anisata* two new alkaloids, 1-methyl-3,4-dimethoxy-2-quinolone and 3-formyl-1-hydroxycarbazole, and four known alkaloids identified as heptaphylline, girinimbine, ekeberginine and 3-methylcarbazole were isolated (Ito et al., 2009). Another study led to the isolation of four new carbazole alkaloids, named clausamine D, E, F, and G, from roots of *C. anisata* (Ito et al., 2000). The study of chemical constituents of the stems of *C. anisata* collected in Thailand led to the isolation and identification of eight known and two new carbazole alkaloids named furanoclausamines A and B (Ito et al., 2009).

Coumarins: A reinvestigation of *C. anisata* has yielded imperatorin, xanthotoxol, lansamide-I and three new furanocoumarin lactone derivatives: Indicolactone, anisolactone and 2′,3′-epoxyanisolactone. Two new geranyl coumarins have been isolated from the leaves of *C. anisata* and identified as anisocoumarins I and J on the basis of spectral data and chemical correlation. The

Figure 3. *C. lansium* (Lour.) Skeels; (A) the appearance of the overall plant; (B) the leaves and fruits.
Source: (A) www.oramsnurseries.com.au; (B) www.en.wikipedia.org

isolation of 21 coumarins from the leaves, stem-bark and roots of this plant and their biogenesis is also discussed.

Essential oils: Hydrodistilled leaves of *C. anisata* yielded 0.55% (v/w) of essential oil. Analyses of the oil by GC and GC/MS revealed that the oil was characterized by the abundance of phenylpropanoids, with anethole (31.1%) as the most abundant compound. Other principal constituents of the oil were trans-β-ocimene (20.0%), β-elemene (10.5%), estragole (6.9%), α-pinene (6.7%) and γ-cadinene (5.4%) (Usman et al., 2010). The essential oil from the leaves of *C. anisata* (Willd.) J.D. Hook ex Benth. was isolated by hydrodistillation. The oil was analysed by a combination of GC and GC-MS. The oil contained mainly sabinene (33.0%), germacrene-D (17.0%) Z-β-ocimene (6.0%), germacrene-B (5.5%), (*E*)-β-ocimene (4.9%) and terpinen-4-ol (4.7%) (Senthilkumar et al., 2009).

Clausena lansium (Lour.) Skeels

Description and distribution

This species (Figure 3A and B) differs widely from all other species of the genus, as has been noted. The tree is fairly fast-growing or rather slow, depending on its situation; attractive, reaching 20 ft (6 m), with long, upward-slanting, flexible branches, and gray-brown bark rough to the touch. The plant is a highly esteemed fruit tree in Southern China, where sour, subacid, and sweet varieties are known. The white or yellow fruits are ovoid or subglobose, about the size of a pigeon's egg, but varying in size and shape with the variety cultivated. *C. lansium* is native in Southern China and Indo-China; widely cultivated in tropical and subtropical regions. It is locally known as "wampee" with its white or yellow fruits.

Morphology of the plant

Many traditional uses of the plant have been reported; mainly food and medicinal uses are detailed here. A fully ripe, peeled wampee, of the sweet or subacid types, is agreeable to eat out-of-hand, discarding the large seed or seeds. The seeded pulp can be added to fruit cups, gelatins or other desserts, or made into pie or jam. Jelly can be made only from the acid types when under-ripe. The Chinese serve the seeded fruits with meat dishes. In Southeast Asia, a bottled, carbonated beverage resembling champagne is made by fermenting the fruit with sugar and straining off the juice. The fruit is said to have stomachic and cooling effects and to act as a vermifuge. The Chinese say that if one has eaten too many lychees, eating the wampee "will counteract the bad effects (Molino et al., 2000). Lychees should be eaten when one is hungry and wampees only on a full stomach". The halved, sun-dried, immature fruit is a Vietnamese and Chinese remedy for bronchitis. Thin slices of the dried roots are sold in Oriental pharmacies for the same purpose. The leaf decoction is used as a hair wash to remove dandruff and preserve the color of the hair.

Phytochemistry of *C. lansium*

Alkaloids: Three new carbazole alkaloids, mafaicheenamine A to C, along with five known compounds were isolated from the twigs of *C. lansium* (Maneerat et al., 2010). Five carbazole alkaloids and one 2-quinolone alkaloid were isolated from the stems of *C. lansium* Skeels (Maneerat et al., 2010).

Coumarins: Fruits of wampee [*Clausena lansium* (Lour.) Skeels] contain a significant amount of coumarins with

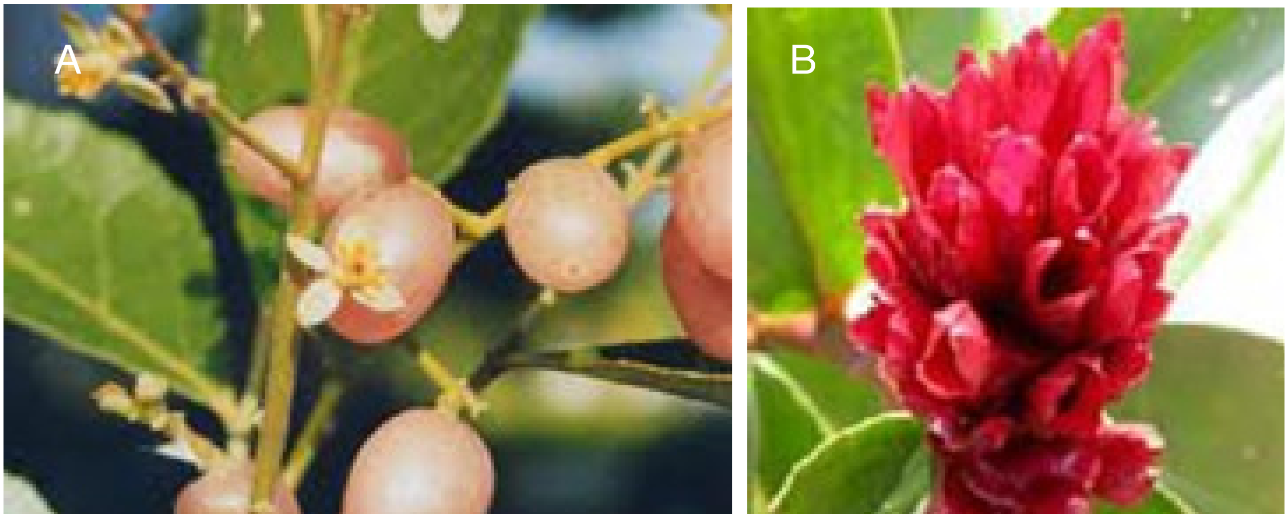

Figure 4. *C. harmandiata* (Pierre) Guill.; (A) the fruit of the plant (B) the flowers and leaves.
Source: (A) www.baungcamp.com; (B) www.rspg.or.th

many health benefits. The activity-guided separation of an ethyl acetate-solvent fraction on a polyamide column followed by silica gel column and high performance liquid chromatography (HPLC) preparation afforded a pure coumarin, which was identified to be 8-hydroxypsoralen (Prasad et al., 2009). Also two new coumarins, namely Clausenalansimin A and B, together with seven known coumarins were isolated from twigs of *C. lansium* (Maneerat et al., 2010). Four furanocoumarins were isolated from the stems of *C. lansium* Skeels (Wu et al., 1999).

Essential oils: The essential oils of wild *C. lansium* collected in Hainan Island, China were extracted from leaves, flowers, sarcocarps and seeds, and then analyzed by using GC/MS. The main constituents of the essential oils were: Î²-santalol (35.2%), bisabolol (13.7%), Me santalol (6.9%), ledol (6.5%) and sinensal (5.6%) in the leaves; Î²-santalol (50.6%), 9-octadecenamide (17.2%) and sinensal (4.1%) in the flowers; Î²-santalol (52.0%), Î±-santalol (15.5%), farnesol (5.2%) and sinensal (4.0%) in the sarcocarps; and phellandrene (54.8%), limonene (23.6%), and p-menth-1-en-4-ol (7.5%) in the seeds (Zhao et al., 2004).

Clausena harmandiata (Pierre) Guill.

Description and distribution

C. harmandiata (Figure 4A and B) is an evergreen shrub 1 to 1.5 m tall, with all parts giving a citrus smell and containing aromatic oil. In Thailand, it is locally known as "Song- fa". The leaves grow to 20 cm long and have three leaflets, each sized 2 cm-4 cm × 5 cm-11 cm. The clusters of four yellow-green flowers are up to 20 cm long. Its fruit is an egg-shaped berry that is 3 to 5 mm in diameter, dark red when ripe, and contains one or two seeds. *C. harmandiata* is a shrubby vigorous plant native to Asia. It is mainly distributed in a large part of Asia, starting from indo-china covering Cambodia, Laos, Thailand and Vietnam up to Malaysia and Indonesia in the parts of Malacca and Java, respectively. The plant is found everywhere in Laos in the under storey of deciduous and evergreen forests on various soil types, or along streams, but mainly on poor sandy soils (Adebajo et al., 2009).

Morphology of the plant

In terms of traditional uses, the roots, young leaves, bark and flowers of *C. harmandiata* are often mixed with other herbs and used to reduce intestinal gas and food poisoning. The roots also help relieve eye-pain, headaches and fever. The young leaves and leaves are used as fodder for cattle and buffalo. It is also used by humans for food. The fruit and sour young shoots are eaten with "*laap"* and bamboo soup.

Phytochemistry of C. harmandiana

Alkaloids: Phytochemical study on roots of *C. harmandiana* have been resulted in isolation of four new carbazole alkaloids, claurailas A to D, as well as 12 known carbazoles (Songsiang et al., 2010). Two new carbazole alkaloids have also been isolated from the stem bark of *C. harmandiana* (Noipha et al., 2010). The activity guided fractionation of the *C. harmandiana* root extracts led to the isolation of eight carbazoles (Yenjai et

Figure 5. *C. anisum*-olens (Bl.) Merr.; (a) the overall plant; (b) the leaves of the plant.
Source: www.plant.csdb.cn

al., 2000).

Coumarins: A new coumarin together with three known coumarins were isolated from the roots of *C. harmandiana*. The activity guided fractionation of the *C. harmandiana* root extracts led to the isolation of a coumarin, a ferulate (Thongthoom et al., 2010).

Essential oils: Hydrodistillation process of *C. harmandiana*, Feroniella lucida and Suringlea glutinosa, 0.25, 0.15 and 0.20% essential oils were obtained respectively. The GC-MS analysis results shows that the essential oil of *C. harmandiana* contains α- pinene (12.23%) and copaene (12.40%).

Clausena anisum-olens (Bl.) Merr.

Description and distribution

C. lanisum (Figure 5A and B) is a tree 3 to 6 m tall. Leaves 5 to 11-foliolate; petiolules 2 to 4 mm; leaflet blades falcately lanceolate to obliquely ovate, 5-12 × 2-4 cm, margin repand, apex acuminate to slightly obtuse. Inflorescences terminal. Flowers globose in bud, fragrant. Calyx lobes ovate, ca. 1 mm. Petals white, oblong, ca. 3 mm. Stamens 8 or 10; filaments slightly expanded in ± their basal half, geniculate. Style slightly shorter than ovary. Fruit pale yellow, globose, 1 to 2 cm in diameter, 1- or 2-seeded. The plant is distributed in Philippine Islands: Luzon, Masbate, Basilan, Mindanao islands (He et al., 2003).

Morphology of the plant

The plant is traditionally used as food, drink and medicine. In the Philippines, leaves of *C. anisum-olens* are used as a condiment in preparing local dishes and beverages. It is also well known in traditional medicine in the Philippines. The leaves are stuffed into pillows for a soporific effect, they are used in baths against rheumatism, or in decoction for nausea during pregnancy. Cough with fever is treated with a decoction of the roots and fruit. The essential oil from the leaves is a potential substitute of anise oil, e.g. for the preparation of the Philippine drink 'Anisado'. Other products: In the Philippines leaves of *C. anisum*-olens are used to flavour cigarettes.

Phytochemistry of C. anisum-olens

Coumarins: In Nigeria, four coumarins could be found from the root bark, among these chalepin and imperatorin. A new *O*-terpenoidal coumarin, named hekumarone, was isolated from the leaves and twigs of *C. anisum-olens* Merr (Wang et al., 2009) (Rutaceae) collected in Hekou County in Yunnan Province, P. R. China. Two new monoterpenoid coumarins: Anisucumarin A and B, a pair of epimers, were isolated from *C. anisum*-olens (Wang et al., 2008). Seven coumarins, including a new O-terpenoidal coumarin, named anisumarin, were isolated from *C. anisum*-olens Merr (Wang et al., 2010). Extracts from *C. anisum*-olens afforded two new O-terpenoidal coumarins, hekumarins A and B as inseparable epimers (Wang et al., 2008).

Clausena dentata (Willd.) M. Roem.

Description and distribution

C. dentate (Willd.) Roem. (Figure 6A and B) is a small

Figure 6. *C. dentata* (Willd.) M. Roem. (A) the leaves of the plant; (b) the appearance of the overall plant. Source: (A) www.ringsofsilverpv.blogspot.com; (B) www.madraswanderer.blogspot.com

tree plant, belonging to the family of Rutaceae and found in India, Sri Lanka and China. It is a small tree; 2 to 6 m high with a delicious fruit not uncommon on the Anamallays up to 3,000 feet both in the moist woods and in the drier forests, it flowers in April and the fruit begins to ripen at the end of June. The tree is well known to the hill tribes and called 'Mor Koorangee.' it has leaves that are more membranaceous, highly odoriferous, more prominently dotted, and very erose toward the apex (Diep et al., 2009).

Morphology of the plant

It is popularly known as "Anai chedi" in Tamil. *C. dentata* is used by local peoples of Yercaud and Boda Hills for its medicinal and nutritive value. The leaves were bigger than its namesake the karuveppalia (curry leaves) that is used so often in South indian cooking. A small portion of one leaf was tore off and smelt - very citrus like. The fruits of this plant are considered edible in central China. It has been thought by some botanists that this plant is sometimes cultivated in Hupeh Province. It should be introduced into culture in other regions and hybridized with species that produce edible fruits ((Fan et al., 2001).

Phytochemistry of *C. dentata*

3-(1,1-Dimethylallyl) xanthyletin has been isolated from the stem bark of *C. dentate* (Kamaraj et al., 2003). Imperatorin and two new coumarins, dentatin and nordentatin, have been isolated from the root bark of *C. dentata* (Willd.) R. Essential oil and some compounds were isolated from *C. dentata* leaves. GC-MS analysis of essential oil revealed the presence of fourteen compounds of which the major compounds were sabinene (21.27%), biofloratriene (19.61%), borneol (18.34%) and Î²-bisabolol (17.68%) (Rajkumar et al., 2010). Another study led to the isolation of essential oil from the leaves of *C. dentata*. The yield of *C. dentata* leaf essential oil was 1.8 ml/kg fresh weight. Chemical constituents of 12 compounds were identified in the oil of *C. dentata* representing for 99.17% and The major chemical compositions of oil were sabinene (28.57%), borneol (14.62%), δ – cadinol (12.49%). β - bisabolol (15.56%) and biofloratriene (18.54%). The percentage compositions of remaining seven compounds ranged from 0.59 to 2.38%.

PHARMACOLOGICAL ASPECTS OF CLAUSENA GENUS:

As shown previously, phytochemical studies led to the isolation of a large number of secondary metabolites of different chemical groups as well as many essential oils of several components. It was found that most of the identified compounds have exerted different biological activities. The overall survey on the literature of this part of the study was summarized in Table 1. The percentages of the biological activities with respect to each species are calculated according to the total number of biologically active compounds for each biological activity for each plant species. Pharmacological aspects of *C. excavata* are elaborated in details, because of its importance compared to other species of the genus.

Pharmacological aspects of *C. excavata*

Anticancers

Cancer remains as one of the most leading cause of death worldwide. For the past decade, there have been a

Table 1. The percentages of biological activities of the members of *Clausena* genus.

Biological activity	Plant species					
	C. excavate **(%)**	***C. anisata*** **(%)**	***C. lanisum*** **(%)**	***C. harmandian*** **(%)*a***	***C. dentate*** **(%)**	***C. indica*** **(%)**
Anticancer	69	32	26	29	19	13
Antimicrobial	56	25	12	22	05	00
Antioxidant	66	19	21	22	12	12
Anti-fungal	18	12	00	09	03	00
Anti-viral	22	11	00	08	11	02
Anti-diabetic	34	00	02	05	00	08
Antidiarrhoeal	33	03	11	00	23	07
Antimalerial	45	22	33	00	11	10
Immunomodulatory	51	13	21	14	09	11
Larvicidal	44	06	00	17	08	04
Antiplasmodial	27	04	09	02	02	00
Anti-inflammatory	48	15	00	16	00	03

tremendous number of studies and investigations conducted in drug development for cancer treatment (Yamamoto and Gaynor, 2001). Interesting background on the cancer cell killing properties of the stem barks, roots and leaves of *C. excavata* could provide avenues to investigate extensively on the basic mechanistic actions of cell death (Chinsembu and Hedimbi, 2006). Hence, further studies are required to investigate the anti cancer activities of the extracts and chemical constituents isolated towards various cancer cell lines (Malek et al., 2011).

In one pharmacological study, Clausine-B was found to be active (IC_{50}<30 µg/ml) against four cancer cell lines tested (Zain, 2009). The IC_{50} values for these four lines were determined to be 21.50 µg/ml (MDA-MB-231), 22.90 µg/ml (HeLa), 27.00 µg/ml (CAOV3) and 28.94 µg/ml (HepG2) respectively. Clausine-B was found to inhibit the MCF-7 cancer cell line at 52.90 µg/ml, but no IC_{50} value was obtained against Chang liver (Brunner et al., 2009). A new carbazole alkaloid, 3-carbomethoxy-2-hydroxy-7-methoxycarbazole, Clausine-TY, was isolated from the ethyl acetate extract of the stem bark of the Malaysian *C. excavata*. This new carbazole alkaloid showed significant cytotoxicity against CEM-SS cell line with IC_{50} value of 44.80 µg/Ml (Taufiq-Yap et al. 2007). Four other natural pyranocoumarins which included clausenidin, nordentatin, clausarin, and xanthoxyletin were isolated from the Malaysian medicinal plant *C. excavata* (Chin et al., 2006). The first three compounds showed cytotoxic activity against four human cancer cell lines (A549, MCF7, KB, and KB-VIN) (Su et al., 2009). In a study conducted by (Patil et al., 1995) to determine the major flavonoid compounds and the composition of essential oils predominant in *C. excavata*, and also to examine its antioxidant and anticancer activities, the flavonoids of crude extracts of the leaves and fruit of the plant were investigated. The study concluded that the antioxidant activity of flavonoids was associated with anticancer properties (Look et al., 1991). The MTT assay, however, showed fruit oil having better cytotoxic activity than that in methanol crude leaf extract against MCF-7 cells. This implied that *C. excavata* fruit oil might be a good source for breast cancer treatment due to the presence of possible active anticancer agents (Lewis and Elvin-Lewis, 1995). This result could partly explain the popularity of this plant in folk medicine as a remedy for cancer and HIV patients in the eastern part of Thailand as well as in Malaysia (Nakamura et al., 1998).

Antibacterial activity

It was reported that, four known coumarins, dentatin, nor-dentatin, clausenidin and xanthoxyletin, and six known carbazole derivatives, 3-formylcarbazole, mukonal, 3-methoxycarbonylcarbazole, murrayanine, 2-hydroxy-3-formyl-7-methoxycarbazole and clauszoline J were isolated from *C. excavata*. All compounds showed antimycobacterial activity at a minimum inhibitory concentration (MIC) of 50, 100, 200, 100, 200, 50, 100, 200, 50 and 100 µg/ml, respectively. O-Methylated clausenidin, prepared from 3, exhibited antimycobacterial activity at MIC 50 µg/ml (Sunthitikawinsakul et al., 2003).

Antifungal activity

Few studies have been conducted concerning the antifungal activity of phytochemicals of *C. excavata*. Three compounds from the aforementioned compounds in antibacterial activity section, namely 3-formylcarbazole, mukonal and 3-methoxycarbonylcarbazole showed antifungal activities with IC_{50} values of 13.6, 29.3, 9.5 and 2.8 µg/ml, respectively (Sunthitikawinsakul et al., 2003).

Anti-HIV-1 activity

A limonoid, clausenolide-1-ethyl ether and two coumarins, dentatin and nor-dentatin, were isolated from *C. excavata*. Coumarins, dentain and nor-dentain, with their structures related to an anti-HIV-1 substance, (+)-calanolide A, were obtained from the crude chloroform extract of the rhizomes (DiLella et al., 1986). Both induced toxicity to cells used in a syncytium assay for anti-HIV-1 activity (Hughes, 2003). In addition, three carbazole derivatives, O-methylmukonal, 3-formyl-2,7-dimethoxycarbazole and clauszoline J, and a pyranocoumarin, clausenidin, were isolated from the rhizomes and roots of *C. excavata* (Singh and Bodiwala, 2010). O-methylmukonal, isolated from this plant for the first time, has been reported currently to have anti-HIV-1 activity (Ravi et al., 2006). All compounds displayed anti-HIV-1 activity in the syncytial assay with $EC_{(50)}$ values of 12, 29.1, 34.2 and 5.3 (microm), respectively, thus, exhibited potential therapeutic index (PTI) values of 56.7, 8.0, 1.6 and 7.0, respectively (Kongkathip et al., 2005).

Immunomodulatory activity

The term "immunomodulation" denotes a change or strengthening of suppression, of indicators, of cellular, and humoral immunity and nonspecific defense factors. The essence of immunomodulation is that a pharmacological agent acting under various doses and time regimens displaying an immunomodulating effect (Manosroi et al., 2004). In *vitro immunomodulatory* activities of aqueous extract, acetone extract and the Thai folklore extract of *C. excavata* Burm. f. on mouse immune system were investigated. The phagocytic activity of macrophages and splenocyte proliferation in the absence and presence of mitogens (lipopolysaccharide, LPS) or pokeweed mitogen, PWM) were assayed. The results indicated that the aqueous extract exhibited maximum effect on both respiratory burst response and lysosomal enzyme activity more than the acetone extract and the Thai folklore extract; indicating effective phagocytic activation. For splenocyte proliferation assay, the Thai folklore extract with LPS gave maximum activity, higher than that with PWM, suggesting specificity towards B cell proliferation through T cell independent pathway similarly as LPS. Previous study had revealed the immunomodulating activity, which could explain the traditional use of this plant in Thailand as anti-malarial and anti-dysentery (Manosroi et al., 2003).

The effects of fractions from hot aqueous extract, acetone extract and the folklore preparation of *C. excavata* were studied on mouse splenocyte proliferation (Wang et al., 2008). The fractions of hot aqueous and acetone extracts were found to be the most active (Knio et al., 2008). On the contrary, the fractions from the crude folklore preparation resulted less active. This result could partly explain the popularity of this plant in folk medicine as a remedy for cancer and HIV patients in the eastern part of Thailand (Manosroi et al., 2004). Immunomodulating effects of the aqueous extract and the Thai folklore preparation (CEHF) of *C. excavata* Burm. f. in Balb/C mice (CEHW) were investigated. Haemagglutinating antibody (HA) titers at day 0, 7, 14, 21, 28 and 35 from the serum of animals fed or injected intraperitoneally with the extracts for 5 days were compared and evaluated for humoral mediated immunity (HMI). Both extracts given orally reached maximum antibody titer at day 7, which was 2 weeks faster than by intraperitoneal administration (Manosroi et al., 2005). In a study conducted by (Lin and Tang 2007), the effects of fractions isolated from hot aqueous extract, acetone extract and folklore preparations of *C. excavata* were studied on mouse splenocyte proliferation. The fractions of hot aqueous and acetone extracts were found to be the most active (Cazacu et al., 2003). On the contrary, the fractions from the crude folklore preparation become less active.

Antinociceptive activity

No antinociceptive activity has been reported except an investigation on an ethanolic extract of *C. excavata* leaves given orally at doses of 125.25 and 500 mg/kg body weight. The study showed significant antinociceptive activity on acetic acid induced writhing in mice (Rahman et al., 2002).

Antiplatelet activity

Clausine-D that was isolated from *C. excavata* exhibited an antiplatelet effect, which was mediated by inhibition of thromboxine A_2 formation. A higher concentration of Clausine-D (150 µM) was required to produce almost complete inhibition of collagen induced platelet aggregation.

Anti-malarial activity

Malaria continues to be a major infectious disease of the developing world and the problem is compounded not only by the emergence of drug resistant strains but also from a lack of a vaccine. Malaria is a disease caused by protozoans in the genus Plasmodium (Isaka et al., 2002). There are only 4 species of the Plasmodium that can infect humans; the remainder infects other mammals, as well as birds and reptiles. Among the 4 species, *Plasmodium falciparum*, *Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae* infect humans. *P. falciparum* and to a lesser extent, *P. vivax* accounts for the majority of 300 to 500 million clinical attacks per year, resulting in an annual death toll of 1 to 2 million. Most of these cases occur in African countries, especially among children younger than 5 years (Jaturapat et al., 2001). Few investigations have been done by the phytochemists concerning the anti-malarial activity of *C. excavat* (David Phillipson and Wright, 1991). A new carbazole alkaloid, sansoakamine, which has been isolated from the stems of *C. excavata* showed moderate anti-malarial activity against *P. falciparum* with a MIC value of 6.74 µg/ml (Lastra-Gonzalez et al., 2005).

Insecticidal activity

Insecticidal activity is one of the interested biological activities considered by researchers in the field of pharmacology (Knio et al., 2008). Few investigations also have been conducted based on the isolated pure compounds as well as crude extracts of *C. excavata* (Ravi et al., 2006). In one study, Fourth-instar larvae of *Aedes aegypti* and *Aedes* albopictus served as test organisms (Pitasawat et al., 2007). The larva colonies of the mosquito collected from the Kaoshiung strain were reared in the Department of Parasitology, Chang-Gung University, at 27°C with a 12:12 h light : dark photoperiod in 80±10% relative humidity. A 10% yeast suspension was used as food source (Cheng et al., 2009). As a summary, the following table shows the most important biologically active compounds isolated from *C. excavata* and their pharmacological properties. In fact, most of the isolated chemical compounds from different parts of this plant are proved to be biologically active (Begum et al., 2010).

From these data, we can observe that most of the isolated compounds of the different species show different biological activities. What is distinguished also is the highest percentages of anticancer and antioxidant activities compared to other biological activities amongst all the species under investigation. Within the species, the highest anticancer and antioxidant activities are observed in *C. excavata*. Consequently, all the species under investigation should be considered for further studies in general and *C. excavata* in specific as sources of anticancer and antioxidant phytochemicals (Begum et al., 2008).

CONCLUSION

In broad terms, herbal drugs which are used in traditional medicine needs further detailed investigation considering ethno-pharmacological approach. Members of *Clausena* genus are widely distributed all over the world particularly through Indo-China, Malaysia and some parts of Africa. In the present review, we tried to explore the all details of six members of *Clausena* genus, their botany, habitat, traditional uses, phytochemistry and pharmacology. Numerous studies have been conducted on different parts of the species of *Clausena* genus, but these members have not yet developed as drugs by pharmaceutical industries. Therefore, a detailed and systematic study is required for identification, cataloguing and documentation of these plants, which may provide a meaningful way for the promotion of the traditional knowledge of the herbal medicinal plants. The present review revealed that the plants are used in treating various ailments. All members of the genus contain different bioactive compounds from different chemical classes. Several plant parts have interesting anticancer, antibacterial, antifungal, antimicrobial, antioxidant, antiviral, anti-inflammatory, larvicidal, antiplasmodial, immunomodulatory, ant-diabetic and antidiarrhoeal properties. Consequently, further studies on these members should be considered by the researchers in the fields of phytochemistry and pharmacology looking for bioactive compounds particularly antioxidant and anticancer ones.

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