Alkaloids from the Genus *Dehaasia*: Phytochemistry and Biological Activities

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**ABSTRACT**

The genus *Dehaasia* is one of the genera of evergreen trees or shrubs belong to Lauraceae, and comprise about 35 species of tree that are distributed worldwide. The purpose of this review is to provide an update and comprehensive information on the phytochemistry and pharmacological research of *Dehaasia* species in order to explore their therapeutic potential and evaluate future research opportunities. All the available information on *Dehaasia* species was actualized systematically by searching the scientific literatures databases such as PubMed, SciFinder, Web of Science, and Google Scholar. From the data collected in this review, the genus *Dehaasia* has attracted much attention due to their richness in alkaloids with various bioactivities, and it comprises a wide range of therapeutically promising plants. Therefore, a detailed study and clinical evaluation of *Dehaasia* species should be carried out in future for the safety approval of therapeutic applications.

**INTRODUCTION**

*Dehaasia* is a member of the Lauraceae family. It is an evergreen tree of moderate size, with large leaves, found growing in the western parts of Malaysia, China, and the Philippines (Burkill, 1935). About 35 species of *Dehaasia* are spread out worldwide and nine species are found in Malaysia. According to the current listing reported in the taxonomical internet database lead by the Royal Botanical Gardens at Kew and the Missouri Botanical Garden (www.theplantlist.org-accessed 25 December 2016), the genus *Dehaasia* encompasses the following 38 accepted (65.5%) taxons, as listed in Table 1.

*Dehaasia* is locally known as ‘gajus hutan’ or ‘pekan’, and its timber is durable and used for building houses (Hsuen, 1969). This genus presents several alkaloids, with isoquinolines as the main class reported in the literature.

The isoquinoline alkaloids are formed from the amino acid tyrosine by consecutive reactions forming the tetrahydroisoquinoline core and are of great importance due to several pharmacological activities described to the benzyltetrahydroisoquinoline, aporphine and pavine skeletons (Houlihan, 1972). This review aims to examine the phytochemical and pharmacological perspectives of the *Dehaasia* species reported in the literature.

**PHYTOCHEMISTRY STUDIES**

A substructure search is performed using the SciFinder Scholar database and keywords research in PubMed, Medline, and Scopus. A bibliographic search carried out from the year 1986 to 2014 of the genus *Dehaasia* revealed that only six species were investigated at chemical or biological level. These species are *D. Triandra* Merr., *D. Longipedicellata* (Ridl.) Kosterm., *D. Hainanensis* Kosterm., *D. Candolleana* (Meisn.) Kosterm. *D. incrassata* (Jack) Kosterm. and *D. Kurzii* King ex Hook. f. The chemical structures of alkaloids isolated from *Dehaasia* species are shown in Figure 1.
Compound (1996) have reinvestigated this species, in which they have successfully isolated two new bisbenzylisoquinoline alkaloids, homoaromoline20, daphnandrine26, aromoline17, daphnoline27, pangkorimine28, colorflammine21, thalrugosine22, obamegine18, 2-norobamegine29, dehatridine1 and 1,2-dehydroapateline30 from the leaves extract.

**D. longipedicellata (Ridl.) Kosterm**

*Dehaasia longipedicellata* is a small tree with 12 m tall and 30 cm girth. Its leaves are apex pointed; blade softly hairy on the underside, broadly elliptic to obovate, 13-27.5 cm × 6.5-13.5 cm and stalk is about 1.0-2.5 cm long. The leaves also have 10-14 pairs of secondary nerves, raised below; faint above and tertiary nerves scalar form. They are also having reticulations visible on both surfaces. The fruit of this species is globosely with depressed 1836, while poisonous (Ng, 1989). Three studies have been reported on the phytochemical studies of *D. longipedicellata*. Mukhtar and co-workers (2004) had successfully isolated five morphinoid alkaloids, identified as (+)-pallidine31, (+)-pallididine32, (+)-milonine33, (+)-8,14-dehydroalutaridine34, and (-)-sinoacutine35 from the leaves extract. Compound 31 was reported as a new compound. Four years later, the authors investigated the bark part and successfully identified 2,7-dihydroxy-3,6-dimethoxyphenanthrene 36. Phytochemical investigation of the bark of this species was also reported by Zahari and co-workers (2014). They managed to isolate six alkaloid identified as (+)-sebiferine 37, (-)-milonine 33, (+)-boldine 38, (+)-norboldine 39, (-)-reticuline 40, and (-)-O,O-dimethylgrisabine 41.

**D. hainanensis Kosterm**

*Dehaasia hainanensis* locally known as ‘liangui’ in China. It is a shrub or small tree and up to 5 m tall. Its’ leaves are alternate, petiole brown, concave-convex, and glabrous, whereas its’ flowers are small and glabrous up to 1.5 mm (Xiwen et al., 1836). Only one study has been reported in the literature about this species in 2007 when Chen and co-workers (2007) described the isolation from leaves extract and structural characterization of (+)-laurulisin 42, (+)-corydine 43, (+)-laurotetanine 44, (+)-lindcarpine 45, (+)-sinoacutine 35, (-)-ocobotrine 46, (+)-reticuline 40, (+)-roefractine 47, (+)-reticuline-N-oxide 48, O-methylarmepavine 49, and (-)-N,N-dimethylindoldhamine 50.
$R_1 = Me; R_2 = R_3 = OMe; R_4 = H; R_5 = OH$

$R_1 = Me; R_2 = R_3 = OMe; R_4 = H; R_5 = OMe; R_6 = H$

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$R_1 = OMe; R_2 = OH$

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$R_1 = OMe; R_2 = OMe; R_3 = OMe; R_4 = OMe; R_5 = OMe$
D. candolleana (Meisn.) Kosterm

*D. candolleana* is a small tree with 8 m tall and 10 cm in diameter. Its bark is whitish grey; inner bark is white and grey twigs with large leaf-scars; leaves spirally simple, crowded at the end of the twigs, elliptic, apex shortly acuminate or acute, base obtuse, 17.5–25.0 cm × 5.5–13.5 cm, bright green and rugose above, paler below, nerves 8–11 pairs, distinct below; petioles 2.5 cm long; in fluorescence in axillary panicles, dark red flowers and densely hairy (Ng, 1989). Only one report on this species appeared in the literature in 2008 when Hadi and co-workers (2008) described the isolation from the bark extract and structural characterization of (+)-sebiferine 37, (+)-O,O-dimethylgrisabine 41, and grisabine 51.

D. incrassata (Jack) Kosterm

*D. incrassata* known as ‘yaoguo nan’ is a small tree with 5 m tall and 10 cm in diameter. The bark is grey-brown, smooth, and lenticellate while the inner bark is yellow. Its leaves are spirally simple, leathery from elliptic-oblong to oblanceolate or obovate, apex acuminate, base 8.0–15.0×5.5–10.0 cm, bright green above, paler below, nerves 8–11 pairs, crving and joining near the margin; petiole 3 cm long, grooved above; fruit terminal, oblong, 5×2 cm, bright green, ripening shiny purplish black; stalks 3 cm long (Ng, 1989). The first phytochemical study of this species appeared in the literature in 1988 when Rahman and co-workers described the isolation of boldine 38 from the stem bark extract (Rahman et al., 1988a; 1988b).

**BIOLOGICAL ACTIVITIES**

Antiplasmodial activity

(-)-O,O-Dimethylgrisabine 41 isolated from *D. longipedicellata* showed a potent antiplasmodial activity with IC₅₀ value of 0.031 μM, followed by (+)-milonine 33 with IC₅₀ value of 0.097 μM. Besides, (+)-sebiferine 37 and (-)-O,O-dimethylgrisabine 41 exhibited potent *in vitro* antiplasmodial activities to two strains of *Plasmodium falciparum*: D10 strain (sensitive strain) and Gombak A isolate (resistant strain). In addition, the crude alkaloid extract of the leaves was also found to have antiplasmodial activity against *Plasmodium falciparum* with IC₅₀ value of 1.30 μg/mL (Zahari et al., 2014).
Antibacterial activity

The alkaloids extract of _D. kurzii_ exhibited a strong _in vitro_ antibacterial activity against _Shigella flexneri_ and moderate activity against _Vibrio cholerae, Staphylococcus aureus, Proteus, Pseudomonas spp._, and _Shigella dysenteriae_ type-I. The isolated compound from this extract, boldine 38 has shown a strong and specific cytotoxic activity towards human epidermoid carcinoma of larynx (Hep-2 cells). It showed complete inhibition of cultured HEP-2 cells at a concentration of 0.3 mg/mL and partial inhibition at 0.7 mg/mL (Hasan et al., 1987).

Cytotoxicity activity

The tested compounds (36-41) showed no potency against lung (A549) cancer cells, and weak cytotoxicity against skin (A375) cancer cells (IC$_{50}$$<100$ μM) for (-)-norboldine 39 (82.89 μM) and (-)-O,O-Dimethylgrisabinine 41 (82.85 μM). However, for pancreatic cancer cells (BXPC-3), a great potency was shown by (-)-norboldine 39 with IC$_{50}$ of 27.06 μM. The same compounds were tested against normal pancreatic cells (hTERT-HPNE) and no cytotoxicity was observed (Zahari et al., 2014).

Antioxidant activity

(-)-O,O-Dimethylgrisabinine 41 also showed a high scavenging activity on DPPH (IC$_{50}$ of 18.38 μg/mL) and metal chelating activity (IC$_{50}$ of 64.31 μg/mL), with moderate reducing power (44.31%) (Zahari et al., 2014).

Antimalarial activity

The leaves extract of _D. incrassata_ was also screened for antimalarial activity and found to be active at 0.31 μg/mL (Said et al., 1991).

CONCLUSION

According to the presented data, it can be seen that the _Dehaasia_ genus presents a great number of alkaloids with isoquinoline alkaloids as the major class. The overall biological investigations of _Dehaasia_ are far from deep, except for some preliminary works regarding _in vitro_ screenings, in which the isolated compounds showed various biological activities such as antioxidant, antiplasmodial, antimicrobial and cytotoxic activities. Alkaloids are among the most thoroughly investigated ingredients, exhibiting anti-inflammatory activity, antitumor activity, and endotoxemia and vasoconstrictor effects (Cao et al., 2015). Therefore, they represent valuable potential constituents for drug development. In conclusion, further investigations of _Dehaasia_, especially _in-depth in vivo_ and _in vitro_ pharmacological evaluations of alkaloids, are valuable and encouraging.

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