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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 Philipines (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.

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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.

Table 1: Classification taxonomy.

No	Species
1	*Dehaasia acuminata* Koord. & Valeton
2	*Dehaasia annamensis* Kosterm.
3	*Dehaasia arunachalensis* M.Gangop
4	*Dehaasia assamica* Kosterm.
5	*Dehaasia brachybotrys* (Merr.) Kosterm.
6	*Dehaasia caesia* Blume
7	*Dehaasia cairocan* (Vidal) C.K.Allen
8	*Dehaasia candolleana* (Meisn.) Kosterm.
9	*Dehaasia celebica* Kosterm.
10	*Dehaasia corynantha* Kosterm.
11	*Dehaasia cuneata* (Blume) Blume
12	*Dehaasia firma* Blume
13	*Dehaasia gigantocarpa* Kosterm.
14	*Dehaasia hainanensis* Kosterm.
15	*Dehaasiahirsuta* Kosterm.
16	*Dehaasia incrassata* (Jack) Kosterm.
17	*Dehaasia kerrii* Kosterm.
18	*Dehaasia kurzii* King ex Hook.f
19	*Dehaasia kwangtungensis* Kosterm.
20	*Dehaasia lancifolia* Ridl.
21	*Dehaasia longipedicellata* (Ridl.) Kosterm.
22	*Dehaasia longipetiolata* Kosterm.
23	*Dehaasia membranacea* Kosterm.
24	*Dehaasia palembanica* Kosterm.
25	*Dehaasia paradoxa* Blume
26	*Dehaasia pauciflora* Blume
27	*Dehaasia polyneura* (Miq.) Kosterm.
28	*Dehaasia pugerensis* Koord. & Valeton
29	*Dehaasia rangamattiensis* M.Gangop.
30	*Dehaasia subcaesia* (Miq.) Kosterm.
31	*Dehaasia suborbicularis* (Lecomte) Kosterm.
32	*Dehaasia sumatrana* Kosterm.
33	*Dehaasia sumbaensis* Kosterm.
34	*Dehaasia teijsmannii* Kosterm.
35	*Dehaasia titanophylla* (Airy Shaw) Kosterm.
36	*Dehaasia tomentosa* (Blume) Kosterm.
37	*Dehaasia turfosa* Kosterm.
38	*Dehaasia velutinosa* Kosterm.

D. triandra Merr.

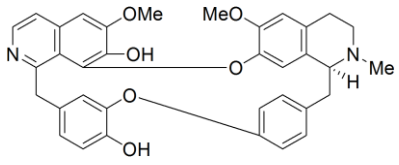
D. triandra a Lauraceous plant indigenous to Taiwan and Philippines.Their phytochemicals have been reported on five different types of studies. Lu and co-workers (1986) have investigated this species collected from Orchid Islands, Taiwan. In this study, they have successfully isolated two new bisbenzylisoquinoline alkaloids, dehatridine **1** and dehatrine **2**, together with six known alkaloids, isocorydine **3**, corytuberine **4**, atheroline **5**, nantenine **6**, obaberine **7**, and xanthoplanine **8**. Except for **6** and **8** which were obtained from the trunk, the other six alkaloids were obtained from the leaves. Seven years later, Lee et al., (1996) have reinvestigated this species, in which his reinvestigation resulted in the isolation of three novel alkaloids, isocorydione (**9**), norisocorydione **10**, and dehatriphine **11**, besides the most abundant aporphine, isocorydine **3** from the leaves extract. In the same year,they also managed to find another five additional new alkaloids, secoxanthoplanine **12**, dehydroisocorydione **13**, (8,8′-*R*)-bisisocorydine **14**, (8,8′-*S*)-bisisocorydine**15**, and 11,8′-*O*-bisisocorydine **16** from the leaves of *D. triandra*. Compound **14**and **15** are the first C-C linked bisaporphines at C-8, while **16**is the first bisaporphine with a diphenyl ether-linkage at C-8 and C-11. The structures of **12**, **14**, and **15** were further confirmed by semisynthesis as reported by the authors. In addition, Chen (1996) have reported that the species contained nine alkaloids, identified as aromoline **17**, obamegine **18**, berbamine **19**, homoaromoline **20**, colorflammine **21**, thalrugosine **22**, norobaberine **23**, tetrandrine **24**, and isotetrandrine **25**. Furthermore, Sun and co-workers (2000) have also reported that isolation of these alkaloids by high-performance liquid chromatography determines the content of such alkaloids present in the stem woods of *D. triandra*. Continuing the investigation of the phytochemicals of this species, Chen and co-workers (2003) have also managed to isolate eleven bisbenzylisoquinoline alkaloids, homoaromoline**20**, daphnandrine **26**, aromoline **17**, daphnoline **27**, pangkorimine **28**, colorflammine **21**, thalrugosine **22**, obamegine **18**, 2-norobamegine **29**, dehatridine **1** and 1,2-dehydroapateline **30** from the leaves extract.

D. longipedicellata (Ridl.) Kosterm

D. longipedicellata is a small tree with 12 m tall and 30 cm girth. Its leaves are apex pointed; blade softy hairy on the undersurface, 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 or flattened apex, 5.5 cm across on 3.5 cm long swollen stalks According to the Sakai of the Tapah Hills, the fruit is very 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 (-)-pallidine **31**, (+)-pallidinine **32**, (+)-milonine **33**, (-)-8,14-dehydrosalutaridine **34**, and (-)-sinoacutine **35** 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

*D. 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 (+)-laurolitsine **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*′-dimethyllindoldhamine **50**.



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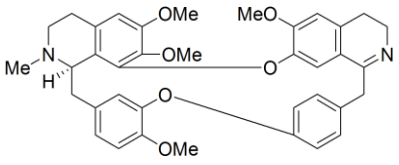

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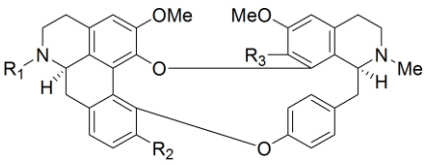
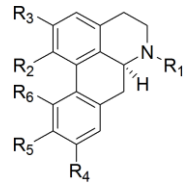
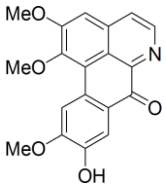
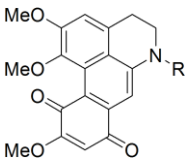
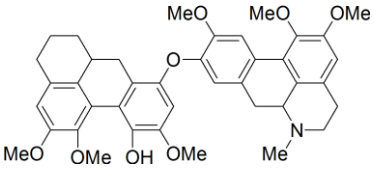


7 R_1 = Me ; R_2 = R_3 = OMe
23 R_1 = H ; R_2 = R_3 = OMe







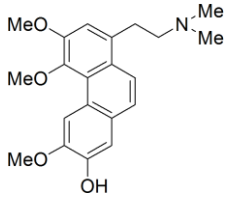


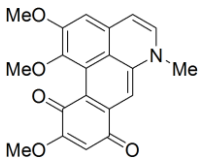
3 R_1 = Me ; R_2 = R_3 = R_5 = OMe ; R_4 = H ; R_6 = OH
4 R_1 = Me ; R_2 = R_6 = OH ; R_3 = R_5 = OMe ; R_4 = H
6 R_1 = Me ; R_2 = R_3 = OMe ; R_4 = R_5 = OCH_2O ; R_6 = H
8 R_1 = $(Me)_2$; R_2 = R_3 = R_5 = OMe ; R_4 = OH ; R_6 = H

5

9 R = Me
10 R = H

11





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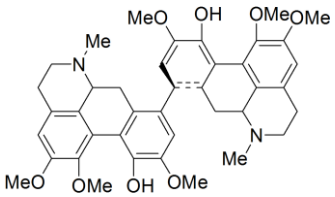

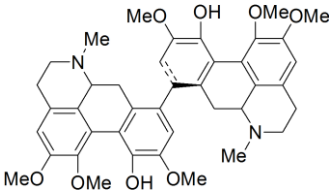

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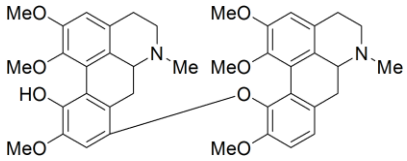

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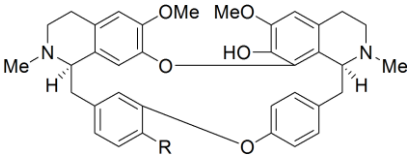
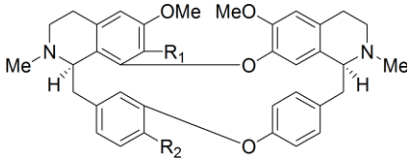
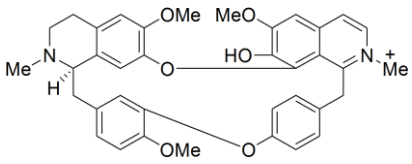


17 R = OH
20 R = OMe



18 R_1 = OH ; R_2 = OH
19 R_1 = OMe ; R_2 = OH
22 R_1 = OH ; R_2 = OMe
25 R_1 = OMe ; R_2 = OMe



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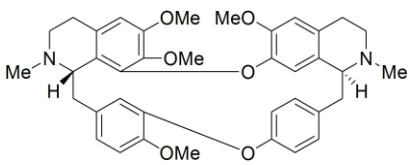

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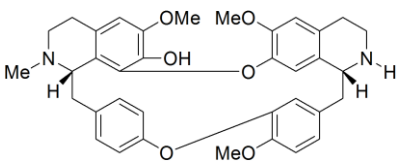

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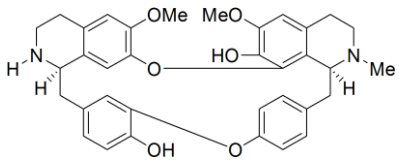

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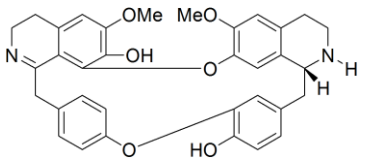

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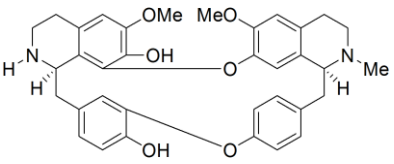

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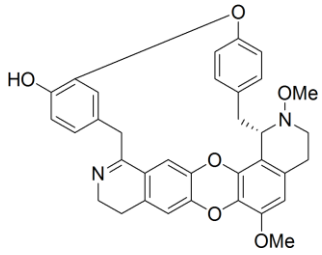

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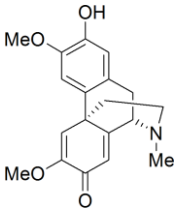

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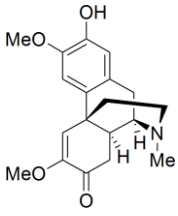

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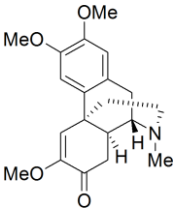

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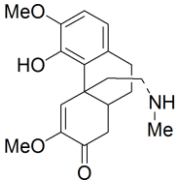

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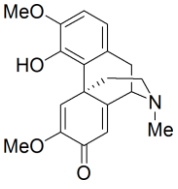

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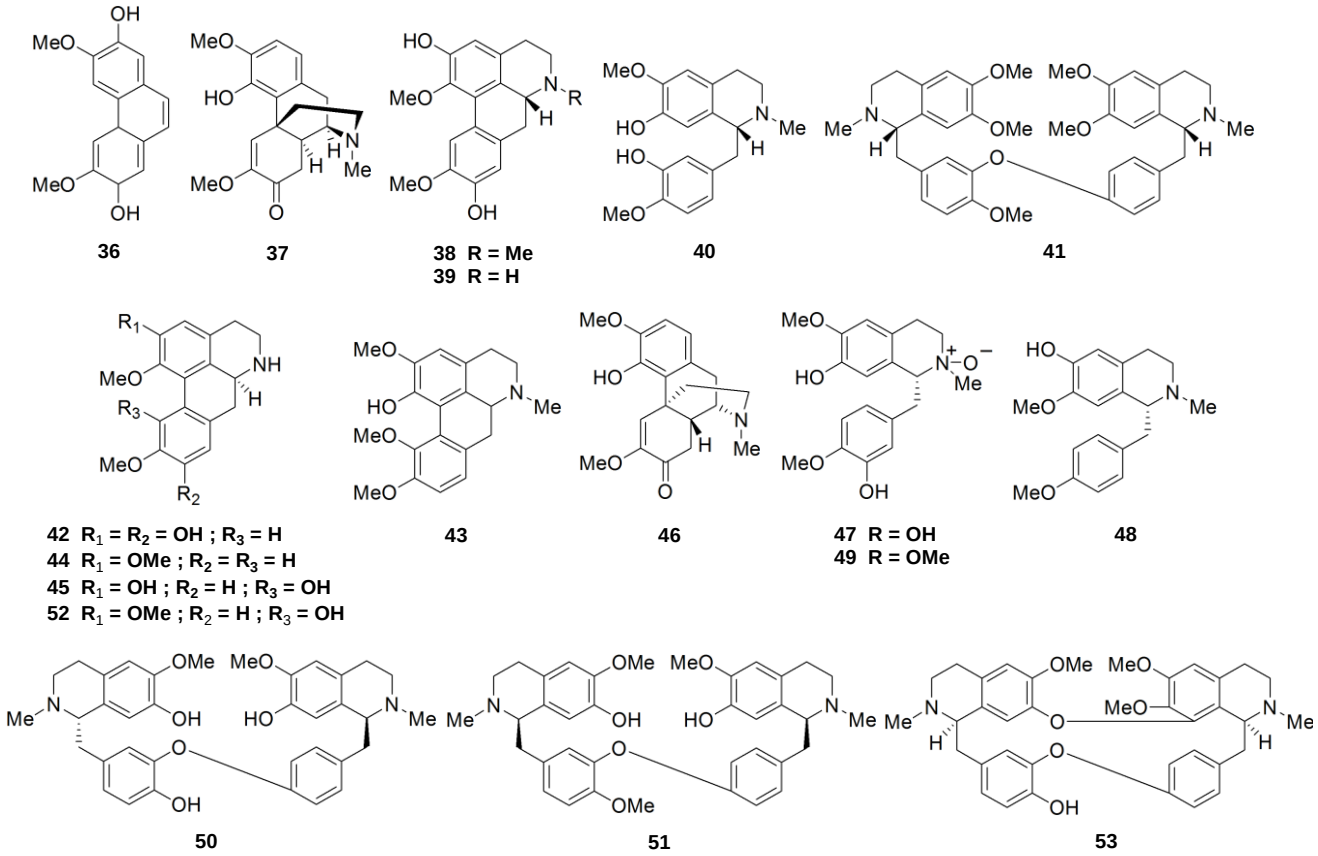

Fig. 1: Chemical structures of alkaloids isolated from *Dehaasia* species.

***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, polar 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 shyny purplish black; stalks 3 cm long (Ng, 1989). The first phytochemical study of this species appeared in the literature in 1991 when Said and co-workers isolated and structurally characterizediscorydine **3**, norisocorydine **52**, and oxyacanthine **53** from the leaves extracts.

***D. kurzii* King ex Hook. f.**

D. kurzii is locally known as '*mojar*', '*mostapata*' or '*modonbocchu*' in Bangladesh. Its leaves and roots are used to treat leucorrhoea (Hasan *et al.*, 1987). Only two brief reports on 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 IC_{50} value of 0.031 µM, followed by (+)-milonine **33** with IC_{50} 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 IC_{50} 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 cholera*, *Staphylococcus aureus*, *Proteus*, *Pseudomonas spp*., and *Shigella dysenteriay* 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*-Dimethylgrisabine **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*-Dimethylgrisabine **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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