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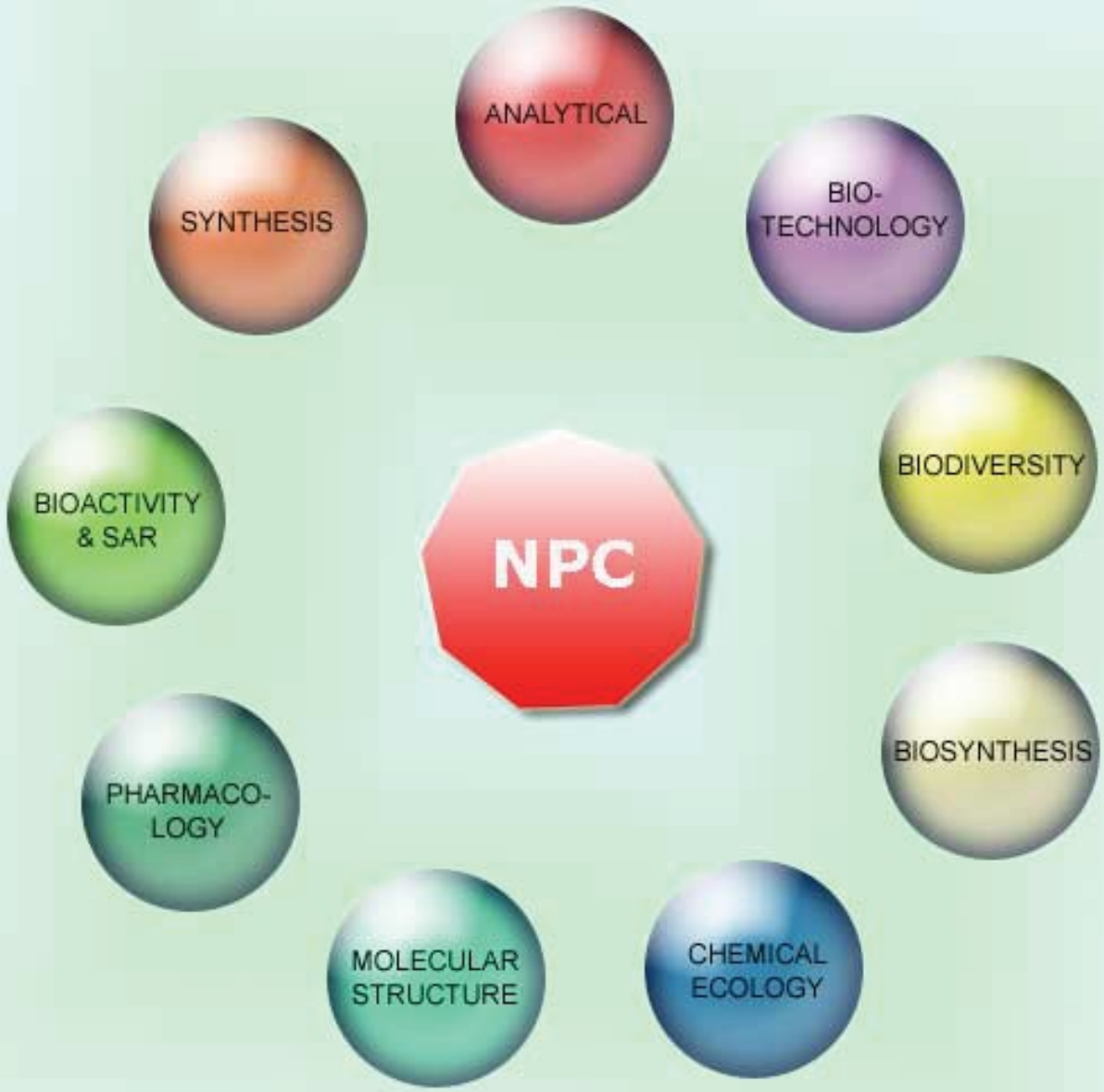

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Phytoconstituents of Genus *Micromelum* and Their Bioactivity—a Review

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Abstract

The genus *Micromelum* belongs to the Rutaceae family. As its rich bioactive constituents its stems, flowers, leaves, and roots have been used in traditional medicine, for the treatment of various diseases from ancient time. Phytochemically, many bioactive compounds, including coumarins, polyoxygenated flavonoids, phenylpropanoic acid derivatives, quinolone alkaloids, and also carbazole alkaloids, have been reported as secondary metabolites of the *Micromelum* spp. including many new compounds. Therefore, *Micromelum* spp. are considered potential for drug leads. In this article, we present an overview of secondary metabolites isolated from genus *Micromelum* and their bioactivities that have been reported between 1982 and 2019.

Keywords

Micromelum, Rutaceae, coumarins, flavonoids, quinolone and carbazole alkaloids

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Introduction to Chemical Constituents of Genus *Mocromelum* and Their Bioactivity

Micromelum spp. (Rutaceae) consist of 9 species found mostly in Samoa, Fiji, and Tonga islands, Australia, Southeast Asia, southern China, Ceylon, northeastern India, and West Pakistan.[1,2] *Micromelum* spp. are known for being rich in coumarins such as the 6- and 8-prenylated coumarins. In addition, the carbazole alkaloids, dihydrocinnamic acid derivatives, and flavonoids have been isolated from it.[3,4] The leaves and stems of *Micromelum* species have been found to contain coumarins, phenylpropanoic acid derivatives, polyoxygenated flavonoids, and also alkaloids.[5,6] The following *Micromelum* species have been well investigated due to their pharmaceutical properties.

M. integerrimum is a tree that grows up to 8 m high. Its young parts have rust-colored pubescent. It usually grows in moist mountain forests, maritime thickets in sandy soil; near sea level to 2000 m and is widely distributed in China, Bhutan, Cambodia, India, Laos, Myanmar, Nepal, Thailand, and Vietnam.[7] *M. integerrimum* is highly diversified for its secondary metabolites, and apart from acridone and carbazole alkaloids, a variety of coumarin derivatives, especially 6,7-di and 7,8-disubstituted coumarin core structures, having at least a prenyl unit have been isolated. Naturally occurring coumarin derivatives from *Micromelum* spp. exhibit a variety of biological activities including anti-corpulence, cytotoxicity, anti-platelet, and antimutagenicity.[3]

M. minutum is a small spineless tree that can reach up to 3 m in height. It is widely distributed in Southeast Asia and in Pacific islands. The stems, flowers, leaves, and roots are used pharmaceutically for a variety of indications.[8,9] The plant is known to contain coumarins, some of which are active compounds showing strong cytotoxic activities. The leaves are traditionally used to treat fever and giddiness. The poultice of the boiled roots is used for ague.[10] In Indochina, the roasted and crushed leaves are rubbed to skin irritated by scabies and are considered to be emmenagogues.[11] Previous phytochemical investigations on the different parts of *M. minutum* have showed the presence of coumarins, triterpenes, alkaloids, and phenylpropanoids.[12]

M. falcatum is a tree of 1-3 m high and its leaflet blades are alternate, ovate to lanceolate, in equilateral. Flowers are ellipsoid or broad in bud. Petals are white, oblong, outside glabrous, or

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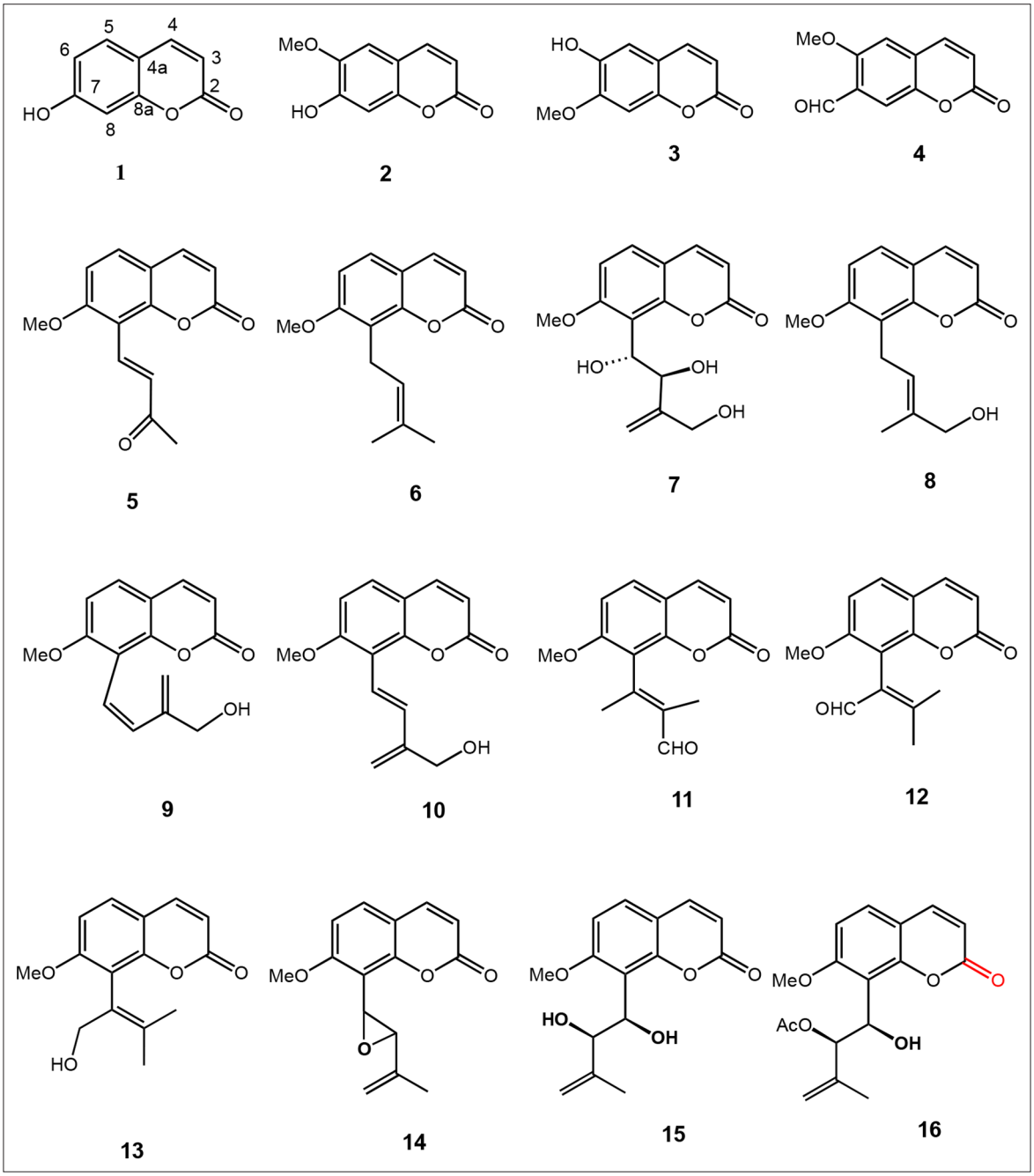

Figure 1. Coumarins from *Micromelum minutum, M. integerrimum, M. falcatum,* and *M. zeylanicum.*

pubescent. Fruits are ellipsoid to ovoid, 1- or 2-seeded. Its flowering period is from January to April. It is usually found in the mountain area at heights below 1200 m in China, Cambodia, Laos, Myanmar, Thailand, and Vietnam.[13] Its leaves and roots are used for treating infected wounds, odynolysis, rheumatism, muscular atrophy, and insect bites.[4,14] *M. falcatum* has been found to contain several coumarins, such as 7-oxygenated coumarins, dihydrocinnamic acid derivatives, the dimeric indole alkaloid (yuehchukene), the carbazole alkaloid, 5,6-pyranoglycozoline, the 6-prenylated coumarin, micromelin, and the 8-prenylated coumarins, phebalosin and murpanidin.[6,15,16] The dimeric indole alkaloid yuehchukene was found to have potent anti-implantation activity.[17]

M. compressum is a tree described as unarmed and glabrous. Its leaves are odd-pinnate, the leaflets are alternate, and the fruits are ovoid. Phytochemical efforts on the CH_2Cl_2-methanol extract of *M. compressum* have resulted in the isolation and identification of 3 polymethoxylated flavones.[1]

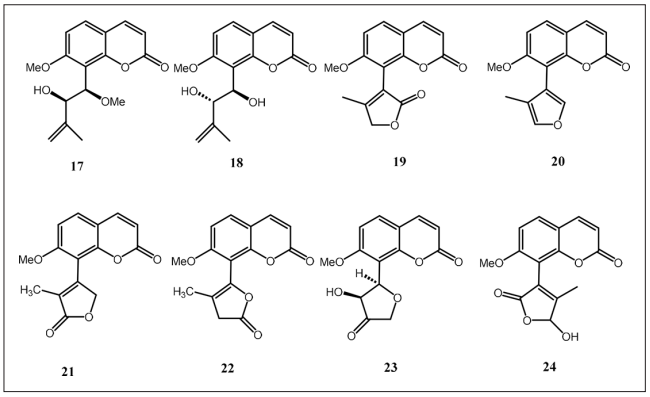

Figure 2. Coumarins isolated from *Micromelum falcatum*.

M. hirsutum is a tree of up to 10 m height with greenish-yellow flowers and aromatic leaves. It is widely distributed in peninsular Malaysia (Melaka and Pahang northward), Andaman Islands, Myanmar, Laos, Thailand, and Vietnam.[18] In 2010, Rodphukdeekul research group investigated antitumor activity of the dichloromethane extract from branches of *M. hirsutum* on human B lymphoma cells, Ramos. The result demonstrated that the extract has antitumor potential against B lymphoma.[19] In Myanmar its leaves are widely used as spices in curries. Phytochemial analysis of this species has reported the presence of many carbazole alkaloids, as well as the *γ*-lactone compounds.[18]

M. glanduliferum is a tropical or subtropical small tree found in Thailand. Coumarins and some carbazole alkaloids compounds, such as osthol, phebalosin, minumicrolin, murrangatin, murralongin, micormarin A, microminutinin, micromelin, and 2,7-dihydroxy-3-formyl-1-(30-methyl-20-butenyl)carbazole and 7-methoxy heptaphylline, were reported from the roots of *M. glanduliferum*.[20]

The chemical analysis of leaves and stems of *M. zeylanicum* has reported an oxazole alkaloid, O-methylhalfordinol, a coumarin, micromelin, and a flavone, 5-hydroxy-3,3′,4′,7-pentame thoxyflavone. In addition, the stems contained 6-formyl-7-methoxycoumarin, and the leaves contained the carbazole alkaloid, koenigine, and *p*-sitosterol.[21]

In this review the articles were collected from 1982 to 2019. The main purpose of this article was to evaluate the diversity of secondary metabolites isolated from *Micromelum* spp. in order to provide a complete reference of the diverse secondary metabolites from *Micromelum* spp. To the best of our knowledge this is the first review about secondary metabolites isolated from genus *Micromelum*.

Phytochemical Aspects of *Micromelum* Spp. and Their Tested Bioactivities

Coumarins

Coumarins are highly active biological substances and major secondary metabolites isolated from *Micromelum* spp. They are widely used in medicine, perfumes, cosmetics, and laser dyes.[6] Coumarins have antioxidant activity and they preserve the

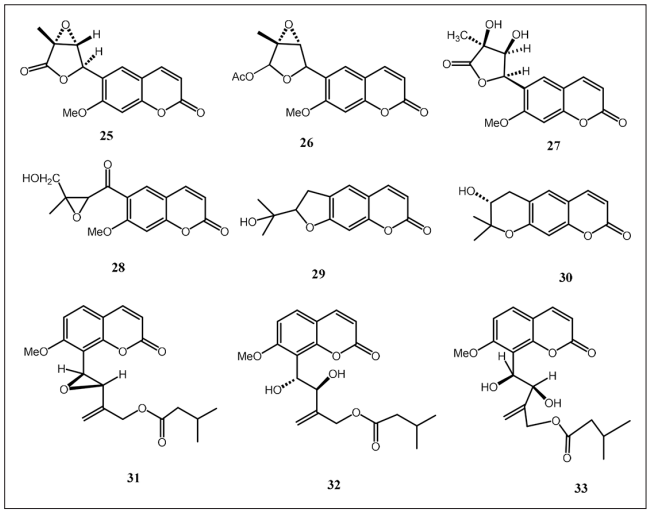

Figure 3. Some coumarins isolated from *Micromelum integerrimum* and *M. minutum*.

levels of other antioxidants in human plasma. Coumarins also inhibited lipid peroxidation and increased the activity of antioxidants, superoxide dismutase, and catalase.[22] Many bioactive coumarins have been reported from genus *Micromelum,* and the basic core coumarin compound, umbelliferone (**1**), was isolated from the roots of *M. minutum*.[8] Scopoletin compound 7-hydro xy-6-methoxy-2H-chromen-2-one (**2**) was isolated the fruits of *M. minutum*[23] and 6-hydroxy-7-methoxy-2H-chromen-2-one (**3**) was isolated from the stems and leaves of *M. integerrimum*.[24] Another coumarin, 6-formyl-7-methoxycoumarin (**4**), was isolated from the leaves and stems of *M. zeylanicum*.[21]

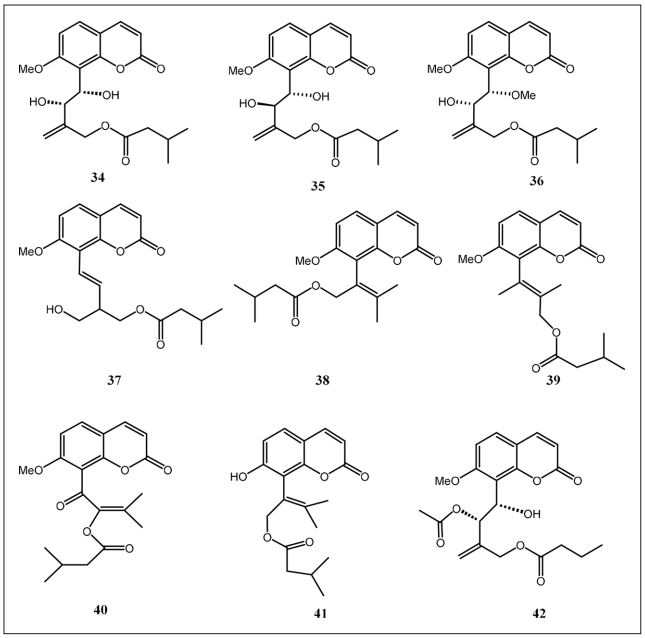

Figure 4. Coumarins from *Micromelum minutum* and *M. falcatum*.

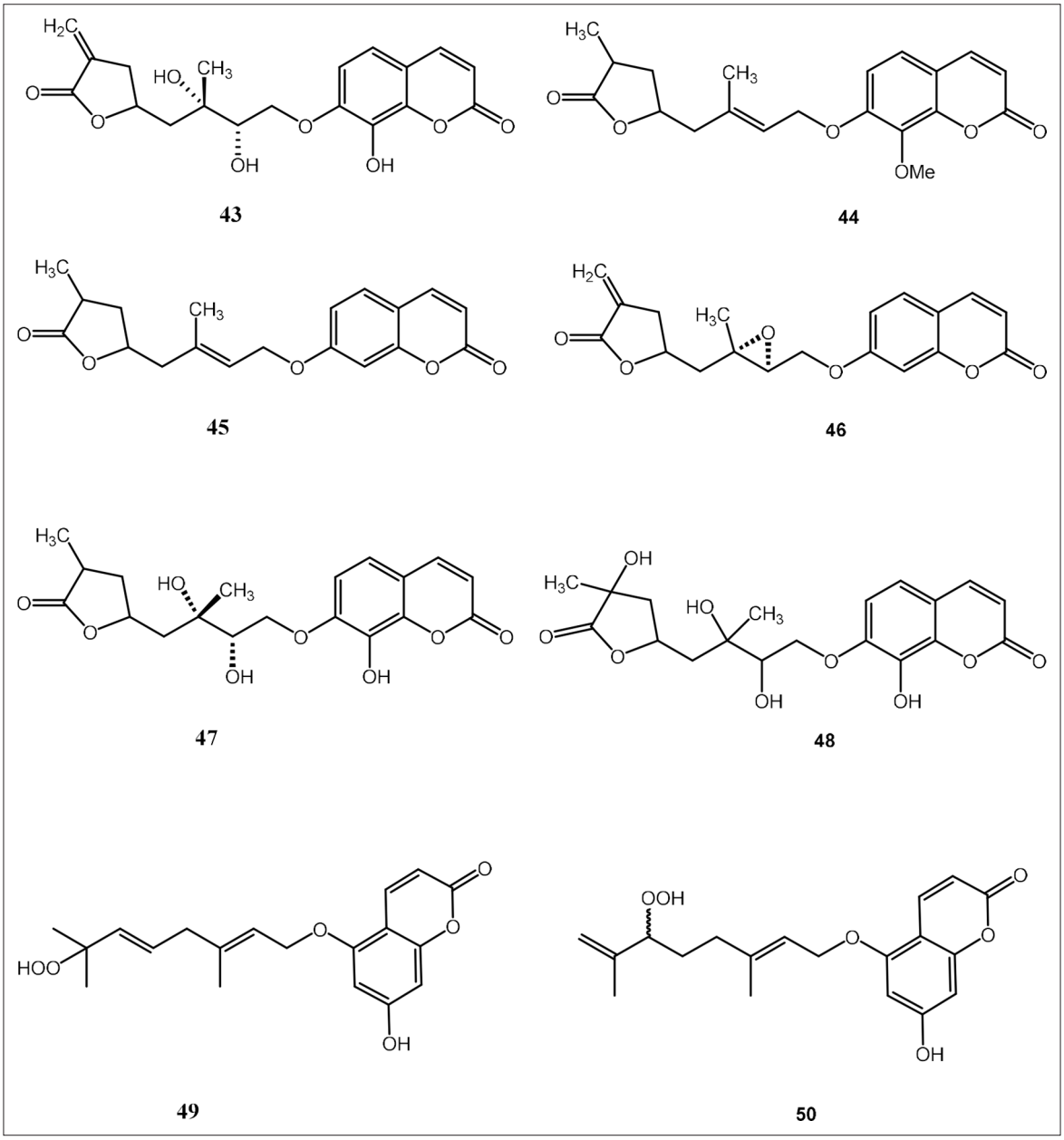

Figure 5. Coumarins from the *Micromelum minutum*.

7-Methoxyprenylated coumarin, osthenon (**5**), and osthol (**6**) were isolated from the roots of *M. minutum*.[8] Microfalcrin (**7**) was isolated from the leaves of *M. falcatum*.[16] This compound (**7**) was also found in *M. minutum*[8] (Figure 1).

One-prenylated coumarins named micromarin-F (**8**), -G (**9**), and -H (**10**) were isolated from the stems of *M. minutum*.[25] The compound murralongin-1 (**11**) was isolated from the roots of *M. minutum*.[8] Murralongin-2 (**12**) and murralonginol (**13**) were isolated from the fruits of *M. minutum*.[23,26] 7-Oxygenated coumarins, phebalosin (**14**), murrangatin (**15**), murrangatin acetate (**16**), murracarpin (**17**), and minumicrolin (**18**) were isolated from the roots of *M. minutum*[8] (Figure 1). Microminutin (**19**) was isolated from the acetone extract of the stems of *M. minutum*.[25] Some coumarins, such as 7-methoxy-8-(4'-methyl-3'-furanyl)coumarin (**20**), microminutin B (**21**), microminutin C (**22**), and micromeloside A (**23**), were isolated from the finely powdered fruits of *M. falcatum*[4] (Figure 2). In 2014, Kouloura et al reported microcoumaririn (**24**) from the leaves of *M. falcatum*. The anti-inflammatory properties of compounds (**24, 32**) were evaluated by measuring the inhibition of the proinflammatory mediator nuclear factor kappa B induction and nitric oxide (NO) production but these 2 compounds did not show any inhibition.[16]

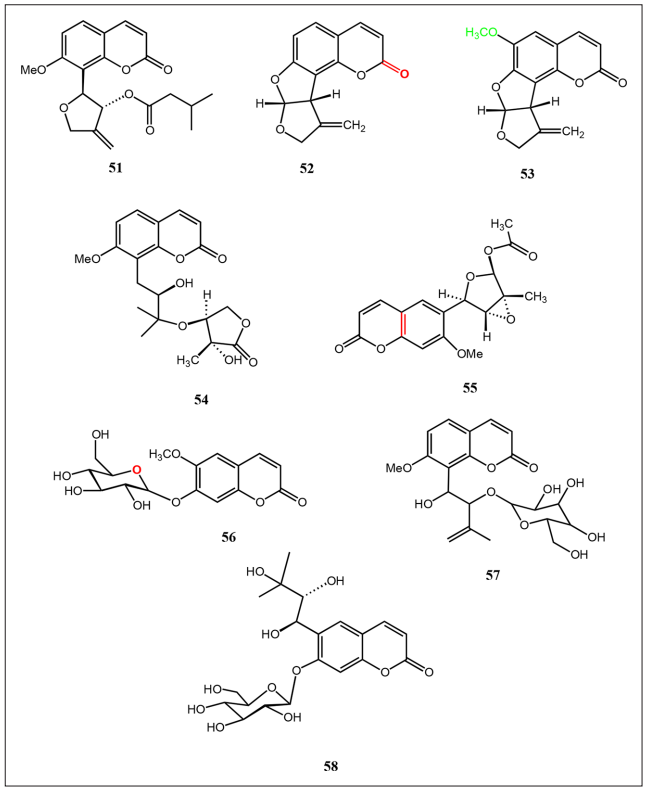

Figure 6. Coumarins from the *Micromelum minutum, M. integerrimum,* and *M. falcatum.*

Micromelin or 7-methoxy-6-((1*R*,2*R*,5*R*)−5-methyl-4-oxo-3,6-dioxabicyclo[3.1.0]hexan-2-yl)−2H-chromen-2-one (**25**) was isolated from the fruits of *M. minutum*.[23] This compound is common to all species of *Micromelum* so far examined and can perhaps be considered as a chemotaxonomic marker for the genus.[27] The compound acetyldihydromicromelin A (**26**) was isolated from the aerial parts of *M. minutum*.[26] One-prenylated coumarin, namely hydramicromelin D (**27**), was isolated from the twigs of *M. integerrimum*.[3] Hopeyhopol (**28**) and marmesin (**29**) were isolated from the whole plants of *M. minutum*.[28] (−) Decursinol (**30**) was isolated from the finely powdered fruits of *M. falcatum*.[4] One-prenylated coumarins named micromarin-A (**31**), -B (**32**), and -C (**33**) were isolated from the seeds of *M. minutum*[22] and fruits of *M. falcatum*[16] (Figure 3).

Ester coumarinoids, (3*S*,4*S*)−3,4-dihydroxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl)−2-ethylenebutyl 3-methylbutanoate (**34**), (3R,4*S*)−3,4-dihydroxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl)−2-methylenebutyl-3-methylbutanoate (**35**), and 3-hydroxy-4-methoxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl) −2-methylenebutyl-3-ethylbutanoate (**36**), were isolated from the finely powdered fruits of *M. falcatum*[4,16] (Figure 4). Another ester coumarin, 7-methoxy-8-(2-hydroxymethyl-1-*O*-isovaleryl -4-butenyl) coumarin (**37**), was isolated from the stem bark of *M. falcatum*.[29]

Murralonginol isovalerate-1 (**38**) was isolated from the stems of *M. minutum*.[23] Toxicity of compound (**37**) isolated from *M. falcatum* was tested against brine shrimp larvae using a 96-well plate assay and the compound (**37**) exhibited an LC_{50} value of 6.8 μM, indicating that it was a potent toxic natural product and its in vitro antiproliferative activities against lung cancer (HvEvc) cell lines by the MTT method, and (**37**) displayed moderate activity against the HvEvc cell line with IC_{50} value of 35.7.[29] Two-prenylated coumarins, murralonginol isovalerate-2 (**39**), minutuminolate (**40**), and 7-demethylmurralon ginolisovalerate (**41**), were isolated from the fruits and roots of *M. minutum*[8,23] (Figure 4). Micromarinate (**42**) was isolated from the EtOAc extract fruits of *M. falcatum*[4] (Figure 4).

Five other geranylcoumarins, such as 8-hydroxyisocapnolac tone-2′,3′-diol (**43**), isolated from *M. minutum* have in vitro antiplasmodial activity against *Plasmodium falciparum* FCR-3 and D-10 strains with IC_{50} values of 6.39 μg/mL (16.99 μM) and 24.23mg/mL(64.45μM),respectively.[10] 8-methoxycapnolactone (**44**), 3",4"-dihydrocapnolactone (**45**), 2′,3′ epoxyisocapnolactone (**46**), 8-hydroxy-3",4"-dihydrocapnolactone-2′,3′-diol (**47**), and 8,4-dihydroxy-3,4-dihydrocapnolactone-2,3-diol (**48**) were isolated from the leaves of *M. minutum*[10,11,30] (Figure 5). These coumarins contained a lactone ring in their structure. In 2009, Ratna et al reported the cytotoxicity of these lactone coumarins on T-lymphoblastic leukemia (CEM-SS), promyeolocytic leukemia (HL60), cervical cancer (HeLa), and liver cancer (HepG2) cell lines. Among the tested compounds, (**43**) showed the most active with IC_{50} values of 2.9, 2.5, 6.9, and 5.9 μg/mL, respectively.[11] In 2014, the same group investigated the cytotoxic activity of compound (**43**) on MCF-7 and T47D cells. The results showed IC_{50} values of 8 μg/mL (21.2 μM) and 4 μg/mL (10.6 μM) respectively.[31]

Two monoterpene coumarins, minutin A (**49**) and minutin B (**50**), were isolated from the leaves of *M. minutum* (Figure 5) and their cytotoxic activity against *Leishmania major* and cancer cells were already studied. It has been reported that minutin B (**50**) has strong cytotoxic activity against the cancer cell lines such as SBC3, A549, K562, and K562/ADM with IC_{50} values of 8.8, 10.1, 16.9, and 10.1 μM, respectively.[32]

The 7-methoxylated coumarin, micromelosidester (**51**), was isolated from the leaves of *M. falcatum*.[16] Two compounds microminutinin (**52**) and 6-methoxymicrominutinin (**53**) were isolated from the leaves of *M. falcatum*.[4] These 2 compounds are different from other compounds shown previously, because the prenyl attached on coumarin core forms a bicyclic structure. Other 2-prenylated coumarins named integerrimelin (**54**), (1*R*,3*R*,4*R*,6*S*)−4-(7-Methoxy-2-oxo-2H-chromen-6-yl)−1-methyl-3,6-dioxabicyclo[3.1.0]hexan-2-yl acetate (**55**), and scopolin (**56**) were isolated from the twigs, stems, and leaves of *M. integerrimum*.[3,24,33] A glycoside coumarin 7-methoxy-8-(1-hydro xy-2-*O*-*β*-glucopyranosyl-3-methyl-4-butene-1-yl) coumarin (**57**) was isolated from the stem bark of *M. falcatum*.[29] Another coumarin, micromelumoside D (**58**), was isolated from the aerial portions of *M. minutum*[6] (Figure 6).

In 2018, Kassim et al reported a lignan sesamin (**118**) (Figure 7) together with 3 couramins, hydramicromelinin (**59**), micromelinin (**60**), and 1-*O*-*β*-D-glucopyranosylmarmesin (**61**)

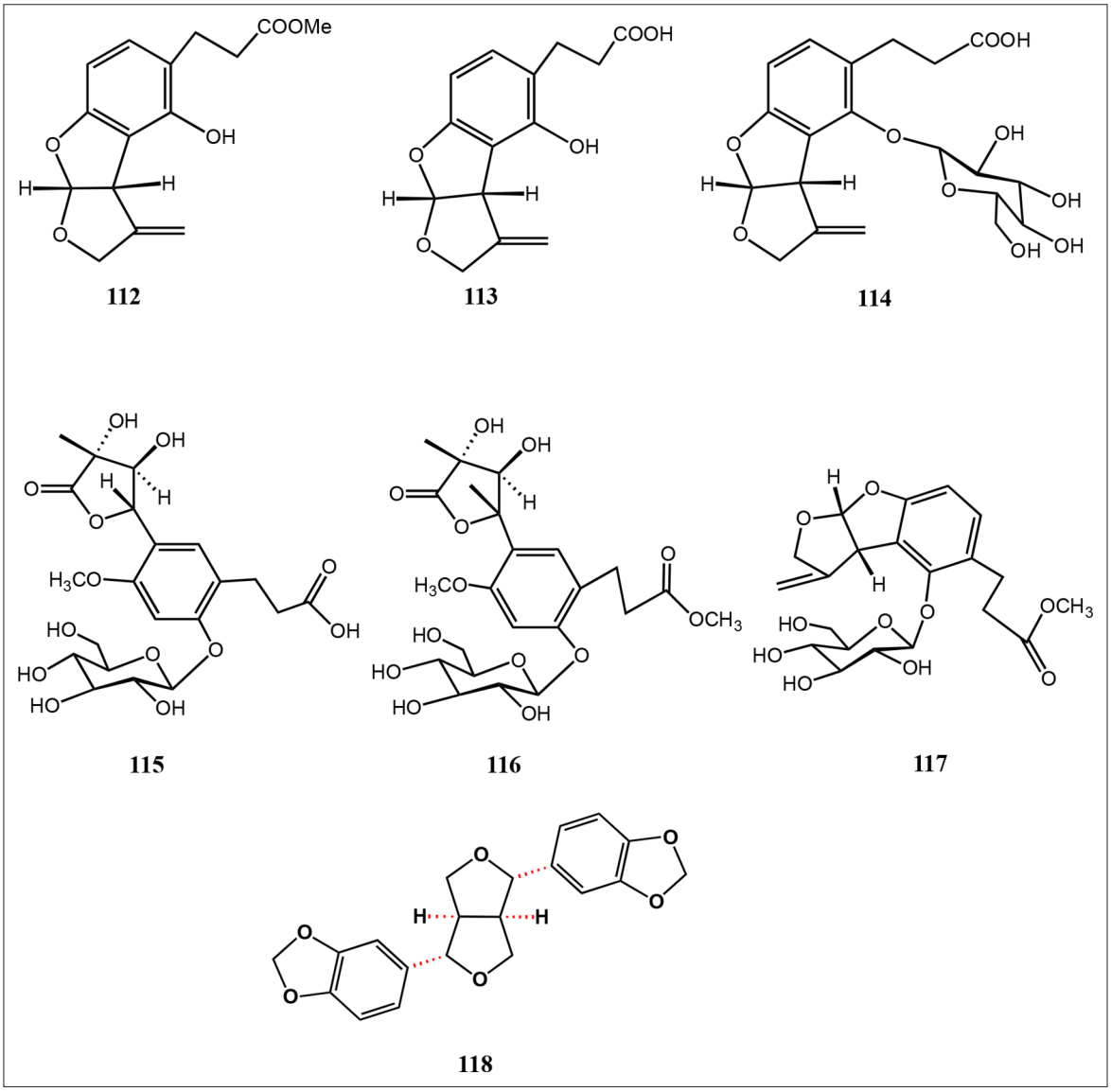

Figure 7. Miscellaneous compounds from the *Micromelum integerrimum, M. hirsutum, M. minutum,* and *M. falcatum.*

(Figure 8) from *M. minutum* methanol bark extract. Of the reported compounds, the ORAC measurements of compounds **59** and **118** showed potent antioxidant activity with the values of 5539 and 4031 μmol TE/g, respectively.[34]

Alkaloids

Alkaloids have inspired the development of several antibacterial drugs through the synthesis of quinine serendipitously yielding the quinolones, structural alteration of azomycin yielding metronidazole, and working with the quinoline scaffold yielding bedaquiline. In other drugs, alkaloids are present as scaffold substructures, eg linezolid and trimethoprim. Alkaloids remain the focus of much research. Their development as antibacterial drugs pursued within academia, industry, and joint-ventures.[35] A large number of carbazole alkaloids have been isolated from higher plants of the genera *Murraya, Glycosmis*, *Micromelum,* and *Clausena*, all belonging to the family rutaceae.[36,37]

The quinoldione alkaloids 2-(3-hydroxy-1-methyl-2,4-dioxo -1,2,3,4-tetrahydroquinolin-3-yl)acetate (**62**) and 3-hydroxy-1-methyl-3-(2-oxopropyl)quinoline-2,4(1H,3H)-dione (**63**) along with 2 quinolinone alkaloids *N*-methylflindersine (**64**), 4-hydro xy-3-methoxy-1-methyl-2(1 H)-quinolinone (**65**), and the *N*-methylswietenidine-B (**66**) were reported from the stem of *M. falcatum* (Figure 9). The toxicity of all compounds (**62-66**) was tested in the brine shrimp larvae assay, and their LD_{50} values were 143, 355.0, 1.39, 2020.0, and 70.5 mg/mL, respectively, indicating that compound (**64**) was a potent toxic substance.[17]

The alkaloids myosmine (**67**), halfordinol (**68**), and *O*-methylhalfordinol (**69**) were reported from the leaves and

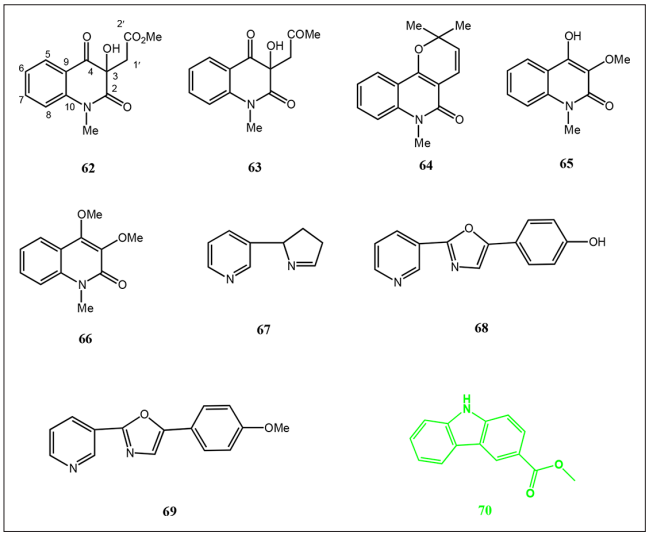

Figure 8. Coumarins from the *Micromelum minutum*.

young stems of *M. zeylanicum*.[21] The methyl carbazole-3-carboxylate (**70**) was isolated from the leaves of *M. integerrimum*[38] (Figure 9).

Increased death rates due to lung cancer have necessitated the search for potential novel anticancer compounds such as carbazole derivatives. Carbazoles are aromatic heterocyclic organic compounds, with a tricyclic structure composed of 2 benzene rings each fused onto a 5-membered nitrogen-containing ring with anticancer, antibacterial, and anti-inflammatory activity.

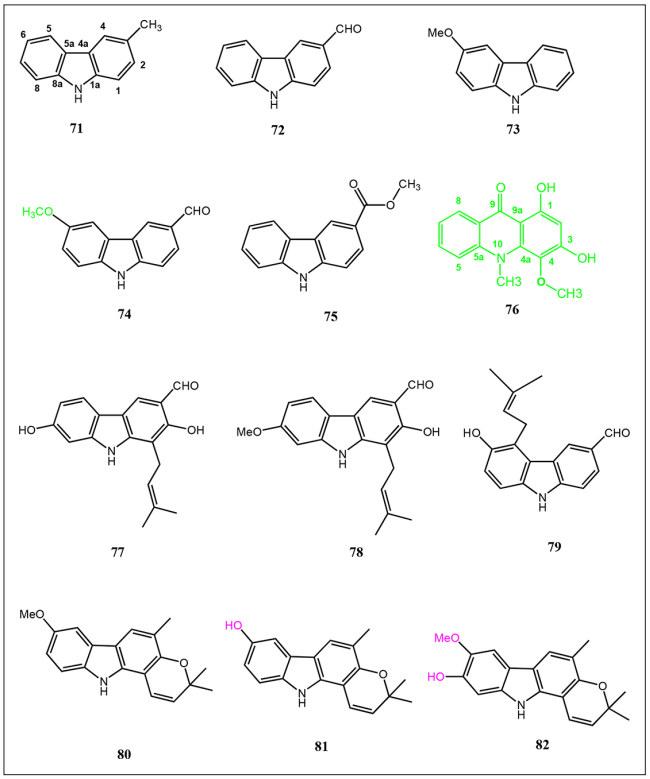

Figure 9. Alkaloids from *Micromelum falcatum, M. zeylanicum, and M. integerrimum*.

Anti-TB bioassay-directed fractionation led to the isolation of 6 carbazole alkaloids from the CH_2Cl_2 extract of the stem bark of *M. hirsutum*. The carbazoles including 3-methylcarbazole (**71**), 3-formylcarbazole (**72**), lansine (**73**), 3-formyl-6-methoxycarbazole (**74**), and methyl carbazole-3-carboxylate (**75**) were reported from the stem barks of *M. hirsutum*.[18] A acridone alkaloid, 1,3-dihydroxy-4-methoxy-10-met hylacridone (**76**), was isolated from the leaves of *M. integerrimum*[38] (Figure 10).

Two carbazole alkaloids, 2,7-dihydroxy-3-formyl-1-(30-met hyl-20-butenyl)carbazole (**77**) and 7-methoxy heptaphylline (**78**), were isolated from the roots of *M. glanduliferum by* Siridechakorn et al in 1985. They might be a useful chemotaxonomic marker of the species *M. glanduliferum* and could be used to differentiate *M. glanduliferum* from other species of *Micromelum*.[20] Micromeline (**79**) was isolated from the stem barks of *M. hirsutum*.[18] The alkaloid compounds koenimbine (**80**), koenine (**81**), koenigine (**82**), and koenidine (**83**) were isolated from the leaves and young stems of *M. zeylanicum*[21] (Figures 10 and 11).

In addition, a carbazole alkaloid, mahanine (**84**), was isolated from the leaves of *M. minutum* (Figure 11). It has been shown to exhibit a wide range of pharmacological effects including antimutagenicity against heterocyclic amines, antimicrobial activity against Gram positive bacteria, an anti-inflammatory effect, and it appeared to be cytotoxic against several cancer cell lines.[35]

Phenethyl cinnamides, micrometam A (**85**), micrometam D (**86**), micrometam E (**87**), and micrometam B (**88**), and a core of novel marine compound, micrometam C (**89**), were reported from the whole plant of *M. falcatum*[15,39] (Figure 11).

Flavones

A number of phytochemical studies dealing with polymethoxylated flavones from *Micromelum* spp. have been reported and a large number of flavonol-type metabolites were identified with the occurrence of partially methylated derivatives.[1]

Polymethoxylated flavones, 5-hydroxy-3,4′,7,8-tetramethox yflavone (**90**), 5,7-dihydroxy-3,4’,8-trimethoxyflavone (**91**), 5-h ydroxy-3,4’,7,8-tetramethoxyflavone (**92**), and 5-hydroxy-3,4’,6 ,7,8-pentamethoxyflavone (**93**), were reported from *M. minutum*.[40] Other polymethoxylated flavones such as 3,5,7,4′-tetramethoxyflavone (**94**), 3,5,7,8,4’-pentamethoxyflavone (**95**), and 3,5,6,7,4’-pentamethoxyflavone (**96**) were also reported from the leaves of *M. compressum*[1] (Figure 12).

Three compounds, 5,7-dihydroxy-4’,6,8-trimethoxyflavone (**97**), 7-hydroxy-4’,5,6,8-tetramethoxyflavone (**98**), and 7-hydro xy-4’,6,8-trimethoxyflavone-5-ylacetate (**99**), were isolated from the aerial parts of *M. minutum*.[26] 5-hydroxy-3,3’,4’,7,8-pen

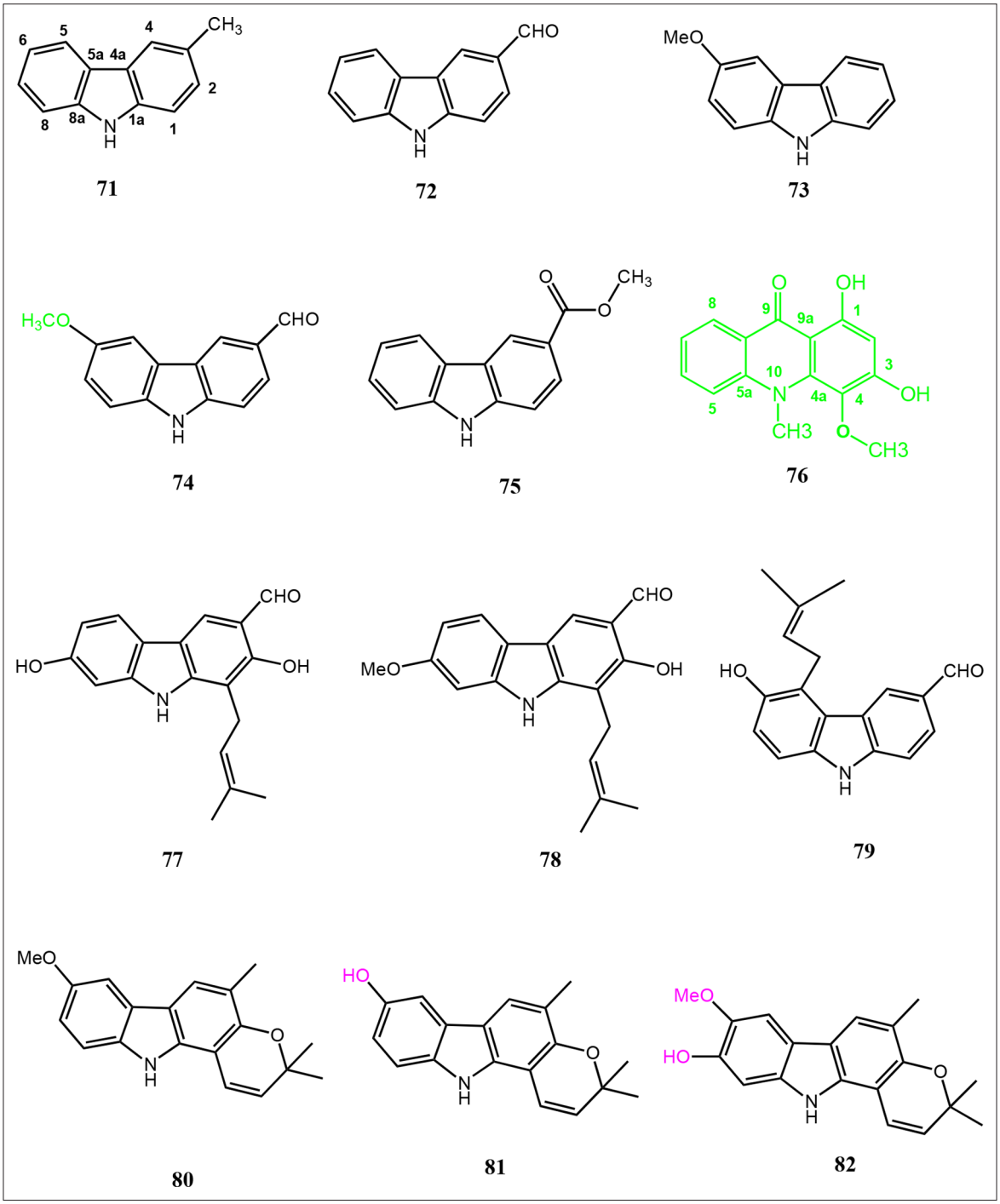

Figure 10. Alkaloids from *Micromelum minutum, M. hirsutum, M. zeylanicum, M. glanduliferum, M. falcatum,* and *M. integerrimum.*

tamethoxyflavone (**100**) was also isolated from the leaves and stems of *M. zeylanicum*[21] (Figure 12).

Coumarin and Flavone Condensed Binary Compounds

The compounds 8-((1*S*,2*R*)−1-hydroxy-2-(5-hydroxy-6, 8-dim ethoxy-2-(4-methoxyphenyl)−4-oxo-4H-chromen-7-yloxy)−3-methylbut-3-enyl)−7-methoxy-2H-chromen-2-one (**101**), 8-((1*S*,2*R*) −1-hydroxy-3-methyl-2-(5,6,8-trimethoxy-2-(4-met hoxyphenyl)−4-oxo-4H-chromen-7-yloxy)but-3-enyl)−7-methoxy-2H-chromen-2-one (**102**), and 7-((1*S*,2*R*)−1-hydroxy-1-(7-methoxy-2-oxo -2H-chromen-8-yl)−3-methylbut-3 -en-2-yloxy)−6,8-dimethoxy-2-(4-methoxyphenyl)−4-oxo-4H-chromen-5-yl acetate (**103**) were reported from the above ground parts of *M. mtnutum*[26] (Figure 13).

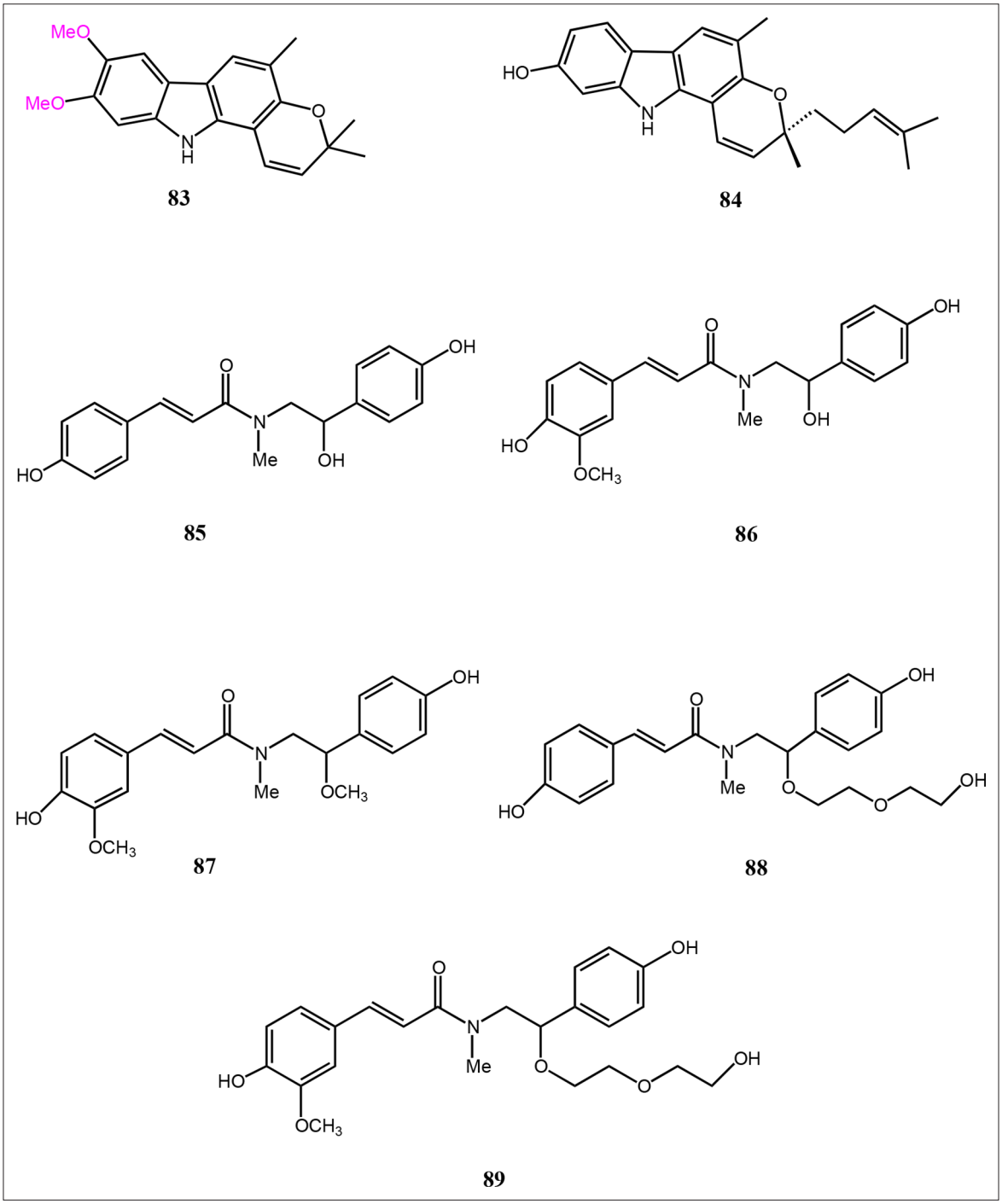

Figure 11. Alkaloids from *Micromelum falcatum*.

Miscellaneous Compounds

The stigmasterol (**104**) was isolated from the leaves of *M. minutum*.[10] Two triterpenes, 5(6)-gluten-3α-ol (**105**) and 5(6)-gluten-3-on (**106**), were isolated from the leaves' and barks' crude petroleum ether and chloroform extracts of *M. minutum*.[11] The derivative of oleic acid with trivial name micromolide (**107**) was isolated from the stem barks of *M. hirsutum*[18] (Figure 14).

In 2014, Zhi-yao et al have reported 2 phenylpropanoids, microintegerrin A (**108**) and microintegerrin B (**109**), from the air-dried stems and leaves of *M. integerrimum*. These 2 compounds were tested for their cytotoxicity against 3 cancer cell lines (HeLa, A549, and BGC-823) but did not show any activity.[24] Dihydrocinnamic methyl ester derivatives, 3-(5-((2R,3R,4R)−3,4-dihydroxy-4-methyl-5-oxotetrahydrofuran-2-yl)−2-hydroxy-4-methoxyphenyl)

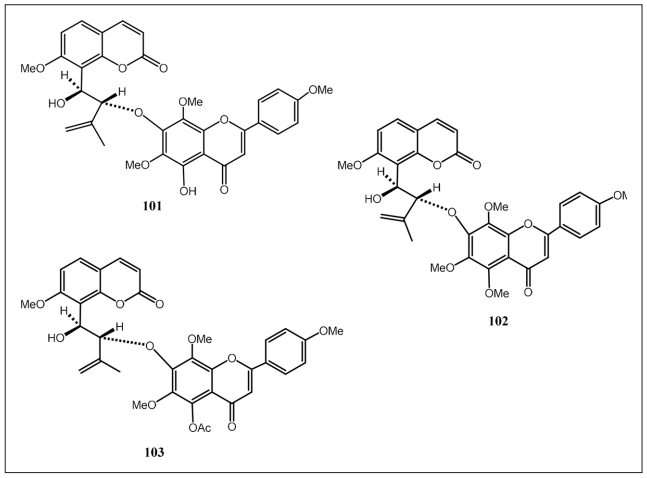

Figure 12. Flavones from *Micromelum minutum, M. zeylanicum,* and *M. compressum*.

propanoic acid (**110**) and secomicromelin (**111**), were isolated from the fruits of *M. falcatum*[4] (Figures 7 and 14). Three dihydrocinnamic acid derivatives, 3,4-dihydro-1,2-secomicrominutinin (**112**), 3,4-dihydro-1,2-secomicrominutinin methylester (**113**), and 3,4-dihydro-1,2-secomicrominutinin-9-*O*-glucoside (**114**), were isolated from the leaves of *M. falcatum*.[14] Other 3 glucosides of phenylpropanoic acid derivatives,

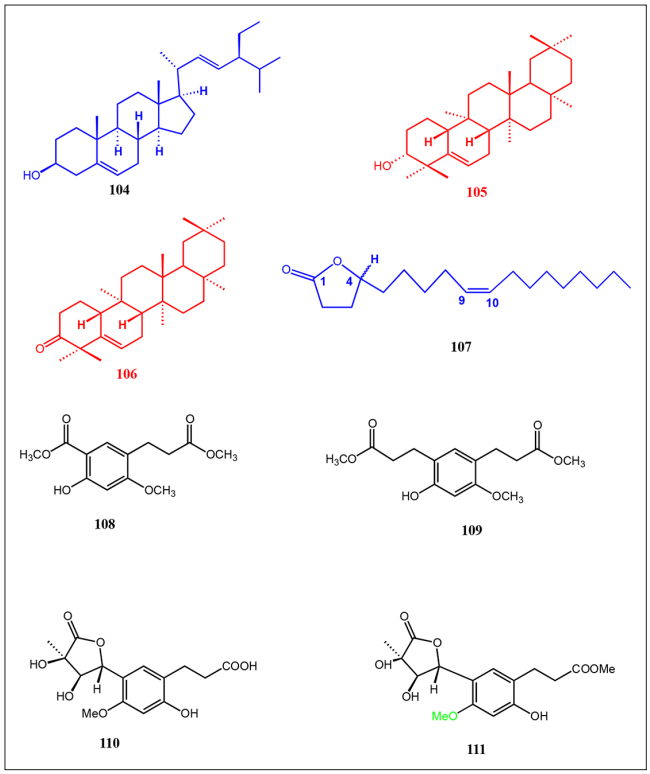

Figure 13. Coumarin and flavone condensed compounds from *Micromelum minutum*.

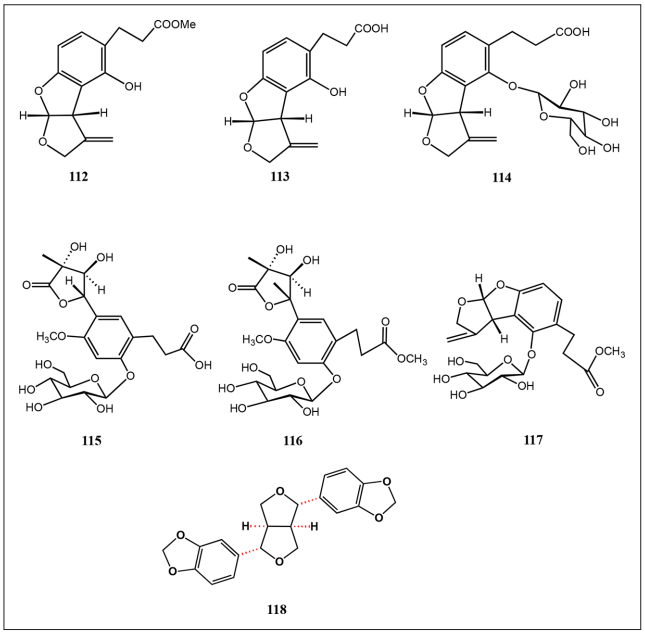

Figure 14. Miscellaneous compounds from *Micromelum minutum* and *M. hirsutum*.

micromelumosides A (**115**), micromelumosides B (**116**), and micromelumosides C (**117**), and sesamin (**118**) were reported from the aerial parts of *M. minutum*[6] (Figure 7).

Conclusion

Micromelum spp. possess very rich sources of bioactive secondary metabolites. As a member of rutaceae family it contains mainly coumarins (from simple to prenly, and geranyl), alkaloids (quinolidine and carbazole), polymethoxyflavones, and a few glycosides and phenylpropanoic acid derivatives (Table 1). The coumarins are the most abundant compounds from *Micromelum* spp., and some compounds, such as 8-hydro xyisocapnolactone-2′,3′-diol, have positive effects on the anticancer activity. Currently, at least 118 compounds have been reported from different plant parts of *M. integerrimum*, *M. minutum*, *M. falcatum*, *M. compressum, M. glanduliferum*, *M. hirsutum,* and *M. zeylanicum* (Table 1). Among them, *M. integerrimum*, *M. minutum*, and *M. falcatum* were well studied chemically and pharmacologically and others, *M. compressum, M. glanduliferum, M. hirsutum,* and *M. zeylanicum,* have been studied less. So, the review suggests that there is a great potential for researchers to search drug lead secondary metabolites from the genus *Micromelum*.

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Table 1. Isolated Compounds Reported From *Micromelum* Spp.

No. of compounds	Plant parts	Name of species	References
Simple coumarins			
Umbelliferone (**1**)	Roots	*M. minutum*	8,13
7-Hydroxy-6-methoxy-2H-chromen-2-one (**2**)	Fruits	*M. minutum*	23
6-Hydroxy-7-methoxy-2H-chromen-2-one (**3**)	Leaves and stems	*M. integerrimum*	24
6-Formyl-7-methoxycoumarin (**4**)	Leaves and stems	*M. zeylanicum*	21
Osthenon (**5**)	Roots	*M. minutum*	8
Prenylated coumarins			
Osthol (**6**)	Leaves	*M. minutum*	8
Microfalcrin (7)	Roots	*M. falcatum*	16
Micromarin-F (**8**)	Stems	*M. minutum*	25
Micromarin-G (**9**)	Stems	*M. minutum*	25
Micromarin-H (**10**)	Stems	*M. minutum*	25
Murralongin-1 (**11**)	Fruits	*M. minutum*	8,23
Murralongin-2 (**12**)	Fruits	*M. minutum*	8,23
Murralonginol (**13**)	Fruits	*M. minutum*	8,23
Phebalosin (**14**)	Roots	*M. minutum*	8
Murrangatin (**15**)	Roots	*M. minutum*	8
Murrangatin acetate (**16**)	Roots	*M. minutum*	8
Murracarpin (**17**)	Roots	*M. minutum*	8
Minumicrolin (**18**)	Roots	*M. minutum*	8
Microminutin (**19**)	Stem	*M. minutum*	25
7-Methoxy-8-(4'-methyl-3'-furanyl)coumarin (**20**)	Fruits	*M. falcatum*	4
Microminutin B (**21**)	Fruits	*M. falcatum*	4
Microminutin C (**22**)	Fruits	*M. falcatum*	4
Micromeloside A (**23**)	Fruits	*M. falcatum*	4
Microcoumaririn (**24**)	Leaves	*M. falcatum*	16
Micromelin (**25**)	Fruits	*M. minutum*	23
Acetyldihydromicromelin A (**26**)	Aerial parts	*M. minutum*	26
Hydramicromelin D (**27**)	Twigs	*M. integerrimum*	3
Hopeyhopol (**28**)	Whole plants	*M. minutum*	28
Marmesin (**29**)	Whole plants	*M. minutum*	28
(−) Decursinol (**30**)	Fruits	*M. falcatum*	4
Micromarin-A (**31**)	Stems	*M. falcatum*	16,22
Micromarin-B (**32**)	Stems	*M. minutum*	16,22
Micromarin-C (**33**)	Stems	*M. minutum*	22
(3*S*,4*S*)−3,4-Dihydroxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl)−2-ethylenebutyl 3-methylbutanoate (**34**)	Fruits	*M. falcatum*	4
(3*R*,4*S*)−3,4-Dihydroxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl)−2-methylenebutyl 3-methylbutanoate (**35**)	Fruits	*M. falcatum*	4
3-Hydroxy-4-methoxy-4-(7-methoxy-2-oxo-2H-chromen-8-yl)−2-methylenebutyl3-ethylbutanoate (**36**)	Fruits	*M. falcatum*	4
7-Methoxy-8-(2-hydroxymethyl-1-O-isovaleryl-4-butenyl) coumarin (**37**)	Stem bark	*M. falcatum*	29
Murralonginol isovalerate-1 (**38**)	Stems	*M. minutum*	23
Murralonginol isovalerate-2 (**39**)	Roots	*M. minutum*	8
Minutuminolate (**40**)	Roots	*M. minutum*	8
7-Demethylmurralonginol isovalerate (**41**)	Roots	*M. minutum*	23
Micromarinate (**42**)	Fruits	*M. falcatum*	4
8-Hydroxyisocapnolactone-2′,3′-diol (**43**)	Leaves	*M. minutum*	10,11,28,32
8-Methoxycapnolactone (**44**)	Leaves	*M. minutum*	10,11,28,32
3",4"-Dihydrocapnolactone (**45**)	Leaves	*M. minutum*	10,11,28,32
2′,3′-Epoxyisocapnolactone (**46**)	Leaves	*M. minutum*	10,11,28,32
8-Hydroxy-3",4"-dihydrocapno lactone-2′,3′-diol (**47**)	Leaves	*M. minutum*	10,11,32
8,4-Dihydroxy-3,4-dihydro capnolactone-2,3-diol (**48**)	Leaves	*M. minutum*	10,11,32
Minutin A (**49**)	Leaves	*M. minutum*	10,11,32
Minutin B (**50**)	Leaves	*M. minutum*	10,11,32
Micromelosidester (**51**)	Leaves	*M. falcatum*	4

(Continued)

Table 1. Continued

No. of compounds	Plant parts	Name of species	References
Microminutinin (**52**)	Leaves	*M. falcatum*	4
6-Methoxymicrominutinin (**53**)	Leaves	*M. falcatum*	16,25
Integerrimelin (**54**)	Twigs	*M. integerrimum*	3
(1*R*,3*R*,4R,6S)−4-(7-Methoxy-2-oxo-2H-chromen-6-yl)−1-methyl-3,6-dioxabicyclo[3.1.0]hexan-2-yl acetate (**55**)	Leaves	*M. integerrimum*	33
scopolin (**56**)	Stems and leaves	*M. integerrimum*	24
7-Methoxy-8-(1-hydroxy-2-O-β-glucopyranosyl-3-Methyl-4-butene-1-yl) coumarin (**57**)	Stem bark	*M. falcatum*	29
Micromelumoside D (**58**)	Aerial parts	*M. minutum*	6
Hydramicromelinin (**59**)	Bark	*M. minutum*	34
Micromelinin (**60**)	Bark	*M. minutum*	34
1-*O*-*β*-D-Glucopyranosylmarmesin (**61**)	Bark	*M. minutum*	34
Alkaloids			
2-(3-Hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)acetate (**62**)	Stems	*M. falcatum*	17
3-Hydroxy-1-methyl-3-(2-oxopropyl)quinoline-2,4(1H,3H)-dione (**63**)	Stems	*M. falcatum*	17
N-Methylflindersine (**64**)	Stems	*M. falcatum*	17
4-Hydroxy-3-methoxy-1-methyl-2(1 H)-quinolinone (**65**)	Stems	*M. falcatum*	17
N-Methylswietenidine-B (**66**)	Stems	*M. falcatum*	17
Myosmine (**67**)	Leaves and stem	*M. zeylanicum*	21
Halfordinol (**68**)	Leaves and stem	*M. zeylanicum*	21
O-Methylhalfordinol (**69**)	Leaves and stem	*M. zeylanicum*	21
Methyl carbazole-3-carboxylate (**70**)	Leaves	*M. integerrimum*	38
3-Methylcarbazole (**71**)	Stem barks	*M. hirsutum*	18
3-Formylcarbazole (**72**)	Stem barks	*M. hirsutum*	18
Lansine (**73**)	Stem barks	*M. hirsutum*	18
3-Formyl-6-methoxycarbazole (**74**)	Stem barks	*M. hirsutum*	18
Methyl carbazole-3-carboxylate (75)	Leaves	*M. integerrimum*	38
1,3-Dihydroxy-4-methoxy-10-methylacridone (**76**)	Stem bark	*M. hirsutum*	18
2,7-Dihydroxy-3-formyl-1-(30-methyl-20-butenyl)carbazole (**77**)	Roots	*M. glanduliferlum*	20
7-Methoxy heptaphylline (**78**)	Roots	*M. glanduliferlum*	20
Micromeline (**79**)	Stem bark	*M. hirsutum*	18
Koenimbine (**80**)	Leaves and stem	*M. zeylanicum*	21
Koenine (**81**)	Leaves and stem	*M. zeylanicum*	21
Koenigine (**82**)	Leaves and stem	*M. zeylanicum*	21
Koenidine (**83**)	Leaves and stem	*M. zeylanicum*	21
Mahanine (**84**)	Roots	*M. minutum*	35
Miscellaneous compounds			
Micrometam A (**85**)	Whole plants	*M. falcatum*	15
Micrometam D (**86**)	Whole plants	*M. falcatum*	15
Micrometam E (**87**)	Whole plants	*M. falcatum*	15
Micrometam B (**88**)	Whole plants	*M. falcatum*	15
Micrometam C (**89**)	Whole plants	*M. falcatum*	15
Polymethoxylated flavones			
5-Hydroxy-3,4′,7,8-tetramethoxyflavone (**90**)	Aerial parts	*M. minutum*	40
5,7-Dihydroxy-3,4’,8-trimethoxyflavone (**91**)	Aerial parts	*M. minutum*	40
5-Hydroxy-3,4’,7,8-tetramethoxyflavone (**92**)	Aerial parts	*M. minutum*	40
5-Hydroxy-3,4’,6,7,8-pentamethoxyflavone (**93**)	Leaves	*M. minutum*	40
3,5,7,4′-Tetramethoxyflavone (**94**)	Leaves	*M. compressum*	1
3,5,7,8,4’-Pentamethoxyflavone (**95**)	Leaves	*M. compressum*	1

(Continued)

Table 1. Continued

No. of compounds	Plant parts	Name of species	References
3,5,6,7,4'-Pentamethoxyflavone (**96**)	Leaves	*M. compressum*	1
5,7-Dihydroxy-4',6,8-trimethoxyflavone (**97**)	Aerial parts	*M. minutum*	26
7-Hydroxy-4',5,6,8-tetramethoxyflavone (**98**)	Aerial parts	*M. minutum*	26
7-Hydroxy-4',6,8-trimethoxyflavone −5-ylacetate (**99**)	Aerial parts	*M. minutum*	26
5-Hydroxy-3,3',4',7,8-pentamethoxyflavone (**100**)	Leaves and stems	*M. zeylanicum*	21
Coumarin and flavone condensed compounds			
8-((1*S*,2*R*)−1-Hydroxy-2-(5-hydroxy-6,8-dimethoxy-2-(4-methoxyphenyl)−4-oxo-4H-chromen-7-yloxy)−3-methylbut-3-enyl)−7-methoxy-2H-chromen-2-one (**101**)	Aerial parts	*M. minutum*	26
8-((1*S*,2*R*)−1-Hydroxy-3-methyl-2-(5,6,8-trimethoxy-2-(4-methoxyphenyl)−4-oxo-4H-chromen-7-yloxy)but-3-enyl)−7-methoxy-2H-chromen-2-one (**102**)	Aerial parts	*M. minutum*	26
7-((1*S*,2*R*)−1-Hydroxy-1-(7-methoxy-2-oxo-2H-chromen-8-yl)−3-methylbut-3-en-2-yloxy)−6,8-dimethoxy-2-(4-methoxyphenyl)−4-oxo-4H-chromen-5-yl acetate (**103**)	Aerial parts	*M. minutum*	26
Stigmasterol and triterpenes			
Stigmasterol (**104**)	Leaves	*M. minutum*	10
5(6)-Gluten-3α-ol (**105**)	Leaves and barks	*M. minutum*	23
5(6)-Gluten-3-one (**106**)	Leaves and barks	*M. minutum*	23
Derivative of oleic acid and phenylpropanoic acid			
Micromolide (**107**)	Stem barks	*M. hirsutum*	18
Microintegerrin A (**108**)	stems and leaves	*M. integerrimum*	24
Microintegerrin B (**109**)	stems and leaves	*M. integerrimum*	24
3-(5-((2*R*,3*R*,4*R*)−3,4-Dihydroxy-4-methyl-5-oxotetrahydrofuran-2-yl)−2-hydroxy-4-methoxyphenyl) propanoic acid (**110**)	fruits	*M. falcatum*	4
Secomicromelin (**111**)	fruits	*M. falcatum*	4
3,4-Dihydro-1,2-secomicrominutinin (**112**)	leaves	*M. falcatum*	14
3,4-Dihydro-1,2-secomicrominutinin methylester (**113**)	leaves	*M. falcatum*	14
3,4-Dihydro-1,2-secomicrominutinin-9-*O*-glucoside (**114**)	leaves	*M. falcatum*	14
Micromelumosides A (**115**)	aerial parts	*M. minutum*	6
Micromelumosides B (**116**)	aerial parts	*M. minutum*	6
Micromelumosides C (**117**)	aerial parts	*M. minutum*	6
Sesamin (**118**)	bark	*M. minutum*	34

Declaration of Conflicting Interests

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Natural product communications

Country	United States - SIR Ranking of United States
Subject Area and Category	Agricultural and Biological Sciences Plant Science Medicine Complementary and Alternative Medicine Medicine (miscellaneous) Pharmacology, Toxicology and Pharmaceutics Drug Discovery Pharmacology
Publisher	Natural Product Communications
Publication type	Journals
ISSN	15559475, 1934578X
Coverage	2008-ongoing
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35

H Index

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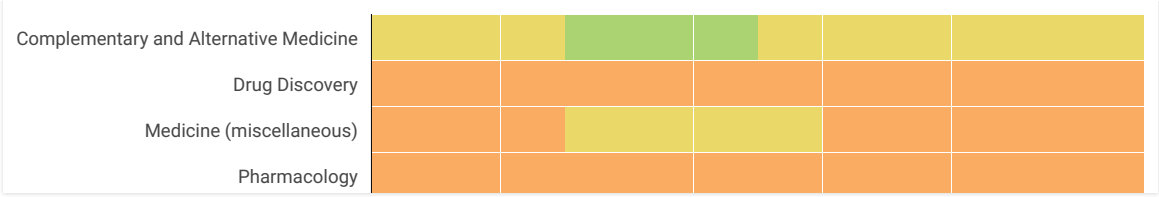
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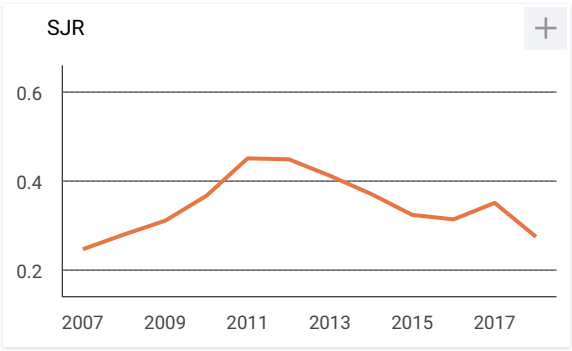
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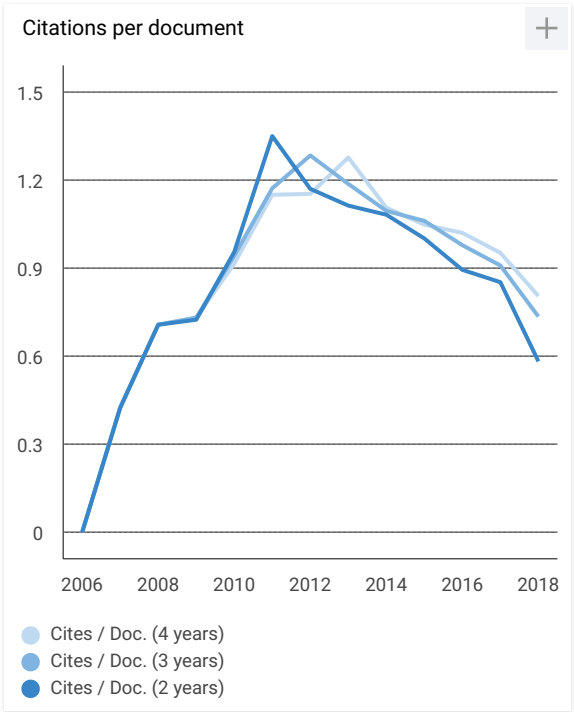
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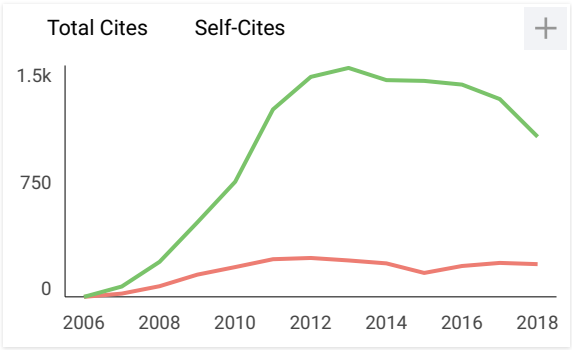
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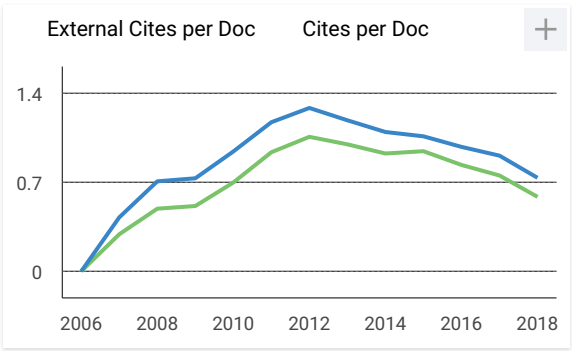
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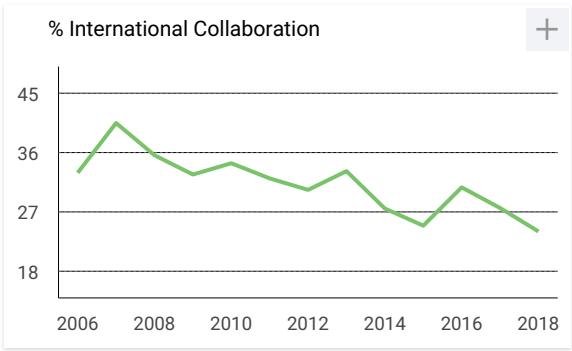
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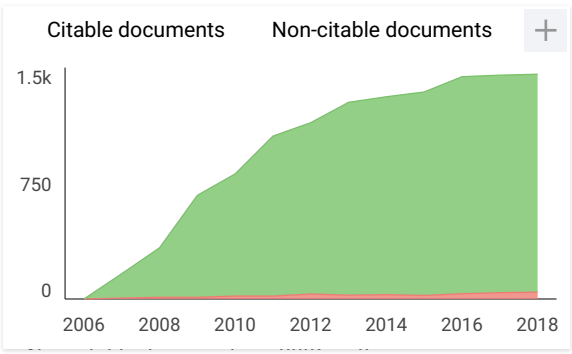
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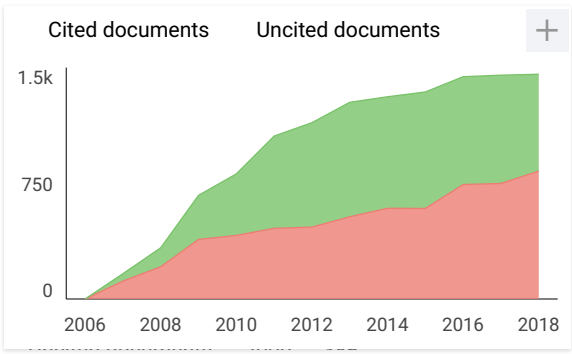
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More about this journal

Description

Aims and Scope

Abstracting/Indexing

Submit Paper

Natural Product Communications

Table of Contents

Volume 15 Issue 5, May 2020

Special Collection in honor of Professor Dr. Gerald Blunden's 80th Birthday Review

Aspects in the Total Syntheses of Higher Terpenoids Starting From Wieland–Miescher Ketone and Its Derivative: A Review

Hisahiro Hagiwara

First Published May 29, 2020

Abstract
› Preview

Review

Phytoconstituents of Genus *Micromelum* and Their Bioactivity—a Review

Tin Myo Thant, Nanik Siti Aminah, Alfinda Novi Kristanti, Rico Ramadhan, Hnin Thanda Aung, Yoshiaki Takaya

First Published May 29, 2020

Abstract
› Preview

Original Article

Quantitative Analysis of 7 Compounds in *Diospyros lotus* Leaf Extract and Its Biological Effects on Neuroprotection and Antineuroinflammation

Yu Jin Kim, **Hye-Sun Lim**, **Joo-Hwan Kim**, **MinKyun Na**, **Soo-Jin Jeong**

First Published May 28, 2020

Abstract
> Preview

Special Collection in Honor of Professor Dr. Gerald Blunden's 80th Birthday
Original Article

23-*O*-Substituted-2,3-Dehydrosilybins Selectively Suppress Androgen Receptor-Positive LNCaP Prostate Cancer Cell Proliferation

Ziran Jiang, **Arman Sekhon**, **Yogeshwari Oka**, **Guanglin Chen**, **Nagat Alrubati**, **Jasleen Kaur**, **Alexia Orozco**, **Qiang Zhang**, **Guangdi Wang**, **Qiao-Hong Chen**

First Published May 27, 2020

Abstract
> Preview

Natural Products as Sources of Cytotoxic Compounds with Potential for Development into Anti-cancer Agents
Original Article

In Vitro Antitumor Activities of Biologically Active Extracts and Isolated Phytochemicals From *Rabdosia latifolia* C. Y. Wu Et H. W. Li in Addenda

Guang-Ping Liang, **Ji-Xin Li**, **Jue Zhang**, **Ming Zhang**, **Jun Yang**, **Guang Ping Liang**, **Jie Wu**

First Published May 27, 2020

Abstract
> Preview

Short Communication

Oleanane-Type Saponins From the Aerial Parts of *Panax bipinnatifidus*

Nguyen Huu Tung, **Nguyen Thi Hoang Anh**, **Chu Van Tan**, **Pham Trung Hieu**, **Pham Quang Duong**, **Le Dang Quang**, **Vu Dinh Hoang**

First Published May 20, 2020

Abstract
> Preview

Natural Products as Sources of Cytotoxic Compounds with Potential for Development into Anti-cancer Agents
Original Article

Mechanism Analysis of Coix Seed in Gastric Cancer Treatment Based on Biological Network Modules

Fengbin Zhang, **Xiaoyan Liu**, **Bingjie Huo**, **Bing Li**, **Ruixing Zhang**

First Published May 20, 2020

Abstract
> Preview

Bioactive Natural Products from Terrestrial and Marine Resources, Especially Terpenes, but Not Limited to
Original Article

Chemical Composition, Antioxidant, and Antimicrobial Activities of the Essential Oils From *Artemisia annua* L. Growing Wild in Tajikistan

Farukh S Sharopov, **Aminjon Salimov**, **Sodik Numonov**, **Abduahad Safomuddin**, **Mahinur Bakri**, **Tojiddin Salimov**, **William N Setzer**, **Maidina Habasi**

First Published May 20, 2020

Abstract
> Preview

Bioactive Natural Products from Terrestrial and Marine Resources, Especially Terpenes, but not limited to
Original Article

Chemical Composition of Volatile Oils of Fresh and Air-Dried Buds of Cannabis *chemovars*, Their Insecticidal and Repellent Activities

Amira S. Wanas, **Mohamed M. Radwan**, **Suman Chandra**, **Hemant Lata**, **Zlatko Mehmedic**, **Abbas Ali**, **KHC Baser**, **Betul Demirci**, **Mahmoud A. ElSohly**

First Published May 19, 2020

Abstract
> Preview

Natural Products as Sources of Cytotoxic Compounds With Potential for Development Into Anti-Cancer Agents
Original Article

Pinus maritima Extract Induces Apoptosis in Human Malignant Melanoma Cells via ROS/Caspase-3 Signaling

Sunisa Thaichinda, **Salunya Tancharoen**, **Takuro Kanekura**, **Yuko Higashi**, **Pornpen Dararat**, **Kiyoshi Kikuchi**, **Thamthiwat Nararatwanchai**

First Published May 19, 2020

Abstract
> Preview

Bioactive Natural Products from Terrestrial and Marine Resources, Especially Terpenes, but not limited to
Original Article

Antimycobacterial Activity of Milemarinol, a New Squalene-Type Triterpene, and Other Isolate?

Samyra I. S. Boeno, Michel de S. Passos, Mariana Félix, Sanderson D. Calixto, Almir R. C. Júnior, Lara F. Barbosa Siqueira, Michelle F. Muzitano, Raimundo Braz-Filho, Ivo J. Curcino Vieira

First Published May 18, 2020

Abstract
› Preview

Original Article

Synthesis of 3,15-Disuccinate-12-Coumarin Substituted Andrographolide Derivatives and Their Antiplatelet Aggregation Activities In Vitro

Xue Li, Jiang-Wei Wang, Bin Huang, Zhi-Xiang Peng, Yuan-Yuan Zhang, Shi-Yun Zhao

First Published May 12, 2020

Abstract
› Preview

Nonacosan-10-ol and *n*-Alkanes in Needles of *Pinus halepensis*

Biljana Nikolić, Marina Todosijević, Iris Đorđević, Jovana Stanković, Zorica S. Mitić, Vele Tešević, Petar D. Marin

First Published May 12, 2020

Abstract
› Preview

A Survey of Antifungal Activity of Selected South African Plant Species Used for the Treatment of Skin Infections

Ndzalama Shikwambana, **Salome Mamokone Mahlo**

First Published May 12, 2020

Abstract
> Preview

Special Collection in Honor of Professor Dr. Gerald Blunden's 80th Birthday
Original Article

Chemical Profiling of *Astragalus membranaceus* Roots (Fish.) Bunge Herbal Preparation and Evaluation of Its Bioactivity

Valentina Santoro, **Valentina Parisi**, **Massimiliano D'Ambola**, **Chiara Sinisgalli**, **Magnus Monné**, **Luigi Milella**, **Rosario Russo**, **Lorella Severino**, **Alessandra Braca**, **Nunziatina De Tommasi**

First Published May 12, 2020

Abstract
> Preview

Short Communication

Piceid Nanoparticles Stabilized by Anionic Phospholipids for Transdermal Delivery

Noriyuki Uchida, **Masayoshi Yanagi**, **Hiroki Hamada**

First Published May 12, 2020

Abstract
> Preview

Original Article

Nonacosan-10-ol and *n*-Alkanes in Leaves of *Pinus pinaster*

Biljana Nikolić, **Marina Todosijević**, **Iris Đorđević**, **Jovana Stanković**, **Zorica S. Mitić**, **Vele Tešević**, **Petar D. Marin**

First Published May 12, 2020

Abstract
> Preview

Network Pharmacology Research and Preliminary Verification of Gegen Qinlian Decoction for the Treatment of Non-Alcoholic Fatty Liver Disease

Pengfei Hao, **Yiyi Xiong**, **Hezhen Wu**, **Yanfang Yang**

First Published May 11, 2020

Abstract
> Preview

Natural Products as Sources of Cytotoxic Compounds with Potential for Development into Anti-Cancer Agents
Original Article

Cytotoxic Triterpenes From *Trametes orientalis*

Kun-Min Xiao, **Jun-Ming Wang**, **Ling-Yun Zhou**, **Lei Guo**, **Da-Cong Tan**, **Qi Yan**, **Yan Hua**

First Published May 11, 2020

Abstract
> Preview

Flavonoids and Related Compounds as Natural Products
Original Article

The Role of C-8 OH on the Antioxidant Activity of Norwogonin and Isowogonin

Qiushan Zhang, **Jin Shao**, **Tong Zhao**, **Lei He**, **Huiping Ma**, **Linlin Jing**

First Published May 8, 2020

Abstract
> Preview

Terpenoids and Related Compounds – Structure, Synthesis, and Biological Activity
Preface

Preface

Motoo Tori

First Published May 7, 2020

Abstract

Original Article

Novel 1,3-Benzodioxole From Marine-Derived Actinomycete in East Vietnam Sea

Dao Phi Thi, **Huong Doan Thi Mai**, **Duc Danh Cao**, **Quyen Vu Thi**, **Mai Anh Nguyen**, **Hong Minh Le Thi**, **Dang Thach Tran**, **Van Minh Chau**, **Van Cuong Pham**

First Published May 7, 2020

Abstract
> Preview

Flavonoids and Related Compounds as Natural Products
Original Article

Anthocyanin Profile and Antioxidant Property of Anti-asthma Flowers of *Cordyline terminalis* (L.) Kunth (Agavaceae)

Christopher Adaku, **Irene Skaar**, **Robert Byamukama**, **Monica Jordheim**, **Øyvind M. Andersen**

First Published May 7, 2020

Abstract
> Preview

Original Article

Justicidin B Inhibits PDGF-BB-Induced Proliferation and ECM Accumulation in Mesangial Cells via Nrf2/HO-1 and Akt/mTOR Signaling Pathway

Zhong-zhu Ai, **Shan-shan Zhou**, **Song-tao Wu**, **Zong-chao Hong**, **Yu Zhang**, **Meng-fan Wang**, **Yan-fang Yang**, **He-zhen Wu**

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Items per page: 10 1 - 10 of 12

ACTION	STATUS	ID	TITLE	SUBMITTED	DECIS
Approval to Transfer denied on 29-May-2020	ADM: Barthwal, Shivani Reject. Refer to SAGE Path (14-May-2020) view decision letter	NPX-20-0234	Vladinol F, Neolignan Compound from The Stem Bark of Dryobalanops oblongifolia (Dipterocarpaceae) and Antiplasmodial Activity View Submission	24-Apr-2020	14-May
Forms Completion submitted (24-Apr-2020) - view	ADM: Barthwal, Shivani Immediate Accept (22-Apr-2020) view decision letter	NPX-19-0388.R8	Phytoconstituents of Genus Micromelum, and Their Bioactivity-A Review View Submission	19-Apr-2020	22-Apr
a revision has been submitted (NPX-19-0388.R8)	ADM: Barthwal, Shivani Minor Revision (17-Apr-2020) a revision has been submitted view decision letter	NPX-19-0388.R7	Phytoconstituents of Genus Micromelum, and Their Bioactivity-A Review View Submission	16-Apr-2020	17-Apr
a revision has been submitted (NPX-19-0388.R7)	ADM: Barthwal, Shivani Minor Revision (15-Apr-2020) a revision has been submitted view decision letter	NPX-19-0388.R6	Phytoconstituents of Genus Micromelum, and Their Bioactivity-A Review View Submission	14-Apr-2020	15-Apr
a revision has been submitted (NPX-19-0388.R6)	ADM: Barthwal, Shivani Minor Revision (13-Apr-2020) a revision has been submitted view decision letter	NPX-19-0388.R5	Phytoconstituent of Genus Micromelum, and Their Bioactivity-A Review View Submission	10-Apr-2020	13-Apr
a revision has been submitted (NPX-19-0388.R5)	ADM: Barthwal, Shivani Major Revision (01-Apr-2020)	NPX-19-0388.R4	Phytoconstituent of Genus Micromelum, and Their Bioactivity-A Review View Submission	30-Mar-2020	01-Apr

Author Dashboard
12 Manuscripts with Decisions
Start New Submission
5 Most Recent E-mails

	• a revision has been submitted view decision letter				
a revision has been submitted (NPX-19-0388.R4)	ADM: Barthwal, Shivani • Major Revision (29-Mar-2020) • a revision has been submitted view decision letter	NPX-19-0388.R3	Phytoconstituent of Genus Micromelum, and Their Bioactivity-A Review View Submission	24-Mar-2020	29-Mar
a revision has been submitted (NPX-19-0388.R3)	ADM: Barthwal, Shivani • Major Revision (06-Mar-2020) • a revision has been submitted view decision letter	NPX-19-0388.R2	Phytoconstituent of Genus Mocromelum, and Their Bioactivity-A Review View Submission	04-Mar-2020	06-Mar
a revision has been submitted (NPX-19-0388.R2)	ADM: Barthwal, Shivani • Major Revision (05-Feb-2020) • a revision has been submitted view decision letter	NPX-19-0388.R1	Phytoconstituent of Genus Mocromelum, and Their Bioactivity-A Review View Submission	29-Jan-2020	05-Feb
a revision has been submitted (NPX-19-0388.R1)	ADM: Barthwal, Shivani • Major Revision (10-Jan-2020) • a revision has been submitted view decision letter	NPX-19-0388	Phytoconstituents and Bioactivity of Genus Micromelum View Submission	27-Nov-2019	10-Jan

Items per page: 10 1 - 10 of 12

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