Tropical Journal of Pharmaceutical Research November 2015; 14 (11): 2139-2150
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v14i11.28

Review Article

A Review on Chemical Constituents and Biological Activities of the Genus *Beilschmiedia* (Lauraceae)

Wan Mohd Nuzul Hakimi Wan Salleh[1], Farediah Ahmad[1]*, Khong Heng Yen[2] and Razauden Mohamed Zulkifli[3]

[1]Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, Skudai, 81310 Johor Bahru, Johor, [2]School of Chemistry and Environmental Studies, Faculty of Applied Sciences, Universiti Teknologi MARA Sarawak, Kota Samarahan, 94300, Sarawak, [3]Department of Bioscience and Health Sciences, Faculty of Biosciences and Medical Engineering, Universiti Teknologi Malaysia (UTM), 81310 Skudai, Johor, Malaysia

For correspondence: **Email: farediah@kimia.fs.utm.my; **Tel:** +607-5534137; **Fax:** +607-5566162*

Received: 9 July 2015 *Revised accepted: 12 October 2015*

Abstract

The current review is aimed to deliver some updates on the ethnobotany, phytochemistry and biological activities of Beilschmiedia species in order to throw more light on their therapeutic potentials and future research priorities. Phytochemical studies on Beilschmiedia genus yielded essential oils, endiandric acid derivatives, amides/alkaloids, lignans/neoligans, flavonoids and miscellaneous compounds, while bioactivity studies revealed that the extracts and compounds displayed a broad spectrum of biological activities. Only 24 species of the genus Beilschmiedia have been studied phytochemically thus far. Therefore, there is a need to ascertain the pharmacological properties of the plant extracts and new compounds from this genus. More studies on the standardization and pharmacology of Beilschmiedia extracts need to be conducted to ascertain new pharmacological properties and their biochemical and physiological mechanisms. Furthermore, detailed preclinical toxicity, bioavailability, pharmacokinetics and pharmacodynamics of extracts of the species and their isolated compounds require additional investigation in order to verify their safety and determine their suitability as sources of some current medicines.

Keywords: *Beilschmiedia, Lauraceae, ethnobotany, phytochemistry, pharmacology*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

The genus *Beilschmiedia* is a pantropical genus of about 287 species mainly in Southeast Asia and Africa. About 81 *Beilschmiedia* species have been identified in inter-tropical Africa with 41 species in Cameroon alone [1,2]. Plants of the genus *Beilschmiedia* have been listed in the plant list (2013). 287 of the genus names are accepted and the remaining names are either synonym or unresolved names. Revisional studies of the genus have been made in several regions, such as China, Madagascar, Australia and the Neotropics. In recent years, Kostermans described many new taxa of *Beilschmiedia* from Malay Peninsular and Southern Thailand [3-9]. Kochummen also revised Lauraceae and published in Tree Flora of Malaya [10]. Van der Werff studied the genera of Lauraceae in the Flora Malesiana Region and two reports on the synopsis of genus *Beilschmiedia* in Madagascar have been published [11,12].

The ethnopharmacological history of *Beilschmiedia* indicates that some species have been used in local medicine to treat various

conditions, including uterine tumors, rheumatism, pulmonary disorders, bacterial infections, malaria and tuberculosis [13-17]. Because of their versatile therapeutic traditional uses, extensive phytochemical investigations have been carried out on *Beilschmiedia* plants which led to isolation of numerous classes of secondary metabolites such as terpenoids, endiandric acid derivatives, essential oils, fatty acids, lignans/neolignans, flavonoids, amide/alkaloids and other components. Endiandric acid derivatives are considered to be the main constituents in *Beilschmiedia* species and are responsible for many of their biological and pharmacological activities [18-22].

Both *in vivo* and *in vitro* experiments have indicated that the *Beilschmiedia* plant extracts possess a variety of pharmacological aspects with antioxidant, anti-inflammatory, cytotoxicity, antibacterial and antifungal activities [23-26]. With consideration of the importance of the therapeutic property of this genus to heal various ailments. Therefore a broader range of studies on the bioactivities need to be performed to ascertain the pharmacological properties. These gaps lead to systematic research activities on phytochemicals and pharmacology of genus *Beilschmiedia*. As extensive studies on *Beilschmiedia* species have not been conducted, there are thus significant opportunities to discover novel bioactive compounds and beneficial medicinal and pharmacological properties from various extracts of the species are warranted. The available information on various species belonging to the genus *Beilschmiedia* were collected via electronic search (using Pubmed, SciFinder, Scopus, Google Scholar, JCCC@INSTIRC and Web of Science) and a library search for articles published in peer-reviewed journals.

DISTRIBUTION, BOTANICAL DESCRIPTION AND ETHNOBOTANY

The genus *Beilschmiedia* comprises more of trees and rarely shrubs, and is usually distinguished from other genera of the Lauraceae by the following characteristics: paniculate or racemose inflorescences that are not strictly cymose at the terminal division, bisexual and trimerous flowers with six equal to subequal tepals, six to nine fertile stamens representing the outer two or three whorls, two-celled anthers, and fruits lacking cupules. This family is also recognized by the simple, alternate, stiff and aromatic elliptic to obovate leaves, and by the fruits often borne in a cup [27]. It is placed in the tribe Cryptocaryeae Nees together with other core genera such as Cryptocarya, Endiandra and Potameia based on the wood and bark anatomy and inflorescence structure [27]. Most of the species grow in tropical climates but few of them are native to the temperate regions. They are widespread in tropical Asia, Africa, Australia, New Zealand, Central America, Caribbean and South America [28]. In the Southeast Asia, the genus can be found in Myanmar, Vietnam, Cambodia, Thailand, Malaysia, Philippines, Indonesia and various islands, such as Sumatra and Java [29]. *Beilschmiedia* is categorized as a genus of forest trees, predominantly from low to high elevation. *B. glauca* is found in the upper evergreen forest and rarely found in the lowland evergreen forest, *B. maingayi* is found in the upper evergreen forest, over 1,200 m altitude, *B. membranacea* is found in the montane evergreen forest and *B. palembanica* is found in the lower evergreen forest to the upper evergreen forest. Many species of *Beilschmiedia* were reported in Bhutan and Sikkim, such as *B. gammieana* in montane forest with oaks, and broad leaves forest at 1,750 - 2,050 m altitude, *B. assamica* in subtropical forest and broad leaves forest and in temperate zone at 300-1,800 m altitude and *B. roxburghiana* in subtropical forest at 200 - 400 m altitude [30,31].

Available literature and information show that several *Beilschmiedia* species have been applied as traditional medicines in various parts of the world. This genus has an economic importance in forest products for use as timber and herbal medicine. The most prevalent usages are for treating bone related problems which include arthritis, rheumatism and renal ailments. The important ethnomedicinal properties possessed by this genus can be the basis for further research to determine the phytochemical and pharmacological aspects of the above mentioned genus. The lists of the various medicinal uses of *Beilschmiedia* species in different parts of the world are shown in Table 1.

CHEMICAL CONSTITUENTS

Systematic phytochemical investigation is important to understand the pharmacology of the species as well as the mechanisms of action and for quality control purposes. The phytochemical studies of various species of the genus have successfully afforded numerous chemical components. They were essential oils, endiandric acid derivatives, amides and alkaloids, lignans and neolignans, flavonoids and also miscellaneous compounds (cyanogenic glycosides, benzopyran, benzenoid, terpenes, benzaldehyde, and fatty acid). The major

components of the essential oil compositions from several species of *Beilschmiedia* species are tabulated in Table 2. The phytochemical studies of *Beilschmiedia* species are shown in Table 3.

Table 1: Medicinal uses of several *Beilschmiedia* species

Species	Local name	Locality	Plant parts and medicinal uses	Ref
B. gaboonensis	Kanda	Cameroon	Fruits: as appetite stimulants and spices Bark: analgesic and healing ointments	[13]
B. manii	Bubueh sapo	Cameroon	Fruits: as appetite stimulants, spices and treatment of dysentery and headache	
B. zenkeri	Not reported	Cameroon	Fruits: as appetite stimulants and spices	
B. cryptocaryoides	Not reported	Madagascar	Fruits/bark: to treat infectious diseases and malaria	[21]
B. acuta	Ndareh	Cameroon	Leaf: cancer and gastrointestinal infections	[24]
B. obscura	Not reported	Cameroon	Bark: gastrointestinal infection	[25]
B. sphaerocarpa	Not reported	Indochina	Bark :herbs to cure skin related disease such as scabies, acne and pustule	[32]
B. pahangensis	Not reported	Malaysia	Bark: as a drink after childbirth and also to assuage stomach ache, diarrhea and dysentery	[33]
B. tonkinensis	Perapoh	Malaysia	Leaf: to make medicine for easing pain, inflammation and broken bone	
B. madang	Medang merah	Indonesia	Wood: the decoction as an antimalarial preparation	[34]
B. anacardioides	Ntseum	Cameroon	Stem bark: to cure uterine tumors, rubella, female genital infections, and rheumatisms	[56]
B. lancilimba	Not reported	Cameroon	Bark: to cure skin bacterial infections	[57]
B. podagrica	Kunana	New Guinea	Leaf/bark: treatment of stomach ailments	[58]
B. tawa	Tawa	New Zealand	Bark: stomachaches, colds and decoction for wounds	[59]

Table 2: Major components of the essential oils of *Beilschmiedia* species

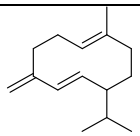
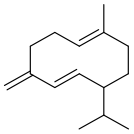
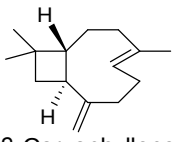
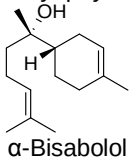
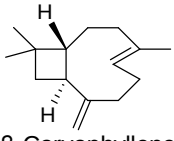
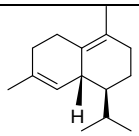
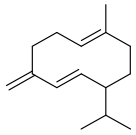
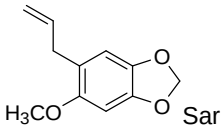
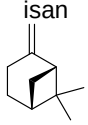
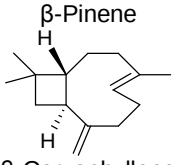
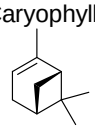
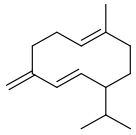
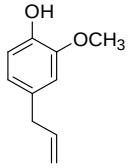
Species (Locality)	Part	Major groups and components (%)	Structures	Ref
B. alloiophylla (Costa Rica)	Leaf	Monoterpene hydrocarbons (50.5%) Germacrene D (18.9%), *cis*-β-ocimene (18.8%), α-pinene (11.8%)	 Germacrene D	[37]
B. brenesii (Costa Rica)	Leaf	Sesquiterpene hydrocarbons (66.9%) Germacrene D (19.3%), β-caryophyllene (13.4%)	 Germacrene D	
B.'chancho blanco' (Costa Rica)	Leaf	Sesquiterpene hydrocarbons (58.5%) β-Caryophyllene (16.6%), bicyclogermacrene (14.1%)	 β-Caryophyllene	
B. costaricensis (Costa Rica)	Leaf	Oxygenated sesquiterpenes (82.0%) α-Bisabolol (72.1%), *cis*-3-hexenol (5.2%), α-pinene (3.0%)	 α-Bisabolol	
B. erythrophloia (Taiwan)	Leaf	Sesquiterpene hydrocarbons (51.7%) β-Caryophyllene (22.6%), α-humulene (21.9%)	 β-Caryophyllene	[39]

Table 2: Major components of the essential oils of *Beilschmiedia* species **(continued)**

Species (Locality)	Part	Major groups and components (%)	Structures	Ref
B. madang (Malaysia)	Leaf	Sesquiterpene hydrocarbons (63.8%) δ-Cadinene (17.0%), α-cubebene (11.3%), β-caryophyllene (10.3%)	 δ-Cadinene	[40]
	Bark	Sesquiterpene hydrocarbons (65.3%) δ-Cadinene (20.5%), α-cubebene (15.6%), α-cadinol (10.6%)		
B. miersii (United States/ Chile)	Leaf	Not mention Germacrene D (24.8%), α-terpinene (10.0%), γ-curcumene (9.6%)	 Germacrene D	[36]
	Leaf	Not mention Sarisan, myristicin, elemicin, asarone	 Sarisan	[35]
B. pendula (Costa Rica)	Leaf	Sesquiterpene hydrocarbons (33.0%) β-Pinene (10.4%), β-caryophyllene (8.6%), α-pinene (7.9%)	 β-Pinene	[38]
	Branch	Sesquiterpene hydrocarbons (59.3%) β-Caryophyllene (17.3%), β-selinene (9.1%), bicyclogermacrene (8.9%)	 β-Caryophyllene	
B. tarairie (United States)	Leaf	Not mention α-Pinene (17.8%), β-pinene (9.4%), germacrene D (6.6%)	 α-Pinene	[36]
B. tilaranensis (Costa Rica)	Leaf	Sesquiterpene hydrocarbons (85.1%) Germacrene D (54.9%), β-caryophyllene (14.8%)	 Germacrene D	[37]
B. pulverulenta (Malaysia)	Leaf/ Bark	Phenylpropanoids (51.1%) Eugenol (45.3%)	 Eugenol	[41]

**All essential oils were extracted by hydrodistillation method and characterized by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS)*

Table 3: Chemical constituents isolated from *Beilschmiedia* species

Compound	Species	Plant part	Ref
Endiandric acid derivatives			
Beilcyclone A	*B. erythrophloia*	Roots	[18]
Beilschmiedic acid A	*B. anacardioides*	Stem bark	[44,46]
	Beilschmiedia sp.	Leaves	[20]
Beilschmiedic acid B	*B. anacardioides*	Stem bark	[44]
Beilschmiedic acid C	*B. anacardioides*	Stem bark	[44,46]
	Beilschmiedia sp.	Leaves	[20]
Beilschmiedic acid D	*B. anacardioides*	Stem bark	[17]
Beilschmiedic acid E	*B. anacardioides*	Stem bark	
Beilschmiedic acid F	*B. anacardioides*	Stem bark	[46]
Beilschmiedic acid G	*B. anacardioides*	Stem bark	[46]
Beilschmiedic acid H	*Beilschmiedia* sp.	Leaves	[20]

Table 3: Chemical constituents isolated from *Beilschmiedia* species **(continued)**

Compound	Species	Plant part	Ref
Beilschmiedic acid I	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid J	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid K	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid L	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid M	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid N	*Beilschmiedia* sp.	Leaves	
Beilschmiedic acid O	*Beilschmiedia* sp.	Leaves	
Beilschmiedin	*B. anacardioides*	Stem bark	[17]
Cryptobeilic acid A	*B. cryptocaryoides*	Bark	[21]
Cryptobeilic acid B	*B. cryptocaryoides*	Bark	
Cryptobeilic acid C	*B. cryptocaryoides*	Bark	
Cryptobeilic acid D	*B. cryptocaryoides*	Bark	
Endiandric acid A	*B. obtusifolia*	Leaves	[14]
Endiandric acid B	*B. tooram*	Leaves	
Endiandric acid C	*B. tooram*	Leaves	
Endiandric acid H	*B. fulva*	Stem	[42]
Endiandric acid I	*B. erythrophloia*	Roots	[43]
Endiandric acid J	*B. erythrophloia*	Roots	
Endiandric acid K	*B. tsangii*	Roots	[19]
Endiandric acid L	*B. tsangii*	Roots	
Endiandric acid M	*B. tsangii*	Roots	[45]
Endiandramide A	*B. tsangii*	Roots	[19]
Endiandramide B	*B. tsangii*	Roots	
Erythrophloin A	*B. erythrophloia*	Roots	[18]
Erythrophloin B	*B. erythrophloia*	Roots	
Erythrophloin C	*B. erythrophloia*	Roots	
Erythrophloin D	*B. erythrophloia*	Roots	
Erythrophloin E	*B. erythrophloia*	Roots	
Erythrophloin F	*B. erythrophloia*	Roots	
Ferrugineic acid A	*B. ferruginea*	Leaves/flower	[22]
Ferrugineic acid B	*B. ferruginea*	Leaves/flower	
Ferrugineic acid C	*B. ferruginea*	Leaves/flower	
Ferrugineic acid D	*B. ferruginea*	Leaves/flower	
Ferrugineic acid E	*B. ferruginea*	Leaves/flower	
Ferrugineic acid F	*B. ferruginea*	Leaves/flower	
Ferrugineic acid G	*B. ferruginea*	Leaves/flower	
Ferrugineic acid H	*B. ferruginea*	Leaves/flower	
Ferrugineic acid I	*B. ferruginea*	Leaves/flower	
Ferrugineic acid J	*B. ferruginea*	Leaves/flower	
Ferrugineic acid K	*B. ferruginea*	Leaves/flower	
Tsangibeilin A	*B. tsangii*	Roots	[19]
Tsangibeilin B	*B. tsangii*	Roots	
	B. cryptocaryoides	Bark	[21]
Tsangibeilin C	*B. tsangii*	Roots	[45]
Tsangibeilin D	*B. tsangii*	Roots	
Tricyclotsangibeilin	*B. tsangii*	Roots	
Armepavine	*B. brevipes*	Leaves	[48]
Asimilobine	*B. alloiophylla*	Bark	[49]
(+)-Boldine	*B. kunstleri*	Bark	[47]
	B. alloiophylla	Bark	[49]
(+)-Cassythicine	*B. kunstleri*	Leaves/bark	[47, 51]
(+)-Dehatrine	*B. madang*	Wood	[34]
O,*O*-Dimethylannocherin A	*B. brevipes*	Leaves	[48]
O,*O*-Dimethylcoclaurine	*B. brevipes*	Leaves	
(+)-*N*-Dimethylphyllocaryptine	*B. kunstleri*	Bark	[47, 49]
(6,7-Dimethoxyisoquinolinyl)-(4′-methoxyphenyl)-methanone	*B. brevipes*	Leaves	[48]
(6,7-Dimethoxy-4-methylisoquinolinyl)-(4′-methoxyphenyl)-methanone	*B. brevipes*	Leaves	
Dioxamine	*B. erythrophloia*	Roots	[18]
Glaucine	*B. podagrica*	Leaves	[60]
2-Hydroxy-9-methoxyaporphine	*B. alloiophylla*	Bark	[49]
(+)-2-Hydroxy-1,9,10-trimethoxyaporphine	*B. podagrica*	Leaves	[58]
(+)-2-Hydroxy-l,9,10-trimethoxynoraporphine	*B. podagrica*	Leaves	

Table 3: Chemical constituents isolated from *Beilschmiedia* species **(continued)**

Compound	Species	Plant part	Ref
(+)-2,11-Dihydroxy-1,10-dimethoxyaporphine	*B. podagrica*	Leaves	
Isoboldine	*B. alloiophylla*	Bark	[49]
	B. elliptica	Bark	[62]
	B. podagrica	Bark	[58]
	B. tawa	Berries	[61]
(-)-Isocaryachine	*B. kunstleri*	Bark	[47]
Isocorydine	*B. podagrica*	Leaves	[58]
(-)-Kunstleramide	*B. kunstleri*	Bark	[47]
Laurelliptine	*B. elliptica*	Bark	[60]
	B. podagrica	Bark	[58]
(+)-Laurotetanine	*B. kunstleri*	Bark	[47]
	B. alloiophylla	Bark	[49]
Liriodenine	*B. alloiophylla*	Bark	
(*S*)-3-Methoxynordomesticine	*B. alloiophylla*	Bark	
(+)-*N*-Methylisococlaurine	*B. kunstleri*	Leaves	[51]
O-Methylvelucryptine	*B. brevipes*	Leaves	[48]
(+)-Nornuciferine	*B. kunstleri*	Bark	[47]
Noratherosperminine	*B. kunstleri*	Bark	
Norarmepavine	*B. brevipes*	Leaves	[48]
(+)-Norboldine	*B. kunstleri*	Leaves	[51]
Obscurine	*B. obscura*	Stem bark	[62]
Oreobeiline	*B. alloiophylla*	Bark	[49]
	B. oreophila	Bark/wood	[63]
(-)-Pallidine	*B. kunstleri*	Leaves	[51]
Pipyahyine	*B. zenkeri*	Stem bark	[16]
Secoboldine	*B. alloiophylla*	Bark	[49]
6-Epioreobeiline	*B. alloiophylla*	Bark	
	B. oreophila	Bark/wood	[63]
Zanthomamide	*B. zenkeri*	Stem bark	[16]
Beilschmin A	*B. tsangii*	Stem	[50]
Beilschmin B	*B. tsangii*	Stem	
Beilschmin C	*B. tsangii*	Stem	
Beilschmin D	*B. tsangii*	Leaves	[15]
Beilschminol A	*B. tsangii*	Roots	[19]
Beilschminol B	*B. tsangii*	Roots	[45]
4α,5α-Epoxybeilschmin A	*B. tsangii*	Leaves	[15]
4α,5α-Epoxybeilschmin B	*B. tsangii*	Leaves	
Tsangin A	*B. tsangii*	Stem	[50]
Tsangin B	*B. tsangii*	Stem	
Tsangin C	*B. tsangii*	Roots	[19]
(+)-Kunstlerone	*B. kunstleri*	Leaves	[47, 51]
Magnolol	*B. volckii*	Leaves	[14]
rel-(7*R*,8*R*,7′*R*,8′*R*)-3′,4′-methylenedioxy-3,4,5,5′-tetramethoxy-7,7′-epoxylignan	*B. tsangii*	Roots	[19]
rel-(7*R*,8*R*,7′*R*,8′*R*)-3,4,3′,4′-dimethylenedioxy-5,5′-dimethoxy-7,7′-epoxylignan	*B. tsangii*	Roots	
rel-(7*S*,8*S*,7′*R*,8′*R*)-3,3′,4,4′,5,5′-hexamethoxylignan	*B. tsangii*	Roots	
Beilschmieflavonoid A	*B. tsangii*	Stem	[50]
Beilschmieflavonoid B	*B. zenkeri*	Stem bark	[16]
2′,6′-Dihydroxy-4′-isopentenyloxy-3,4(3″,3″-dimethylpyrano)chalcone	*B. zenkeri*	Stem bark	
5-Hydroxy-7,8-dimethoxyflavanone	*B. tovarensis*	Wood	[52]
Kaempferol 3-rhamnoside	*B. zenkeri*	Stem bark	[16]
Luteolin O-glucoside	*B. miersii*	Leaves	[53]
Quercetin 5-methyl ether	*B. miersii*	Leaves	
Quercetin 3-rhamnoside	*B. miersii*	Leaves	
Quercetin 3-glucuronide	*B. miersii*	Leaves	
4, 2′, 6′-Trihydroxy-3′,4′-methylenedioxo-3-isopentenylchalcone	*B. tovarensis*	Wood	[52]
(2*S*,4*R*)-5,6,7-Trimethoxyflavan-4-ol	*B. zenkeri*	Stem bark	[16]
(2*S*,4*R*)-4,5,6,7-Tetramethoxyflavan	*B. zenkeri*	Stem bark	
Oligandrol	*B. oligandra*	Bark	[14]
	B. erythrophloia	Roots	[43]

Table 3: Chemical constituents isolated from *Beilschmiedia* species **(continued)**

Compound	Species	Plant part	Ref
Betulinic acid	*B. zenkeri*	Stem bark	[16]
Sitosterol 3-*O*-β-D-glucopyranoside	*B. zenkeri*	Stem bark	
Bisabolene	*B. anacardioides*	Stem bark	[17]
Tricosanoic acid	*B. anacardioides*	Stem bark	
Suberosol B	*B. erythrophloia*	Roots	[18]
24(*S*)-3β-Hydroxystigmast-5-en-7-one	*B. erythrophloia*	Roots	
Lupeol	*B. erythrophloia*	Roots	
3-*O*-Acetyl-*epi*-betulinic acid	*B. erythrophloia*	Roots	
Methyl oleate	*B. erythrophloia*	Roots	
Methyl palmitate	*B. erythrophloia*	Roots	
Methyl linoleate	*B. erythrophloia*	Roots	
4-Hydroxy-3-methoxybenzaldehyde	*B. erythrophloia*	Roots	
	B. tsangii	Roots	[19]
	B. tsangii	Stem	[50]
α-Tocopheryl quinone	*B. erythrophloia*	Roots	
	B. tsangii	Stem	[50]
6β-Hydroxystigmast-4-en-3-one	*B. erythrophloia*	Roots	[18]
	B. tsangii	Roots	[19]
	B. tsangii	Stem	[50]
3β-Hydroxystigmast-5-en-7-one	*B. tsangii*	Stem	[50]
Caryophyllene oxide	*B. erythrophloia*	Roots	[43]
Dehydrooligandrol methyl ether	*B. erythrophloia*	Roots	
Farnesylol	*B. erythrophloia*	Roots	
Oligandrol methyl ether	*B. erythrophloia*	Roots	
β-Sitostenone	*B. erythrophloia*	Roots	
	B. tsangii	Stem	[50]
3,4,5-Trimethoxybenzaldehyde	*B. tsangii*	Roots	[45]
Eudesm-4(15)-ene-1β,6α-diol	*B. tsangii*	Roots	
(4*R*,5*R*)-4,5-Dihydroxycaryophyll-8(13)-ene	*B. tsangii*	Roots	
Octahydro-4-hydroxy-3α-methyl-7-methylene-α-(1-methylethyl)-1*H*-indene-1-methanol	*B. tsangii*	Roots	
Ursolic acid	*B. tsangii*	Roots	
(+)-5-Hydroxybarbatenal	*B. tsangii*	Roots	
Sitosterol 3-β-D-glucopyranoside	*B. anacardioides*	Stem bark	[46]
β-Amyrone	*B. alloiophylla*	Bark	[49]
4-Hydroxybenzaldehyde	*B. tsangii*	Stem	[50]
α-Tocospiro B	*B. tsangii*	Stem	
Ergosta-4,6,8(14),22-tetraen-3-one	*B. tsangii*	Stem	
6α-Hydroxystigmast-4-en-3-one	*B. tsangii*	Stem	
Stigmast-4-en-3,6-dione	*B. tsangii*	Stem	
β-Sitosterol	*B. zenkeri*	Stem bark	[16]
	B. tsangii	Roots	[19]
	B. anacardioides	Stem bark	[44]
	B. tsangii	Stem	[50]
Taxiphyllin	*B. collina*	Leaves	[54]

BIOLOGICAL ACTIVITIES

The literature study reveals the need for a thorough investigation of the pharmacological characteristics of the extracts and isolated compounds from *Beilschmiedia* genus. The biological activities including anti-inflammatory, antioxidant, acetylcholinesterase, anti-α-glucosidase, anti-leishmanial, antifungal, antimalarial, anticancer, antitubercular, antiplasmodial, antibacterial and cytotoxicity have been reported in some works. Indeed, the genus *Beilschmiedia* has been exploited traditionally thus revealed the medicinal variation if possesses. In addition, several species that have been used traditionally to treat some types of ailments have not been investigated for their biological activities at all. Thus, this is an opportunity to find new pharmacological properties from this genus, not to mention promising sources for drugs, such as for cancer, hernia, skin and digestive diseases. Furthermore, the toxicity of the genus members has not been studied from this genus. The information of the qualification of the extracts are very important to be applied as drugs.

Anti-inflammatory activity

A methanol extract of the roots of *B. tsangii* has shown potent inhibition of NO production, and negative cytotoxicity against RAW 264.7 cells

[19]. Huang *et al* [19] also studied the anti-inflammatory activity of several compounds isolated from *B. tsangii*. They found that endiandramide A-B exhibited significant iNOS inhibitory activity against RAW 264.7 cells at the concentration range of 0.1 - 100 µM. A year later, they reported moderate iNOS inhibitory activity for endiandric acid M. They also suggested that endiandramide B and endiandric acids K-M having the same skeleton but with different substituents at C-8, exhibited ascending degrees of iNOS inhibitory activity in the order: endiandramide B (16.40 µM) > endiandric acid M (31.70 µM) > endiandric acid L (39.56 µM) > endiandric acid K (58.21 µM). This suggests that the iNOS potency of the substituent at C-8 could be arranged as N-isobutylamido group > an α,β-unsaturated carboxylic acid group > a carboxylic acid group. Endiandric acid M, having four fewer methylenes than endiandric acid L, showed stronger potency than endiandric acid L. This also suggests that fewer methylenes in the alkyl side of endiandric acid analogues result in greater potency of iNOS inhibitory activity [45]. In addition, the mixture extracts of the leaves and of *B. erythrophloia* showed weak inhibitory activity of NO production at dose of 25 µg/mL [23].

Antibacterial activity

B. cinnamomea root extract demonstrated moderate activity against *Enterobacter aerogenes* EA294 with minimum inhibitory concentration (MIC) value of 64 µg/mL [55]. Three years later, Fankam *et al* [25] reported on methanol fruits extract of *B. obscura* which showed strong activity against *Escherichia coli* ATCC8739 with MIC value of 16 µg/mL. Besides, another study reported on *B. tovarensis* wood extract displayed significant results against *Staphylococcus aureus* and *Enterococcus faecalis* [52]. Anti-bacterial activity on methoxylated flavonoid derivatives from *B. zenkeri*, showed that beilschmieflavonoid B displayed the activity against *Streptococcus minor* with MIC value of 197.5 µM. Pipyahyine that was also isolated from this species, showed moderate activity against *Bacillus subtilis* and *Pseudomonas agarici* with MIC of 163 and 81.5 µM, respectively [16].

Talontsi *et al* [21] and a co-worker identified cryptobeilic acids A-D, tested for anti-bacterial activity and showed that cryptobeilic acid A gave moderate activity against *Escherichia coli* (MIC value of 10 µM), while cryptobeilic acid B was active against *Pseudonamas stutzeri* with a MIC value of 10 µM. In another study, Chouna *et al* [44] reported that beilschmiedic acid C demonstrated the best activity against *Bacillus subtilis* and *Micrococcus luteus* with MIC of 89.5, 5.58 and 11.1 µM, respectively. Antibacterial activity on endiandric acid derivatives was further studied by Williams *et al* [20]. It was observed that beilschmiedic acid A, K and L gave moderate activity against clinical isolate of methicillin-resistant *Staphylococcus aureus* with MIC values of 10 - 11 µM.

Cytotoxicity activity

The *in vitro* cytotoxicity of the methanol extracts of *B. erythrophloia* showed weak activity against HUVEC (human umbilical vein endothelial cells), MCF-7 (breast cancer cell) line and HL-60 (human promyelocytic leukemia cell) cell lines, showed weak activity with MIC values reaching more than 100 µg/mL at the range of concentration 25 - 500 µg/mL [23]. In another study, the *B. acuta* fruits, leaves and bark extracts showed the inhibition of CCRF-CEM leukemia cell growth of 65.17, 26.35 and 21.33 %, respectively, as measured by the resazurin reduction assay. In addition, the leaves extract also displayed significant activity towards cell lines HCT116p53 (colon cancer cell), MDA-MB-231 (human breast carcinoma cell) and U87MG (human glioblastoma cell) with IC_{50} of 4.79, 6.45, and 7.46 µg/mL, respectively. The bark extract also showed activity against the cell line MDA-MB-231 with an IC_{50} value of 6.66 µg/mL [24].

The *in vitro* cytotoxicity properties of the leaf oil of *B. erythrophloia* were evaluated against OEC-M1 (human oral squamous cancer cell), J5 (human hepatocellular carcinoma cell), A549 (human lung adenocarcinoma cell), HT-29 (human colon cancer cell), UACC-62 (human melanoma cell) and K562 (human leukemic cell) and shows IC_{50} values of 32.6, 48.6, 38.7, 18.9, 5.8, and 6.8 µg/mL, respectively [39]. Williams *et al* [20] screened the isolated endiandric acids for their *in vitro* cytotoxicity activity against NCI-H460 (large cell lung carcinoma), PC-3 (prostate adenocarcinoma) and M14 (amelanotic melanoma cell) lines using a MTT-based assay. They managed to find moderate activity of beilschmiedic acid L, I and K against the NCI-H460 cell lines with IC_{50} values of 4.4, 5.5 and 5.9 µM, respectively. (-)-Kunstleramide was investigated on MTT assays against A375 (human melanoma cell), HT-29 (human colon adenocarcinoma cell), WRL-68 (normal hepatic cell), A549 and PC-3 cells. The results showed moderate activity among all the tested cell lines with EC_{50} values in the range of 44.74 - 73.87 µg/mL [47]. Chen *et al* [50] studied the *in vitro* cytotoxicity of several compounds isolated from *B. tsangii*. They found that tsangin A-B, α-tocospiro B and beilschmin A displayed from

medium to strong activity against the P-388 (murine leukemia cell) line. In addition, α-tocospiro B, exhibited the most cytotoxic against the HT-29 cell line. In addition, six alkaloids isolated from *B. brevipes* were tested for *in vitro* cytotoxic activity against P-388 cell lines, O, O-dimethylcoclaurine exhibited significant cytotoxicity with an IC_{50} of 6.5 µg/mL [48].

Anti-plasmodial activity

According to Lenta *et al* [16] among the methoxylated flavonoid tested for in vitro anti-plasmodial activity, 5-hydroxy-7,8-dimethoxyflavanone exhibited the most significant activity against *Plasmodium falciparum* chloroquine-resistant strain W2 giving an IC_{50} value of 9.3 µM. The other compounds which showed remarkable activity were pipyahyine and betulinic acid which gave IC_{50} values of 3.7 and 5.2 µM, respectively. Talontsi *et al* [21] studied the anti-plasmodial activity of the isolated endiandric acid derivatives from *B. cryptocaryoides*. Cryptobeilic acid B exhibited anti-plasmodial activity against the erythrocytic stages of chloroquine-resistant *Plasmodium falciparum* strain NF54, followed by tsangibeilin B and cryptobeilic acid D at a concentration of 10 µg/mL.

Anti-tubercular activity

Chen *et al* [15] investigated the *in vitro* anti-tubercular effects of the isolates from the leaves of *B. tsangii* against *Mycobacterium tuberculosis* 90 - 221387. They reported that among the furanoid lignans, beilschmin A-B exhibited potent activity with IC_{50} values of 2.5 and 7.5 µM, respectively. Both compounds also exhibited corresponding epoxy-analogues, 4α,5α-epoxybeilschmin A-B and this revealed that epoxidation of the C-4,5 bond would result in reduced anti-tubercular activity. In another study of anti-tubercular activity, Yang *et al* [18] verified that erythrophloin C showed significant activity against *Mycobacterium tuberculosis* H37Rv (MIC of 50 µg/mL), comparable to ethambutol (MIC of 6.25 µg/mL).

Anti-cancer activity

The anti-apoptotic proteins Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1, members of the Bcl-2 family, have become attractive molecular targets for cancer treatment. The discovery of dual inhibitors acting on Bcl-xL and Mcl-1 could play a significant role in cancer treatment. Apart from that, Apel *et al* [22] had investigated the anti-cancer activity of isolated endiandric acid from *B. ferruginea*, ferrugineic acid A-K against anti-apoptotic proteins Bcl-xL and Mcl-1 by using a fluorescence polarization assay. Ferrugineic acid B-C and ferrugineic acid J were proved to have significantly exhibited binding affinity for both anti-apoptotic proteins, Bcl-xL.

Meanwhile, ferrugineic acid D showed only a strong inhibiting activity for anti-apoptotic protein, Mcl-1. Considering the weak binding affinity for Mcl-1 of other tested compounds, it could be postulated that the length of the saturated carbon side chain (preferentially five or seven CH_2 groups) associated with a terminal 4-hydroxyphenyl ring, play a crucial role for Bcl-xL and Mcl-1 binding affinities.

Antioxidant, antifungal, antimalarial, anti-α-glucosidase, acetyl-cholinesterase, and anti-leishmanial activities

B. erythrophloia extracts showed moderate DPPH radical scavenging assay with an EC_{50} value of 13.51 µg/mL, comparable to ascorbic acid and quercetin that had EC_{50} values of 1.5 and 2.3 µg/mL, respectively [23]. Mollataghi *et al* [47,49] have investigated the antioxidant activity by DPPH assay on a new neolignan, (+)-kunstlerone and a new dienamide, (-) kunstleramide. They found that (+)-kunstlerone showed strong antioxidant activity with SC_{50} of 20.0 µg/mL, while (-)-kunstleramide exhibited very poor dose-dependent inhibition with SC_{50} of 179.5 ± 4.4 µg/mL, at the concentration of 200 - 25 µg/mL. The bark extract of *B. cinnamomea* exhibited moderate *in vivo* anti-fungal activity with MIC and MFC values in the range of 3.12-6.25 mg/mL, towards six fungal; *Candida albicans, Cryptococcus neoformans, Candida tropicali, Candida lusitaniae, Candida guilliermondii* and *Candida glabrata* [26].

Mollataghi *et al* [49] have reported the anti-fungal activity of the new alkaloid, 2-hydroxy-9-methoxyaporphine isolated from *B. alloiophylla*. This compound demonstrated good activity against *Candida albicans* with MIC value of 8.0 µg/mL. More than a decade ago, Kitagawa *et al* [34] successfully isolated a bisbenzylisoquinoline alkaloid, (+)-dehatrine from the Indonesian medicinal plant, *B. madang*. The compound was found to exhibit a potent inhibitory activity against the proliferation of the malarial pathogen, *Plasmodium falciparum* K1 strain (IC_{50} of 0.17 µM), with almost the same activity as quinine (IC_{50} of 0.27 µM). Mollataghi *et al* [49] studied the *in vitro* α-glucosidase activity of the isolated compounds from *B. alloiophylla*. Three compounds that were found to have moderate activity, were characterized as oreobeiline, 6-epioreobeiline and (S)-3-methoxynordomesticine.

In addition, for cholinesterase and leishmanial activities, the results suggested that 2-hydroxy-9-methoxyaporphine, laurotetanine and liriodenine displayed significant acetylcholinesterase (AChE) activity. Meanwhile, the authors deemed that they also possessed significant activity in leishmanial activity.

CONCLUSION

This compilation includes the traditional uses, phytochemical and pharmacological aspects of the genus *Beilschmiedia*, and especially provides some analysis of the literature published. Some members of the genus are reported to possess medicinal properties and are used to treat various ailments. Endiandric acid derivatives are major constituents of this genus, and are important chemotaxonomic markers used to identify *Beilschmiedia* plant species from a phytochemical point of view.

ACKNOWLEDGEMENT

The authors would like to thank the Ministry of Science, Technology and Innovation, Malaysia (MOSTI), for the financial support under vote Q.J130000.2526.03H93 (GUP) and the Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, for research facilities.

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