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Review

Phytochemistry and pharmacology of the genus *Macaranga*: A review

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The genus *Macaranga* Thou. (Euphorbiaceae) comprises of about 300 species that are native mainly to the tropics of Africa, Asia, Australia and the Pacific regions. Plants of this genus have a long history of use in traditional medicine to treat cuts, swellings, boils, bruises and sores. Phytochemical work on this genus has reported over 190 secondary metabolites being isolated mainly from the leave extracts of different species of this genus. The isolated compounds included stilbenes, flavonoids, coumarins, terpenoids, tannins and other types of compounds. The crude extracts and isolated compounds showed a wide spectrum of pharmacological activities including anti-cancer, anti-inflammatory, anti-oxidant, anti-microbial and anti-plasmodial activities. The aim of this review is to coherently document the valuable but scattered reports on the phytochemistry and pharmacology of medicinal plants of the genus *Macaranga* collected from different parts of the global.

Key words: *Macaranga* species, Euphorbiaceae, phytochemistry, pharmacology.

INTRODUCTION

The genus *Macaranga* Thou. belongs to the family Euphorbiaceae. Plants are shrubs or trees that grow up to 15 m tall. Members of this genus are known for their mutual associations with ants (Fiala et al., 1990). The trees of this genus benefit because the ants attack or feed on herbivorous insects. In folk medicine, traditional healers use fresh or dried leaves of some *Macaranga* species to treat swellings, cuts, sores, boils and bruises (Nick et al., 1995). A phytochemical review of literatures indicates the genus *Macaranga* to be a rich source of the isoprenylated, geranylated and farnesylated flavonoids (Schutz et al., 1995; Jang et al., 2002; Phormmart et al., 2005; Kawakami et al., 2008; Thanh et al., 2012) and stilbenes (Beutler et al., 1998; Yoder et al., 2007; Thanh et al., 2012). Furthermore, more classes of secondary metabolites like terpenes (Salah et al., 2003; Jang et al., 2004; Phormmart et al., 2005; Kawakami et al., 2008), tannins (Lin et al., 1990; Gunawan-Puteri and Kawabata, 2010; Ngoumfo et al., 2008), coumarins (Sutthivaiyakit et al., 2002; Darmawan et al., 2012) and other types of compounds (Ramaiah et al., 1979; Ngoumfo et al., 2008; Matsunami et al., 2009; Zakaria et al., 2010) are known to be isolated from different species of the genus *Macaranga.* Flavonoids and stilbenes are regarded as the major constituents and are most likely responsible for most of the activities found in the plants of this genus. An increasing number of phytochemical studies are being carried out on plants belonging to the genus *Macaranga* due to their various traditional uses. Thus, the isolated natural products from this genus have been reported to

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display interesting biological activities including antitumor (Kaaden et al., 2001; Yoder et al., 2007; Zakaria et al., 2012), antioxidant (Sutthivaiyakit et al., 2002; Phormmart et al., 2005; Matsunami et al., 2009), antimicrobial (Salah et al., 2003; Lim et al., 2009) and anti-inflammatory (Jang, et al., 2002).

This is a resourceful area of research as many species of *Macaranga* are used in traditional medicine as well as exhibits various pharmacological properties while their chemistry indicates varied chemical structures. Hence, it is necessary that a systematic and critical assessment of the future directions of research in this field and its application be undertaken. The present work evaluates the scientific evidence for the therapeutic claims for *Macaranga* in traditional medical use and summarizes its bioactive chemical constituents. It also highlights the scientific basis for future research on plants in this genus, including their potential for development as herbal drugs.

Botanical classification

Here underneath is the taxonomic hierarchy of the genus *Macaranga*:
Kingdom: Plantae
Division: Magnoliophyta
Class: Maginoliospida
Order: Malpighiales
Family: Euphorbiaceae
Subfamily: Acalyphoides
Tribe: Acalypheae
Subtribe: Macaranginae
Genus: *Macaranga*

Distribution of the genus

Macaranga is the largest genera in the Euphorbiaceae family. It is known to consist of about 300 species native mainly to the tropics of Africa, South-East Asia, Australia and the South Pacific region (Davies, 1998). The genus is most diverse in South-East Asia and New Guinea (200 species) but also occurs in Africa and Madagascar (37 species), continental Asia (30 species), the Pacific Islands (24 species) and Australia (7 species) (Siregar and Sambas, 2000). In East Africa (Tanzania Kenya and Uganda), there are 7 species growing mainly in forest margins (Bampss et al., 1978) while in South Africa there is only one species (Pujol, 1990).

Phytochemistry

Very little phytochemical work has been done on the genus *Macaranga*. An overview of the literature search indicated that only twenty six (26) *Macaranga* species have been investigated phytochemically as compared to about 300 plant species known from this genus. The species for which their chemical constituents have been investigated includes *Macaranga alnifolia, Macaranga barteri*, *Macaranga bicolour, Macaranga conifer*, *Macaranga denticulata, Macaranga gigantea, Macaranga gigantifolia, Macaranga hemsleyana, Macaranga indica, Macaranga kurzii, Macaranga lowii, Macaranga mappa*, *Macaranga monandra, Macaranga peltata*, *Macaranga pleiostemona, Macaranga pruinosa, Macaranga recurvata, Macaranga rhizinoides, Macaranga sampsonii, Macaranga schweinfurthii, Macaranga sinensis, Macaranga tanarius, Macaranga trichocarpa, Macaranga triloba* and *Macaranga vedeliana.*

In summary, the chemical constituents obtained provides an understanding of the general biological and chemical information like pharmacological activity of the species, mechanisms of action, quality control principles as well as for further exploitation of the plant resources in this genus. So far, 190 secondary metabolites have been isolated and identified from the *Macaranga* plants. The isolated compounds include flavonoids (**1** to **84**), stilbenes (**85** to **100**), tannins (**101** to **144**), terpenes (**145** to **156**), coumarins (**157** to **158**), steroids (**159** to **161**) and other types of compounds (**162** to **190**).

Interestingly, about 90% of the isolated compounds have been reported from the leaves while 10% is from the other parts. This calls for further and extensive research work to be done from other parts like stem and root barks, fruits, seeds and flowers. Further observation of *Macaranga* plants in their natural environment has revealed that they produce threadlike wax crystals on their stems. Chemical analysis has indicated that terpenoids make up a majority of the wax bloom content that helps maintain this symbiotic relationship between plant and insect (Markstaedter, et al., 2000). The names of these constituents and the plant parts from which they are derived are listed in Table 1.

PHARMACOLOGICAL STUDIES

Studies of the pharmacological activities of the genus *Macaranga* indicate the potential of extracts and pure compounds to display specific medical effects. Previous investigation on the chemistry and pharmacology of this genus showed that its crude extracts and compounds displayed interesting bioactivity profiles, possessing various bioactivities including anticancer (Yoder et al., 2007; Zakaria et al., 2012), antioxidant (Phormmart et al., 2005; Matsunami et al., 2009), antmicrobial (Schutz et al., 1995; Lim et al., 2009), anti-inflammatory (Jang et al., 2002; Ngoumfo et al., 2008) and other different types of biological activities (Thanh et al., 2012; Zakaria et al., 2012).

An overview of the known pharmacological evaluations carried out on different species of *Macaranga* is described in details.

Table 1. Compounds isolated from the genus *Macaranga*.

S/N	Class	Name	Plant species	Part	Country of origin	References
1		Macaflavone I (1)	*M. indica*	Leaves	India	Sultana and Ilyas (1986)
2		Macaflavone II (2)	*M. indica*	Leaves	India	Sultana and Ilyas (1986)
3		Macarangin (3)	*M. vedeliana*	Leaves	New Caledonia	Hnawia et al. (1990)
4		Macarangaflavanone A (4)	*M. pleiostemona*	Leaves	Papua New Guinea	Schutz et al. (1995)
5		Macarangaflavanone B (5)	*M. pleiostemona*	Leaves	Papua New Guinea	Schutz et al. (1995)
6		Euchrestaflavanone A (6)	*M. pleiostemona*	Leaves	Papua New Guinea	Schutz et al. (1995)
4		Bonannione A (7)	*M. pleiostemona*	Leaves	Papua New Guinea	Schutz et al. (1995)
5		Tanariflavanone A (8)	*M. tanarius*	Leaves	Taiwan	Tseng et al. (2001)
6		Tanariflavanone B (9)	*M. tanarius*	Leaves	Taiwan	Tseng et al. (2001)
7		(-)-Nymphaeol C (10)	*M. tanarius*	Leaves	Taiwan	Tseng et al. (2001)
8		5-Hydroxy-4′-methoxy-2′′,2′′-dimethylpyrano-(7,8:6′′,5′′)flavanone (11)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
9		5,4′-Dihydroxy-[2′′-(1-hydroxy-1-methylethyl)dihydrofurano]-(7,8:5′′,4′′)flavanone (12)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
10		5,7-Dihydroxy-4′-methoxy-8-(3-methylbut-2-enyl)flavanone (13)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
11		Lonchocarpol A (14)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
12		Sophoraflavanone B (15)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
13		5,7-Dihydroxy-4′-methoxy-8-(2-hydroxy-3-methylbut-3-enyl)flavanone (16)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
14		Tomentosanol D (17)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
15		Lupinifolinol (18)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
16		Isolicoflavonol (19)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
17	Flavonoids	Macarangin (3)	*M. denticulata*	leaves	Thailand	Sutthivaiyakit et al. (2002)
18		3-*O*-methyl-macarangin (20)	*M. denticulata*	leaves	Thailand	Sutthivaiyakit et al. (2002)
19		Denticulaflavonol (21)	*M. denticulata*	leaves	Thailand	Sutthivaiyakit et al. (2002)
20		Sophoraflavanone B (15)	*M. denticulata*	leaves	Thailand	Sutthivaiyakit et al. (2002)
21		3,7,3'4'-tetramethylquercetin (22)	*M. triloba*	Leaves	Indonesia	Jang et al. (2004)
22		3,7,3'-trimethylquercetin (23)	*M. triloba*	Leaves	Indonesia	Jang et al. (2004)
23		3,7-dimethylquercetin (24)	*M. triloba*	Leaves	Indonesia	Jang et al. (2004)
24		Tanariflavanone C (25)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
25		Tanariflavanone D (26)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
26		Nymphaeol A (27)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
27		Nymphaeol B (28)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
28		Nymphaeol C (10)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
29		Tanariflavanone B (9)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
30		2'-hydroxy-macarangaflavanone A (29)	*M. triloba*	Leaves	Vietnam	Dinh et al. (2006)
31		4',7-hydroxy-8-methylflavan (30)	*M. triloba*	Leaves	Vietnam	Dinh et al. (2006)
32		Alnifoliol (31)	*M. alnifolia*	Fruit	Madagascar	Yoder et al. (2007)
33		Bonnaniol A (32)	*M. alnifolia*	Fruit	Madagascar	Yoder et al. (2007)
34		Diplacol (33)	*M. alnifolia*	Fruit	Madagascar	Yoder et al. (2007)
35		Bonnanione A (34)	*M. alnifolia*	Fruit	Madagascar	Yoder et al. (2007)
36		Nymphaeol A (27)	*M. alnifolia*	Fruit	Madagascar	Yoder et al. (2007)
37		Macaflavanone A (35)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)

Table 1. Contd.

38	Macaflavanone B (36)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
39	Macaflavanone C (37)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
40	Macaflavanone D (38)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
41	Macaflavanone E (39)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
42	Macaflavanone F (40)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
43	Macaflavanone G (41)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
44	Tanariflavanone B (9)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
45	Nymphaeol C (10)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
46	Macaranone A (42)	*M. sampsonii*	Leaves	China	Li et al. (2009)
47	Macaranone B (43)	*M. sampsonii*	Leaves	China	Li et al. (2009)
48	Macaranone C (44)	*M. sampsonii*	Leaves	China	Li et al. (2009)
49	Macaranone D (45)	*M. sampsonii*	Leaves	China	Li et al. (2009)
50	Macagigantin (46)	*M. gigantea*	Leaves	Indonesia	Tanjung et al. (2009)
51	Glyasperin A (47)	*M. gigantea*	Leaves	Indonesia	Tanjung et al. (2009)
52	Apigenin (48)	*M. gigantea*	Leaves	Indonesia	Tanjung et al. (2009)
53	Macatrichocarpin A (49)	*M. trichocarpa*	Leaves	Indonesia	Syah et al. (2009)
54	Macatrichocarpin B (50)	*M. trichocarpa*	Leaves	Indonesia	Syah et al. (2009)
55	Macatrichocarpin C (51)	*M. trichocarpa*	Leaves	Indonesia	Syah et al. (2009)
56	Macatrichocarpin D (52)	*M. trichocarpa*	Leaves	Indonesia	Syah et al. (2009)
57	6-Prenyl-3'-methoxy-eriodictyol (53)	*M. triloba*	Flowers	Malaysia	Zakaria et al. (2010)
58	Nymphaeol B (28)	*M. triloba*	Flowers	Malaysia	Zakaria et al. (2010)
59	Nymphaeol C (10)	*M. triloba*	Flowers	Malaysia	Zakaria et al. (2010)
60	6-Farnesyl-3',4',5,7-tetrahydroxyflavanone (54)	*M. triloba*	Flowers	Malaysia	Zakaria et al. (2010)
61	Macarhizinoidin A (55)	*M. rhizinoides*	Leaves	Indonesia	Tanjung et al. (2010)
62	Macarhizinoidin B (56)	*M. rhizinoides*	Leaves	Indonesia	Tanjung et al. (2010)
63	Macapruinosin B (57)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2010)
64	Macapruinosin C (58)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2010)
65	Papyriflavonol A (59)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2010)
66	Nymphaeol C (10)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2010)
67	(2*S*)-5,7,3'-trihydroxy-4'-methoxy-8-(3''-methylbut-2''-enyl)flavanone (60)	*M. conifera*	Leaves	China	Versian et al. (2011)
68	(2*S*)-5,7,3',5'-tetrahydroxy-6,8-(3'',8''-dimethylobut-2'',7''-dienyl)flavanone (61)	*M. conifera*	Leaves	China	Versian et al. (2011)
69	(2*S*)-5,7-dihydroxy-4'-methoxy-8-(3''-methylbut-2''-enyl)flavanone (62)	*M. bicolor*	Leaves	Philippines	Versian et al. (2011)
70	(2*S*)-5,7,4'-trihydroxy-8-(3''-methylbut-2''-enyl)flavanone (63)	*M. bicolor*	Leaves	Philippines	Versian et al. (2011)
71	(2S)-5,7,4'-trihydroxy-8-(3'',8''-dimethylocta-2'',7''-dienyl) flavanone (64)	*M. bicolor*	Leaves	Philippines	Versian et al. (2011)
72	Malaysianone A (65)	*M. triloba*	Inflorescences	Malaysia	Zakaria et al. (2012)
73	Macakurzin A (66)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
74	Macakurzin B (67)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
75	Macakurzin C (68)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
76	5,7-dihydroxy-6-prenylflavanone (69)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
77	Glabranin (70)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
78	Izalpnin A (71)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)

Table 1. Contd.

79		Glepidotin A (72)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
80		8-Prenylgalangin (73)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
81		Galangin (74)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
82		Macalowiinin (75)	*M. lowii*	Leaves	Indonesia	Augustina et al. (2012)
82		4'-*O*-methyl-8-isoprenylnaringenin (76)	*M. lowii*	Leaves	Indonesia	Augustina et al. (2012)
83		4'-*O*-methyl-5,7,4'-trihydroxyflavone (77)	*M. lowii*	Leaves	Indonesia	Augustina et al. (2012)
84		Macarecurvatin A (78)	*M. recurvata*	Leaves	Indonesia	Tanjung et al. (2012)
85		Macarecurvatin B (79)	*M. recurvata*	Leaves	Indonesia	Tanjung et al. (2012)
86		Diisoprenylaromadendrin (80)	*M. recurvata*	Leaves	Indonesia	Tanjung et al. (2012)
87		Glyasperin A (47)	*M. recurvata*	Leaves	Indonesia	Tanjung et al. (2012)
88		Broussoflavonol F (81)	*M. recurvata*	Leaves	Indonesia	Tanjung et al. (2012)
89		Macapruinosin D (82)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2012)
90		Macapruinosin E (83)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2012)
91		Macapruinosin F (84)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2012)
1		Vedelianin (85)	*M. vedeliana*	Leaves	New Caledonia	Thoison et al (1992)
2		Schweinfurthin A (86)	*M. schweinfurthii*	Leaves	Cameroon	Beutler et al. (1998)
3		Schweinfurthin B (87)	*M. schweinfurthii*	Leaves	Cameroon	Beutler et al. (1998)
4		Schweinfurthin C (88)	*M. schweinfurthii*	Leaves	Cameroon	Beutler et al. (1998)
5		Mappain (89)	*M. mappa*	Leaves	Hawaii	Kaaden et al. (2001)
6		Schweinfurthin E (90)	*M. alnifolia*	Leaves	Madagascar	Yoder et al. (2007)
7		Schweinfurthin F (91)	*M. alnifolia*	Leaves	Madagascar	Yoder et al. (2007)
8	Stilbenes	Schweinfurthin G (92)	*M. alnifolia*	Leaves	Madagascar	Yoder et al. (2007)
9		Schweinfurthin H (93)	*M. alnifolia*	Leaves	Madagascar	Yoder et al. (2007)
10		Schweinfurthin I (94)	*M. schweinfurthii*	Leaves	Cameroon	Klausmeyer at al. (2010)
11		Schweinfurthin J (95)	*M. schweinfurthii*	Leaves	Cameroon	Klausmeyer at al. (2010)
12		Macapruinosin A (96)	*M. pruinosa*	Leaves	Indonesia	Syah and Ghisalberti (2010)
13		Furanokurzin (97)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
14		*Cis*-3,5-dimethoxystilbene (98)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
15		*Trans*-3,5-dimethoxystilbene (99)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
16		*Trans*-3,5-dimethoxy-2-prenylstilbene (100)	*M. kurzii*	Leaves	Vietnam	Thanh et al. (2012)
1		3-Desgalloyterchebin (101)	*M. sinensis*	Leaves	China	Lin et al. (1990)
2		Macaranin A (102)	*M. sinensis*	Leaves	China	Lin et al. (1990)
3		Macaranin B (103)	*M. sinensis*	Leaves	China	Lin et al. (1990)
4		Macaranin C (104)	*M. sinensis*	Leaves	China	Lin et al. (1990)
5	Tannins	Macarinin A (105)	*M. sinensis*	Leaves	China	Lin et al. (1990)
6		Macarinin B (106)	*M. sinensis*	Leaves	China	Lin et al. (1990)
7		Macarinin C (107)	*M. sinensis*	Leaves	China	Lin et al. (1990)
8		Marcabarterin (108)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
9		Mallotinic acid (109)	*M. tanarius*	Leaves	Indonesia	Gunawan –Puteri and Kawabata (2010)

Table 1. Contd.

10		Corilagin (110)	*M. tanarius*	Leaves	Indonesia	Gunawan-Puteri and Kawabata (2010)
11		Macatannin A (111)	*M. tanarius*	Leaves	Indonesia	Gunawan-Puteri and Kawabata (2010)
12		Macatannin B (112)	*M. tanarius*	Leaves	Indonesia	Gunawan-Puteri and Kawabata (2010)
13		Chebulagic acid (113)	*M. tanarius*	Leaves	Indonesia	Gunawan-Puteri and Kawabata (2010)
14		1(*β*)-*O*-galloyglucose (114)	*M. tanarius*	Leaves	China	Lin et al. (1990)
15		4-*O*-galloyglucose (115)	*M. tanarius*	Leaves	China	Lin et al. (1990)
16		6-*O*-galloyglucose (116)	*M. tanarius*	Leaves	China	Lin et al. (1990)
17		2,3-*di- O*-galloyglucose (117)	*M. tanarius*	Leaves	China	Lin et al. (1990)
18		1(*β*),2,6-*tri*-*O*-galloyglucose (118)	*M. tanarius*	Leaves	China	Lin et al. (1990)
19		2,4,6-*tri*-*O*-galloyglucose (119)	*M. tanarius*	Leaves	China	Lin et al. (1990)
20		1(*β*),3,4,6-*tetra*-*O*-galloyglucose (120)	*M. tanarius*	Leaves	China	Lin et al. (1990)
21		1(*β*),2,3,4,6-*penta*-*O*-galloyglucose (121)	*M. tanarius*	Leaves	China	Lin et al. (1990)
22		1(*β*),2,4,6-*tetra*-*O*-galloyglucose (122)	*M. tanarius*	Leaves	China	Lin et al. (1990)
23		3-*O*-galloyl-(-)-shikimic acid (123)	*M. tanarius*	Leaves	China	Lin et al. (1990)
24		5-*O*-galloyl-(-)-shikimic acid (124)	*M. tanarius*	Leaves	China	Lin et al. (1990)
25		4-*O*-galloyquinic acid (125)	*M. tanarius*	Leaves	China	Lin et al. (1990)
26		3,4-*di*-*O*-galloyquinic acid (126)	*M. tanarius*	Leaves	China	Lin et al. (1990)
27		3,6-(*S*)-hexahydroxydiphenyl (HHDP)-D-glucopyranose (127)	*M. tanarius*	Leaves	China	Lin et al. (1990)
10		Corilagin (110)	*M. tanarius*	Leaves	China	Lin et al. (1990)
28		Punicafolin (128)	*M. tanarius*	Leaves	China	Lin et al. (1990)
29		Furosin (129)	*M. tanarius*	Leaves	China	Lin et al. (1990)
30		Terchebin (130)	*M. tanarius*	Leaves	China	Lin et al. (1990)
31		Geraniin (131)	*M. tanarius*	Leaves	China	Lin et al. (1990)
9		Mallotusinic acid (109)	*M. tanarius*	Leaves	China	Lin et al. (1990)
32		Repandusinic acid A (132)	*M. tanarius*	Leaves	China	Lin et al. (1990)
33		1,4-di-*O*-galloyl-α-D-glucopyranose (133)	*M. tanarius*	Leaves	China	Lin et al. (1990)
34		3,4-di-*O*-galloyl-D-glucopyranose (134)	*M. tanarius*	Leaves	China	Lin et al. (1990)
35		Galloylpunicafolin (135)	*M. tanarius*	Leaves	China	Lin et al. (1990)
36		Galloylgeraniin (136)	*M. tanarius*	Leaves	China	Lin et al. (1990)
37		1-*O*-galloyl-3-*O*-brevifolincarboxyl-*β*-D-glucopyranose (137)	*M. tanarius*	Leaves	China	Lin et al. (1990)
38		Macaranganin (138)	*M. tanarius*	Leaves	China	Lin et al. (1990)
39		Tanarinin (139)	*M. tanarius*	Leaves	China	Lin et al. (1990)
40		Tergallic acid bislactone (140)	*M. sinensis*	Leaves	China	Lin et al. (1990)
41		3,6-*O*-(R)-hexahydroxydiphenoyl (HHDP)-D-glucose (141)	*M. sinensis*	Leaves	China	Lin et al. (1990)
42		Tercatain (142)	*M. sinensis*	Leaves	China	Lin et al. (1990)
43		Mallorepanin (143)	*M. sinensis*	Leaves	China	Lin et al. (1990)
44		Putranjivain A (144)	*M. sinensis*	Leaves	China	Lin et al. (1990)
1		Macarangonol (145)	*M. tanarius*	Stem bark	Hong Kong	Hui et al. (1971)
2	Terpenes	Kolavenic acid (146)	*M. monandra*	Stem bark	Cameroon	Salah et al. (2003)
3		2-Oxo-kolavenic acid (147)	*M. monandra*	Stem bark	Cameroon	Salah et al. (2003)

Table 1. Contd.

4		Taraxerol (148)	*M. triloba*	Leaves	Indonesia	Jang et al. (2004)
5		3-*epi*-taraxerol (149)	*M. triloba*	Leaves	Indonesia	Jang et al. (2004)
6		3β-*O*-acetyl aleuritolic acid (150)	*M. hemsleyana*	Stem bark	China	Wang et al. (2008)
7		Canophyllol (151)	*M. hemsleyana*	Stem bark	China	Wang et al. (2008)
8		Kolavenol (152)	*M. tanarius*	Leaves	Japan	Kawakami et al. (2008)
9		Blumenol A (153)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
10		Blumenol B (154)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
11		Annuionone E (155)	*M. tanarius*	leaves	Thailand	Phormmart et al. (2005)
12		20-*epi*bryonolic acid (156)	*M. conifera*	Leaves	Indonesia	Jang et al. (2002)
			M. denticulata	Leaves	Thailand	Sutthivaiyakit et al. (2002)
			M. triloba	Leaves	Indonesia	Jang et al. (2004)
1	Coumarins	Scopoletin (157)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
			M. triloba	Inflorescences	Malaysia	Zakaria et al. (2012)
			M. gigantifolia	Leaves	Indonesia	Darmawan et al. (2012)
2		5,7-dihydroxycoumarin (158)	*M. triloba*	Inflorescences	Malaysia	Zakaria et al. (2012)
1	Steroids	β-Sitosterol (159)	*M. hemsleyana*	Stem bark	China	Wang et al. (2008)
			M. peltata	Stem bark	India	Ramaiah et al. (1979)
2		Stigmast-4-en-3-one (160)	*M. hemsleyana*	Stem bark	China	Wang et al. (2008)
3		Stigmast-4-en-3,6-dione (161)	*M. hemsleyana*	Stem bark	China	Wang et al. (2008)
1	Other compounds	Bergenin (162)	*M. peltata*	Stem bark	India	Ramaiah et al. (1979)
2		8,10-*di*-O-methylether (163)	*M. peltata*	Stem bark	India	Ramaiah et al. (1979)
3		*Tri*-O-methyl ether (164)	*M. peltata*	Stem bark	India	Ramaiah et al. (1979)
4		*Tri*-O-methyl ether (165)	*M. peltata*	Stem bark	India	Ramaiah et al. (1979)
5		Chlorogenic acid (166)	*M. sinensis*	Leaves	China	Lin et al. (1990)
6		3-*O*-methylellagic acid 4-*O*-β-D-ylopyranoside (167)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
7		Ellagic acid (168)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
8		3-*O*-Methylellagic acid (169)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
9		Gallic acid (170)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
10		Methyl gallate (171)	*M. barteri*	Stem bark	Cameroon	Ngoumfo et al. (2008)
11		(+)-Pinoresinol 4-*O*-[6''-*O*-galloyl]-β-D-glucopyranoside (172)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2009)
12		Macarangioside E (173)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2009)
13		Macarangioside F (174)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2009)
14		Mallophenol B (175)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
15		Macarangioside A (176)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
16		Macarangioside B (177)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
17		Macarangioside C (178)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
18		Macarangioside D (179)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
19		Lauroside E (180)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)

Table 1. Contd.

20	Methyl brevifolin carboxylate (181)	*M. tanarius*	Leaves	Japan	Matsunami et al. (2006)
21	4,5-dihydro-5'α-hydroxy-4'α-methoxy-6a,12a-dehydro-α-toxicarol (182)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
22	(+)-Clovan-2β,9α-diol (183)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
23	Ferulic acid (184)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
24	Abscisic acid (185)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
25	1β,6α-dihydroxy-4(15)-eudesmene (186)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
26	3β-hydroxy-24-ethylcholest-5-en-7-one (187)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
27	Loliolide (188)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
28	Tanarifuranonol (189)	*M. triloba*	Flower	Malaysia	Zakaria et al. (2010)
29	Methyl 4-isoprenyloxycinnamate (190)	*M. rhizinoides*	Leaves	Indonesia	Tanjung et al. (2010)

Anticancer activity

Cancer is one of the leading causes of mortality, accounting for about 8 million deaths worldwide. Currently, there are about 20 million people with cancer worldwide and the number is projected to increase to 30 million by the year 2020 (WHO, 2008). The report indicates the most prevalent types of cancer being lung, liver, colon, cervical, prostate and breast cancer. Since many people in the tropics live in rural areas, treatment of cancer-related illnesses has mostly involved plant extracts. It is estimated that over 60% of anti-cancer agents presently in clinical use are derived from natural sources, including plants, marine organisms and micro-organisms (Cragg and Newman, 2005). Some examples of anticaner drugs originating in plants include paclitaxel, irinotecan, topotecan, vinblastine, vincristine, camptothecin, and etoposide (Pan et al., 2010).

Although several anticancer drugs such as taxol derivatives are already in the clinic, they are expensive and thus not affordable by these communities. Therefore, there remains a great need for affordable and reliable anticancer drugs particularly of plant origin. Currently, several anticancer compounds from medicinal plants have been characterized and their activities against different types of human cancer cell lines established (Balunas and Kinghorn, 2005). For instance, extracts and purified compounds from *Macaranga* species have been studied for their potential as anticancer agents. Thus, the bioassay guided-isolation from the leaves of *M. schweinfurthii* gave schweinfurthii A (86) and schweinfurthii B (87) which indicated high sensitivity against central nervous system (CNS) tumor-derived lines SF-295 and SF-539. Compound 86 displayed a mean panel GI_{50} of 0.36 µM while compound 87 gave a mean panel GI_{50} of 0.81 µM (Beutler et al., 1999).

In another study from the leaves of *M*. *mappa*, the crude extract of the leaves indicated potent cytotoxicity against both drug-resistant (SKVLB-1) and drug-sensitive (SK-OV-3) ovarian cancer cell lines with an IC_{50} value of 3.5 µg/ml. From the active extract, a cytotoxic compound named mappain (89) was isolated which was cytotoxic but noted to be a poor substrate for P-glycoprotein-mediated transport as it is equally potent and effective against the drug-sensitive (SK-OV-3) and drug-resistant (SKVLB-1) ovarian cancer cell lines, indicating an IC_{50} value of 1.3 µM in both cases (Kaaden et al., 2001).

Yoder and co-researchers investigated a fruit extract of the Malagasy plant, *M. alnifolia*. This extract was found to be active in the A2780 ovarian cancer anti-proliferative activity assay, with an IC_{50} value of 3.5 µg/ml. Ten compounds were isolated and tested for anti-proliferative activity in the A2780 human ovarian cancer cell lines, Table 2 (Yoder et al., 2007).

In this study, vedelianin (85) showed the greatest activity among all isolates, exhibiting the IC_{50} value of 0.13 µM (Yoder et al., 2007).

A study on the anticancer activity from the leaves of *M. tanarius* collected in Japan gave prenylated flavanones that were assayed against the KB and A549 cell lines by means of the 3-[4-5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method. It was reported that the isolated compounds did not show any selectivity between these cell lines. However, macaflavanone G (41) showed the most potent compound against both cell lines with an IC_{50} values of 12.3 ± 3.0 and 13.4 ± 2.1 µM for KB and A549 cells, respectively (Kawakami et al., 2008). Phytochemical investigation of an endemic plant from Indonesia, *M. gigantea* gave three cytotoxic flavonoids, macagigantin (46), glyasperin A (47) and apigenin (48) from the acetone extract of the leaves. The cytotoxic properties of all compounds were evaluated against murine leukemia P-388 cell lines according to the method of MTT. The

Table 2. Antiproliferative Activity of *M. alnifolia* compounds to A2780 cells.

Compound	IC_{50} (µM)
Schweinfurthin E (90)	0.26
Schweinfurthin F (91)	5.0
Schweinfurthin G (92)	0.39
Schweinfurthin H (93)	4.5
Alnifoliol (31)	27.3
Vedelianin (85)	0.13
Bonanniol A (32)	23.5
Diplacol (33)	11.5
Bonannione A (34)	24.5
Diplacone (27)	10.5

Table 3. Anticancer compounds isolated from *M. triloba*.

Compounds	Cell lines (IC_{50} value in µg/ml)*		
	HL-60	MCF-7	Hela
10	11.6±1.5	23.0±2.4	18.2±1.0
28	21.3±3.2	23.5±3.6	17.0±2.8
53	15.1±3.5	22.8±0.8	12.2±2.6
54	3.3±0.6	5.6±0.4	1.3±0.8

*IC_{50} activity (inhibition): < 5 µg/ml (very strong); < 5 to 10 µg/ml (Strong); 10 to 20 µg/ml (moderate); 20 to 100 µg/ml (weak); > 100 µg/ml (not active).

results indicated that compounds 46 to 48 exhibited an IC_{50} values of 11.3 ± 0.4, 6.0 ± 0.9, and 5.1 ± 0.7 µM, respectively (Tanjung et al., 2009). Artonin E, which was used as a positive control, showed the IC_{50} value of 1.38 ± 0.2. In another study by Li and co-workers, a series of prenylated flavonols (42 to 45) were isolated from the leaves of *M. sampsonii*. The isolated compounds were evaluated for their cytotoxicity potential using MTT method against human cancer cell lines [lung cancer (A549), pulmonary carcinoma (LAC), gastric carcinoma (SGC-7901) and hepatoma (HepG2)]. However, all compounds were inactive at 20 µg/ml except for macaranone A (42) that exhibited weak activity against HepG2 cell line with the IC_{50} value of 6.9 µg/ml (Li et al., 2009).

Further search for anticancer compounds from *Macaranga* plants was done on the leaves of *M. rhizinoides* using the MTT method against murine leukemia P-388 cell lines (Tanjung et al., 2010). Bioassay-guided isolation from the methanol extract of the leaves led to the isolation of two cytotoxic flavonoids named macarhizinoidins A (55) and B (56). On cytotoxic evaluation against murine leukemia P-388 cell lines, compounds 55 and 56 indicated the IC_{50} values of 11.4 and 13.9 µM, respectively (Tanjung et al., 2010).

A recent study by Zakaria and co-researchers investigated the dichloromethane extract of the inflorescences of *M. triloba*. Phytochemical analysis of the active extract resulted in the isolation of five flavonoids (10, 28, 53 and 54) which were tested for their activity against three cancer cell lines, namely HL-60 (human leukemia), MCF-7 (human breast cancer) and HeLa (human cervical cancer) using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) dye-reduction assay. The results are recorded in Table 3, indicating compound 54 to exhibit very strong activity against HeLa and HL-60 cell lines with IC_{50} values of 1.3, 3.3 µg/ml, respectively and also a strong inhibition against MCF-7 cells with IC_{50} value 5.6 µg/ml, others were moderately active (Zakaria et al., 2012).

Phytochemical investigations from the leaves of *Macaranga kurzii* lead to the isolation of a series of flavonoids and stilbenes (Thanh et al., 2012). Compound 100 indicated significant activity with IC_{50} of 4 µM, while compounds 67and 72 displayed IC_{50} values of 13 and 10 µM, respectively. The other isolated compounds were non-cytotoxic at 20 µM (Thanh et al., 2012). Continued search for anticancer compounds from *Macaranga* plants was done from an Indonesian species, *M. lowii*. Two isoprenylated dihydroflavonol derivatives (75 to 76) and a flavone (77) were isolated from the methanol extract of the leaves of *M. lowii.* Preliminary cytotoxic investigation of compounds 75 to 77 against murine leukemia P-388 cells showed weak activity values at 119.3, 166.6 and 58.7 µM, respectively (Agustina et al., 2012). Flavonoids (78-81) from *M. recurvata*, isolated by Tanjung and co-workers were evaluated for cytotoxic activity against murine leukemia P-388 cells using MTT assay. These compounds were noted to be active at the IC_{50} values < 10 µM, with compound 79 being the most active with the IC_{50} value of 0.83 µM (Tanjung et al., 2012).

Another study on the anticancer activity from the leaves of *M. gigantifolia* collected in Indonesia gave a cytotoxic coumarin derivative compound named scopoletin (157). Its cytotoxicity was evaluated using MTT assay method against murine leukemia P-338 cells. Compound 157 showed moderate cytotoxic activity with IC_{50} value of 17.42 µg/ml (Darmawan et al., 2012).

Antioxidant activity

Antioxidants are secondary metabolites produced by plants to protect against oxidative damage by free radicals (Larson, 1988). Plants have for so long shown to be important in the human diet as well as in health maintenance. The well known beneficial role provided by plants is protection against cellular damage caused by exposure to high levels of free radicals such as reactive oxygen species (ROS) (Aruoma, 1996). Different parts of *Macaranga* plant species are known to contain high levels of antioxidant compounds such as polyphenols, phenolic acids, flavonoids and carotenoids (Matsunami et al., 2006). These antioxidants are thought to prevent chronic complications in part through their interactions with reactive species and ability to scavenge free radicals

Table 4. Antioxidant activities of four *Macaranga* species.

Species	DPPH	AEAC	FRAP
	IC_{50} (mg/ml)	mg AA/100 g	Mg GAE/g
M. gigantea	0.171±0.006	2250±129	13.9±2.5
M. pruinosa	0.165±0.008	2340±112	15.0±0.7
M. tanarius	0.175±0.013	2190±173	12.3±0.7
M. triloba	0.151±0.008	2580±172	20.2±2.1

(Seifried et al., 2007).

Investigation for antioxidant compounds from *M. denticulata* lead to the isolation of phenolic compounds (3 and 157) which indicated to have significant antioxidant properties (Sutthivaiyakit et al., 2002). These compounds were evaluated for their antioxidant properties using 1,1-diphenyl-2-picrylhydrazyl (DPPH) stable radical.

Macarangin (3) exhibited potent antioxidant activity with IC_{50} value of 0.032 ± 0.001 mM. This result was comparable to the standard antioxidant [2,6-di-(tert-butyl)-4-methylphenol, BHT] which have an IC_{50} value of 0.031 ± 0.001 mM. Scopoletin (157) also showed significant antioxidant property with an IC_{50} value of 0.342 ± 0.026 mM (Sutthivaiyakit et al., 2002).

M. tanarius is well known in Thai traditional medicine as an antipyretic and emetic agent (Phupattanapong and Wongprasert, 1987). Phytochemical work on the leaves of this species gave five flavonols (10, 25 to 28) that were tested for antioxidant activity with the DPPH stable radical (Phormmart et al., 2005). The results indicated that compounds 26 to 28 and 10 indicated comparable radical scavenging properties with IC_{50} values of 20 ± 1, 14 ± 1, 13 ± 2 and 15 ± 2 mM, respectively. These IC_{50} values were higher than that of compound 25 and a standard (BHT) which showed IC_{50} values of 33 ± 1 and 30 ± 1, respectively (Phormmart et al., 2005).

In 2006, Matsunami and co-workers investigated the radical-scavenging activity of the leaves of *M. tanarius* and isolated nine secondary metabolites of the megastigmane-type glucosides (173 to 180). The free radical scavenging activity of these compounds was evaluated by its ability to quench the stable radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH) using Trolox as a reference compound whereas Trolox equivalent (μM) was determined for each isolate. The results indicated compounds 173 to 176 had more potent radical-scavenging activity than the well-known antioxidant flavonoids, quercetin glycosides.

The rest of the compounds could not quench DPPH radical. From the structural point of view, it was established that the radical scavenging activity of these galloylated megastigmane glucosides depended on the galloyl moiety and not megastigmane glucoside moiety (Matsunami et al., 2006).

In the study of the methanolic fresh leaves of four *Macaranga* species (*M. gigantea, M. pruinosa, M. tanarius* and *M. triloba*), the antioxidant properties (AOP) of the crude extracts were evaluated. Three antioxidant techniques namely 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging, ferric-ion reducing power (FRAP) and ascorbic acid equivalent antioxidant activity (AEAC) were used. The results indicate moderate activities to most extracts except *M. triloba* extract that showed the highest ascorbic acid equivalent antioxidant activity (AEAC) and FRAP values. *M. tanarius* showed the lowest AEAC and FRAP activities as indicated in Table 4 (Lim et al., 2009).

Further study on the methanol extract of *M. tanarius* by Matsunami and co-workers lead to the isolation of a lignan glucoside (172) and two megastigmane glucosides, (173) and (174). Thus, the free radical-scavenging activity of these compounds was evaluated using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical with Trolox being used as a standard compound. Compounds 172 and 173 showed potent radical-scavenging activities of 1.07 and 0.55 times of Trolox, respectively (Matsunami et al., 2009).

Antimicrobial activity

The use of plant extracts in the treatment of infectious diseases has been a known practice for many years now (Recio et al., 1989). As a result, a large number of reports of antimicrobial natural products have been documented from various parts of the world. However, owing to the continuing development of microbial resistance, discovery of new antimicrobial substances is of great importance. *Macaranga* plants have been investigated for antimicrobial natural products that yielded several bioactive compounds. One of the reports from *Macaranga* species was the characterization of antibacterial prenylated flavanones isolated from *M. pleiostemona*. This species is well known in New Guinea and is used to relieve headache (Schutz et al., 1995). Bioassay-guided isolation of the dichloromethane extract of *M. pleiostemona* yielded four compounds (4 to 7) which were assayed for antibacterial activities against *Escherichia coli* (ATCC 25922) and *Micrococcus luteus* (ATCC 9341) using a bioautographic method (Orjala et al., 1994). All compounds exhibited significant antibacterial activities with minimum growth inhibition of 0.5 μg/ml each for both bacterial species (Schutz et al., 1995).

Investigation of the Cameroonian plant, *M. monandra* for possible antifungal compounds was undertaken by Salah et al. (2003). Bioassay-guided fractionation of the hexane and ethyl acetate fractions of the methanol extract led to the isolation of two active clerodane-type diterpenes (146 and 147). A 96-well microbioassay revealed that kolavenic acid (146) and 2-oxo-kolavenic acid (147) produced moderate growth inhibition in *Phomopsis viticola* and *Botrytis cinerea* (Salah et al., 2003). Compound 146 was slightly more active against *P. viticola* and showed 50% growth inhibition at 30 μM,

Table 5. Inhibitory activities of compounds 14 to 19 against cyclooxygenase-1 (COX-1) and -2 (COX-2), and in a mouse mammary organ culture (MMOC) model.

Compound	COX-1 [IC_{50} (µM)]	COX-2 [IC_{50} (µM)]	MMOC (at 10 µg/ml)
14	16.9	9.5	86.1
15	72.6	>100	37.5
16	126.2	>100	25.0
17	>100	27.8	68.2
18	12.8	28.9	ND
19	10.4	6.2	58.4
trans-resveratrol*	1.1	1.3	87.5

ND = not determined, * = used as positive control.

whereas 147 showed 46% growth inhibition. There was no significant antifungal activity demonstrated against *C. acutatum*, *C. gloeospioides*, *C. fragariea* or *F. oxysporum* at concentrations ≤ 30 µM (Salah et al., 2003).

Four methanolic extracts from *M. gigantea, M. pruinosa, M. tanarius* and *M. triloba* were screened for their antibacterial activities using the disc-diffusion method (Chan et al., 2007) against the gram-positive bacteria (*Bacillus cereus, Micrococcus luteus* and *Staphylococcus aureus*) and the gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae* and *Salmonella cholerosius*). The results indicated the inhibition was only observed for all gram-positive species which showed moderate inhibition for all *Macaranga* extracts. *M. triloba* showed the best antibacterial activity against gram-positive bacteria species, with minimal inhibition dosage (MID) values as low as 10 µg/disc (Lim et al., 2009). No activity was observed for the gram-negative species which is most likely due to lipoproteins and lipopolysaccharides of the outer membrane.

Anti-inflammatory activity

Inflammation is one of the biological responses of vascular tissue to harmful stimuli like pathogens or damaged cells. The conventional signs of acute inflammation are pain, heat, redness and swelling (Ferrero-Milian et al., 2007). Furthermore, inflammation is regarded as defensive response that induces physiological adaptations to limit tissue damage and removes the pathogenic infections (Roussin et al., 1997). Currently, many synthetic drugs are used to treat inflammation conditions, leading to many side effects. Herbal drugs of plant origin are of most important to produce safe anti-inflammatory drugs.

Plants of the genus *Macaranga* has been reported to be the good source of anti-inflammatory compounds. Isolation of prenylated flavonoids was performed from the ethyl acetate extract of *M. conifera* and tested for their inhibition effects against both cyclooxygenases-1 and -2 (Jang et al., 2002). Cyclooxygenase-2 (COX-2) is responsible for the biosynthesis of prostaglandins under acute inflammatory conditions (O'Banion et al., 1992). Thus, the regulation of the COX pathway provides an excellent approach for the discovery of cancer chemopreventive agents (Cuendet and Pezzuto, 2000). Six compounds (14 to 19) were isolated and tested to exhibit potent inhibitory activities with compound 14 indicating to be a promising cancer chemopreventive agent. Compounds 14 to 19 were also evaluated in a mouse mammary organ culture assay and the results are recorded in Table 5 (Jang et al., 2002).

A study by Ngoumfo and co-workers investigated the anti-inflammatory activity of the methanol extract of the stem bark of *M. barteri* in a cell-based respiratory burst assay. This assay involved water-soluble tetrazolium salt (WST-1) to measure the superoxide production of neutrophils activated by opsonized zymosan, which induces phagocytic activation of neutrophils (Costantino et al., 1998). Compounds 108, 157, 167 to 170 were tested for their anti-inflammatory potential in a cell-based respiratory burst assay indicating good activity (Table 6). Compound 108 was found to be the best inhibitor of the superoxides produced in the cellular system (Ngoumfo et al., 2008).

In another search for anti-inflammatory compounds from leaves of *M. triloba*, an array of phenolic compounds was isolated and evaluated for their potential to inhibit cyclooxygenases-1 and -2 by measuring PGE2 production (Cuendet and Pezzuto, 2000). Compounds 22 to 24 and 183 to 184 showed significant inhibitory activity against cyclooxygenase-1 (COX-1) and -2 (COX-2) as indicated in Table 7 (Jang et al., 2004).

Gandhimathi (2013) studied the leaves of *M. peltata* for anti-inflammatory activity. The petroleum ether extract of this species was evaluated for anti-inflammatory activity at the doses of 200 and 400 mg/kg body weight. The results indicated that the oral administration of extract exhibited a significant and dose dependent protective effect on chemical and thermic painful stimuli at the doses of 200 and 400 mg/kg. This implied that the extract possess both peripheral and central effects. It was further noted that the petroleum ether extract possesses an anti-inflammatory activity against carrageenan induced paw edema in rats. The activity was assumed to be due to the presence of phenolic compounds in the leaves of *M. peltata* (Gandhimathi, 2013).

Other biological activities

Macaranga species are also reported to produce compounds that have different biological effects. Recently, Thanh and co-workers isolated flavonoids (66 to 74) and stilbenes (97 to 100) from *M. kurzii* which were evaluated for their acetylcholinesterase inhibitory activities (Thanh et al., 2012). Acetylcholinesterase (AChE) inhibitors are the therapeutic agents for the treatment of neurological

Table 6. Respiratory burst of inhibition in human neutrophils by compounds 108, 157 and 167 to 170.

Compound	Inhibition (%) at 1000 µg/ml drug concentrations	IC_{50} (µg/ml) ± SEM
108	73.23	821.21±73.30
157	31.20	
167	29.05	
168	27.10	
169	13.70	
170	42.90	
Asprin*	70.45	279.44 ± 4.42

* = used as positive control.

disorders such as senile dementia, ataxia, Alzheimer's disease and myasthenia gravis. Inhibition of AChE activity was determined by the spectroscopic method of Ellman, using acetylthiocholine iodide as substrate, in 96-well microtiter plates. In this assay, tacrine was used as a positive control having an IC_{50} of 50 nM. In all tested compounds, *trans*-3,5-dimethoxystilbene (99) exhibited the greatest activity with an IC_{50} value of 9 µM. Others which showed moderare activities were 69 (IC_{50} = 18 µM), 100 (IC_{50} = 19 µM), 68 (IC_{50} = 20 µM), 70 (IC_{50} = 23 µM) and 97 (IC_{50} = 42 µM) (Thanh et al., 2012).

The study on the dichloromethane crude extract of the inflorescences of *M. triloba* for its *in vitro* antiplasmodial activity against a chloroquine sensitive strain of *Plasmodium falciparum* (3D7) was done for the material collected in Malaysia (Zakaria et al., 2012). The IC_{50} value of the crude extract was 2.01 µg/ml, indicating to be a good source of antiplasmodial compounds. Bioassay-guided isolation gave three flavonoids (10, 28 and 54) that were screened for their antiplasmodial activity. Compound 54 displayed strong antiplasmodial activities with an IC_{50} value of 0.06 µM, followed by a moderate activity for 10 and 28 with IC_{50} values of 2.04 and 4.02 µM, respectively (Zakaria et al., 2012).

Table 7. Inhibitory activities of isolated compounds against cyclooxygenase-1 (COX-1) and -2 (COX-2).

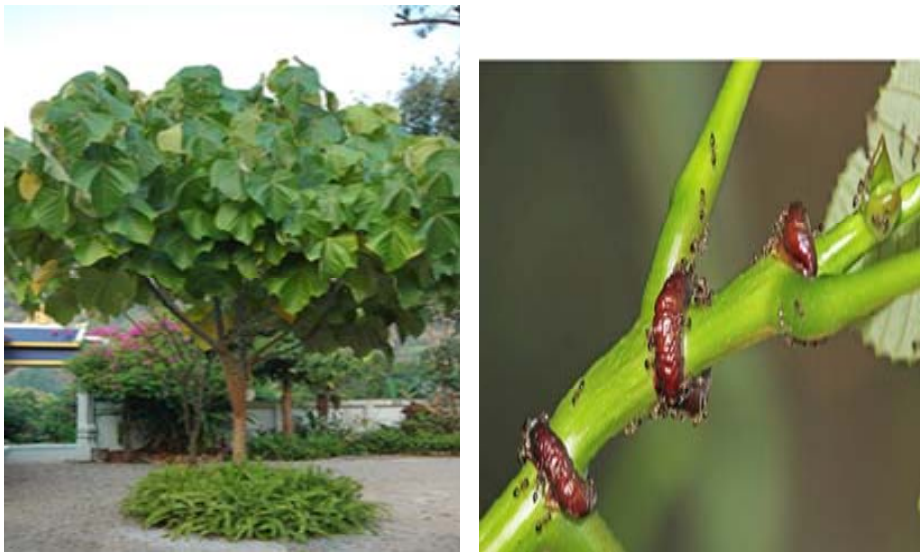
Compound	COX-1 [IC_{50} (µM)]	COX-2 [IC_{50} (µM)]
22	>100	46.6
23	33.7	>100
24	>100	>100
183	>100	>100
184	>100	>100
trans-resveratrol*	0.25	0.30

* = used as positive control.

Conclusion

This article has reviewed the existing knowledge regarding species of the genus *Macaranga*. It is a valuable undertaking as it aims to document the important but scattered reports on phytochemistry and pharmacology of medicinal plants of the genus *Macaranga* collected from different parts of the world. Despite the fact that a wide range of traditional uses of *Macaranga* plants are known and that several plant extracts and pure compounds indicated diverse biological activities (Lim et al., 2009; Zakaria et al., 2012), there are few studies regarding such properties. For instance, out of the 300 known species of *Macaranga* plants, less than 30 plant species have been investigated phytochemically (Table 1). This calls for further work to be done on other known species of this genus. The data provided should help to serve as the basis for further scientific research on this genus. In addition, it is equally important to understand the pharmacological studies on this genus as may be valuable to validate the claimed traditional uses.

Many reviewed literature have shown different species of *Macaranga* to be the good source of various types of natural compounds having diverse and fascinating chemical structures. The major classes of compounds reported in the literature included flavonoids, stilbenes, terpenes, tannins, coumarins and others (Table 1) (Lin et al., 1990; Jang et al., 2002; Salah et al., 2003; Yoder et al., 2007). The pharmacological review of the genus indicated many flavonoids and stilbenes to be isolated from the leaves and exhibited strong, moderate to weak anticancer properties (Kaaden et al., 2001). These two classes of compounds also showed significant antioxidant activities (Sutthivaiyakit et al., 2002). Other compounds indicated anti-inflammatory and antimicrobial properties (Schutz et al., 1995; Ngoumfo et al., 2008). Furthermore, both pharmacological and phytochemical investigations have established that phytochemicals and crude extracts from various parts of *Macaranga* species possess versatile biological activities. However, modern drugs can be developed after extensive investigation of its bioactivity, mechanism of action, toxicity and after proper standardization as well as and clinical trials.



(a) (b)

Figure 1. One of the conserved *Macaranga* species and a branch with ants climbing.

Although many efforts have been made to study some of the plants of this genus, there are profound issues to be considered and improved:

1. There are approximately 300 recorded species of the *Macaranga* genus worldwide, but only approximately 10% of them have been studied, phytochemically or pharmacologically. This implies more efforts to continue with the documentation of the traditional uses, phytochemical and pharmacological investigations should be further encouraged aiming at validating already existing information and for discovering more traditional claims as well as getting leads for drug discovery.
2. Interestingly, this review demonstrated that it is about 90% of the isolated secondary metabolites from *Macaranga* species have been obtained from the leaves while 10% is from the other parts. This calls for further and extensive research work to be done from other plant parts like stem and root barks, fruits, seeds and flowers.
3. Tannins (101 to 144) (Table 1) are characteristic phytochemicals in some species of this genus like *M. sinensis* and *M. tanarius* (Lin et al., 1990). However, presentations of the structures lacked establishment of stereochemistry which is the basic tool in structure identification as well as in biological activities. These compounds were isolated before the discovery of new and advanced spectroscopic techniques. Hence, further study is required to understand the structures as well as the possible structure-activity relationships of these phytoconstituents.
4. Some species of *Macaranga* are well known for their mutual relationship with ants (Figure 1), however, a little is known about the chemical compositions of the hollow shoots that always house the ants. Further study is also needed to discover the phytochemicals therein.

Special attention should be paid to the *Macaranga* genus to validate and establish its medicinal potential and to utilize the various plant sources it contains.

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Conflict of Interests

The author(s) have not declared any conflict of interests

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