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The potential of *Macaranga* plants as skincare cosmetic ingredients: A review

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ABSTRACT

The application of bioactive ingredients extracted from plants utilized as additives in various cosmetic products has gained popularity, since they are safe, with low adverse effects when applied properly, and are environmentally friendly. Moreover, the awareness of healthier cosmetic products has rapidly increased so that the exploration of screened plants with appropriate properties has attracted significant attention worldwide. This review discusses the potential of one of the fastest-growing tropical plants, *Macaranga*, applied in skincare cosmetics. Their interesting characteristics, such as being anti-inflammatory, antioxidant, and antimicrobial, and their tyrosinase inhibitory effect have been comprehensively summarized. Various scientific literature works have further proven ethnopharmacological studies that explore the traditional use of *Macaranga* species by local people in the tropics for medicinal and skincare purposes. Therefore, we believe this will allow *Macaranga* to become a promising material in the future for large-scale industrial skincare cosmetics.

INTRODUCTION

The largest organ on the outside of the human body, the skin, is a barrier to shield interior organs from dehydration, microbial infection, and UV exposure. Besides these important functions, it is well known that a better skin appearance is also responsible for an individual's awareness of looking more beautiful. Hence, various companies have attempted to pursue improving their innovative products in skincare cosmetics. The business sector in this area has been recognized as one of the most promising ones, with an annual revenue worth of billions of dollars (Kouassi *et al*., 2022). Currently, a phenomenon in healthy lifestyles contributes to shifting from synthetic skincare cosmetics to green ones, since synthetic materials reportedly have harmful side effects, such as low absorption ability and allergic reactions (irritation) (Morais *et al*., 2021). A previous study also indicated their negative influences on the environment (Amberg and Fogarassi, 2019). On the other hand, green technology offers several advantages, including safety, nontoxicity, having no adverse effects when used correctly, and biodegradability. These products are generally fabricated by incorporating bioactive compounds obtained from plants.

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Therefore, this trend motivates scientists worldwide to explore plant materials with appropriate properties, particularly those used in skincare cosmetics.

Euphorbiaceae is considered to be one of the largest families among flowering plants, with 218 genera and 5,735 species (Zixi *et al*., 2016). According to ethnobotanical studies, most plants in this family are frequently utilized in local medicine and skincare (Zahidin *et al*., 2017). *Macaranga* is a genus of Euphorbiaceae, which consists of more than 300 species, and it is widely distributed across tropical and subtropical countries in Africa, Asia, Australasia, and the Pacific (Huonga *et al*., 2019). Nevertheless, its distribution center has been recorded in tropical Asia (Syah and Ghisalberti, 2015). This fast-growing tree species, also known as the highest genus in the Euphorbiaceae, can be found in gaps between the forest canopy, disturbed forests, and open areas (Tanjung *et al*., 2018). Due to the change in light conditions after logging activities or forest fires, some *Macaranga* species are usually found with high dominance as pioneer species. The presence of *Macaranga* can be a reliable bioindicator of deforestation (Zapanta *et al*., 2019). Its rapid growth has been recorded to significantly influence the composition of the forest vegetation community during the secondary succession stage (Susanto *et al*., 2018). In Indonesia, its wide distribution has been found in Sumatera and on Kalimantan Island (Tanjung *et al*., 2018). Considering its ability to cover land quickly and attract wildlife, it is also becoming popular as a species to promote revegetation after coal mining in this country (Amirta and Candra, 2016). The leaves of several species from this genus are often utilized in traditional medicine and have the potential for use as antipyretics, antitussives, and anti-inflammatories (Pailee *et al*., 2015). Due to its good adaptation to various types of land, even with low available nutrient status, combined with its interesting properties, further domestication of *Macaranga* will allow the use of these plant species in various applications, including sustainable raw materials for additives in skincare production.

Nowadays, the practice of using direct herbal products for skincare purposes has been declining, since various modern skincare products containing bioactive ingredients with simpler usage have been introduced to the market (Milito *et al*., 2021). As a result, valuable information about crude extraction and isolated compounds, including those obtained from *Macaranga*, will need to be collected, as several authors have reported its remarkable bioactivity (Di *et al*., 2020; Hashim *et al*., 2022; Minarti *et al*., 2021). This review presents a comprehensive summary of the chemical and pharmacological studies on *Macaranga* spp. in terms of their suitability for use as skincare cosmetic products. Furthermore, the range of their potential application in large-scale industrial skincare products is also considered.

METHODOLOGY

The current review was conducted based on a number of publications, specifically, plant extracts and bioactive constituents of various *Macaranga* plants, which can be used as skincare cosmetic ingredients. Other potential applications of *Macaranga*'s bioactive constituents are also presented. There is no limitation on the year of publication. Exhaustive searches were performed on four electronic databases: PubMed, ScienceDirect, Scopus, and Google Scholar. Various keywords, such as *Macaranga* plant, *Macaranga* genus and species, chemical compounds of *Macaranga*, bioactivity of *Macaranga*, anti-inflammatory activity, antioxidant activity, antimicrobial activity, and antityrosinase activity, were employed to find appropriate data and articles.

Bioactive constituents of *Macaranga* plants

An earlier work summarized the chemical investigations of 25 species of *Macaranga* (Magadula, 2014). In this study, the phytochemical characterization has been updated to include 40 species. They are identified as *M. adenantha, M. allorobinsonii, M. alnifolia*, *M. balansae, M. barteri, M. bicolour, M. conglomerata, M. conifera, M. constricta, M. deheiculata, M. denticulata, M. gigantea, M. gigantifolia, M. hemsleyana, M. heynei, M. hosei, M. hurifolia, M. hypoleuca, M. indica, M. javanica, M. kurzii, M. lowii, M. magna, M. mappa, M. monandra, M. peltata, M. pleiostemona, M. pruinosa, M. pustulata, M. recurvata, M. rhizinoides, M. rubiginosa, M. sampsonii, M. schweinfurthii, M. siamensis, M. sinensis, M. tanarius, M. trichocarpa, M. triloba, and M. vedeliana*. This list reveals, however, that only a small percentage of species (less than 15%) have been further chemically investigated, despite the fact that there are more than 300 species of *Macaranga* available in the world.

Each plant species is distinctive regarding its bioactive constituents. Based on the previous study by Mai *et al*. (2020), it has been discovered that some *Macaranga* species are rich in phenolic compounds, particularly flavonoid and stilbene derivatives. Yang *et al*. (2015a, 2015b) reported the presence of two novel stilbenes, denticulatains A and B, and flavonoid derivatives, including denticulatain C, D, and E from *M. denticulata* fronds. C-methylated and isoprenylated chalcone derivatives, dentichalcones A, B, and C, were also discovered in related species. According to Pailee *et al*. (2015), macasiamenenes A-U, macasiamenin A, macasiamenone A, and macasiamenols A and B, were isolated from *M. siamensis* leaves and twigs. Furthermore, secondary metabolites in the class of tannins, terpenes, coumarins, steroids, and many other compounds were also detected. The most prevalent of these is scopoletin, a coumarins that is present in six different species of *Macaranga*: *M. barteri, M. conglomerata*, *M. denticulata, M. kurzii, M. magna, and M. triloba*. The number of compounds isolated from *M. tanarius* has been reported as the highest, with 98 compounds collected from its leaves, stem bark, and fruits. Mostly, the compounds in *Macaranga* are stilbenes and flavonoids, as shown in Figure 1. A list of all summarized constituents is presented in Table 1.

Application of *Macaranga* in cosmetics

Anti-inflammatory activity

Inflammation is the response of body to any kind of disturbance caused by irritation, injury, or bacteria. Anti-inflammatory products work by blocking the body response to this skin disorder by inhibiting the effects of certain enzymes that contribute to swelling and inflammation (Attiq *et al*., 2018). In terms of both skin appearance and health, dealing with inflammation is a major issue. Preventing the impact of skin inflammation is essential for a youthful appearance and avoiding the development of chronic or acute skin diseases

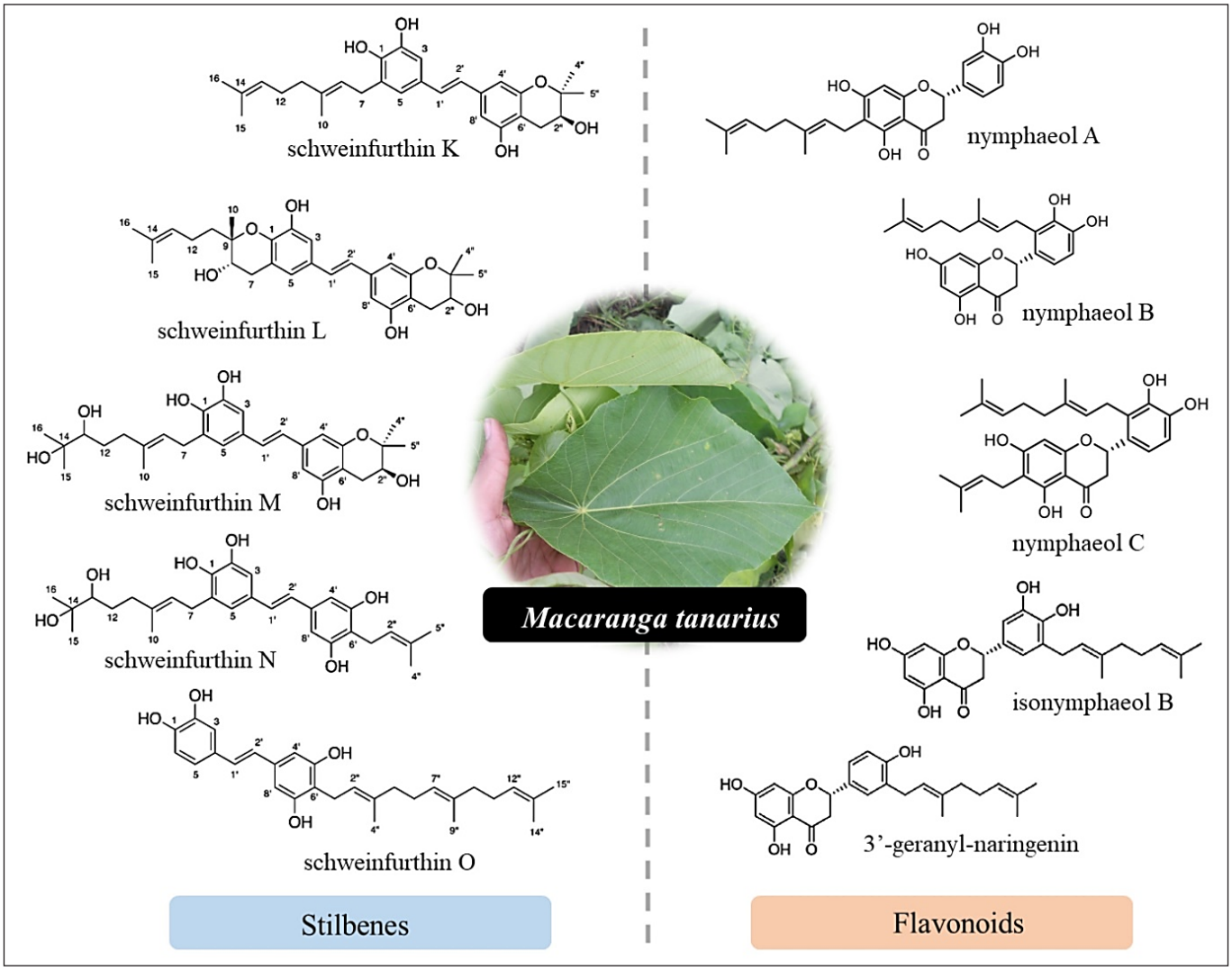

Figure 1. Structure of several stilbenes and flavonoid derivatives isolated from *Macaranga tanarius.*

(Hoang *et al*., 2021). In general, anti-inflammatory skincare products contain antioxidants, which help the body fight damaging free radicals. Antioxidants prevent collagen breakdown and skin DNA damage (Lin *et al*., 2018).

An earlier study found that dichloromethane extracts of *M. siamensis* leaves and twigs had a strong anti-inflammatory effect, with Macasiamenene F isolated from these extracts reducing tumor necrosis factor (TNF) alpha by 20% after 24 hours (Leláková *et al*., 2020). *M. barteri* methanol extract had a strong anti-inflammatory effect with potential compounds such as macabarterin, 3-O-methylellagic acid, 4-O-b-D-xylopyranoside, ellagic acid, 3-O-methylellagic acid, and gallic acid (Ngoumfo *et al*., 2008). Moreover, an assay on rats with carrageenan-induced edema showed that hydroalcoholic *M. barteri* bark extract reduced inflammation and skin hyperalgesia. This report also confirmed the traditional application of *M. barteri*'s bark to treat pain and inflammation, acting as an analgesic (Asante-Kwatia *et al*., 2019). *M. tanarius* demonstrated high inhibition of protein (albumin) denaturation with IC_{50} values of 0.26–1.02 mm with some bioactive compounds such as nymphaeol A, nymphaeol B, nymphaeol C, isonymphaeol B, and 3'-geranyl-naringenin (Shahinozzaman *et al*., 2021). Nymphaeol B of this species strongly inhibits acetylcholinesterase (Ache) at 50 µg/ml (Amir Rawa *et al*., 2022). Another study reported that *M. hurifolia* extract from Nigeria has an inflammatory effect (69.6%) at a dose of 300 mg/kg (Segun *et al*., 2019a).

Antioxidant activity

Natural antioxidants are used in the cosmetics industry for their capacity to reduce oxidative stress on the skin and protect products from oxidative deterioration (He *et al*., 2021; Hoang *et al*., 2021). Due to the natural aging process as well as extrinsic causes including UV radiation, air pollution, and pathogenic microorganisms, oxidative stress is the main factor accelerating skin aging (Farage *et al*., 2008; Rees, 2004). Antioxidant molecules prevent radical chain reactions, which inhibit reactive oxidants' formation; as a result, they can also be used to cure cancer. In cosmetic products, including serums and creams, antioxidants can be employed to stabilize ingredients and prevent the rancidity of

Table 1. Current status of Bioactive Compounds Isolated from *Macaranga* species.

No.	Plant species	Location	Plant part	Constituents	Sources
1	*M. adenantha*	China	Twigs	Macadenanthin A, macadenanthin B, macadenanthin C, glyasperin A, broussoflavonol F, and macarangin	Yang *et al*. (2015c)
2	*M. allorobinsonii*	Indonesia	Leaves	Gallic acid, and methyl gallate	Darmawan *et al*. (2012)
3	*M. alnifolia*	Madagascar	Fruit	Alnifoliol, bonanniol A, diplacol, bonnanione A, and nymphaeol A	Yoder *et al*. (2007)
			Leaves	schweinfurthin E, schweinfurthin F, schweinfurthin G, and schweinfurthin H	
4	*M. balansae*	Vietnam	Fruit	4'-methyl-8-prenyltaxifolin, 6,8-diprenyl-4 -methyl-naringenin, and 4' -deprenyl-4-methoxymappain	Mai *et al*. (2020)
5	*M. barteri*	Cameroon	Stem bark	Macabarterin, scopoletin, 3-O-methylellagic acid 4-O-β-D-xylopyranoside, Ellagic acid, 3-O-Methylellagic acid, Gallic acid, and Methyl gallate	Ngoumfo *et al*. (2008)
		Nigeria	Leaves	Benzamide, 2,2-Bis(4-nitrobenzyl)-1-phenylbutane-1,3-dione, 2-Acetophenone, 1,2,3-Trimethylbenzene, 1,2-Diacetoxypropane, 3-Hydroxy-1-phenyl-4-hexen-1-one, Methyl vinyl carbinol, 2-Isobutyl-3-methylfuran, acetyl tetrahydrofuran, isopropenyl dodecanoate, 2-hydroxy-2-methyl propanoic acid, undecane, Caryophyllene, aromadendrene, a-humulene, 3-Hydroxy-4(3H)-quinolinone, Caryophylla-2,6-dien-5-one, Germacrene B, Germacrene D, nerolidol, Spathulenol, tetradecane, b-elemene, N-acetylbenzamide, a-Linalool-2-penten-4-one, Caryophyllene oxide, N-phenylacrylamide, 2,12-Epoxycaryophyll-5-ene, 4-Methyl-1,3-oxathiolane, Methyl ethynyl carbinol, n-octadecane, Neophytadiene, Citronellyl propionate, trans-Phytol, 4-Methylpentanoic acid, n-Hexadecanoic acid, 2-Hexyl-2-decenal, Ethyl ester hexadecanoic acid, n-docosane, Citronellyl butyrate, cyclodecene, 2,5,8-Heptadecatrien-1-ol, dodecanedialdehyde, 9,12,15-Octadecatrien-1-ol, Ethyl Hept-6-enoate, 2-Keto-butyric-acid, Pentadecanal, 1-Aza-4-thiapentane, 2-Ethoxycarbonyloxy-1-phenyl-2-nonene, mappain, vedelianin, schweinfurthin G, macabartebene A, macabartebene B, and macabartebene C	Ogundajo *et al*. (2017); Segun *et al*. (2019a); Segun *et al*. (2021)
6	*M. bicolour*	Philippines	Leaves	(2S)-5,7-dihydroxy-4'-methoxy-8-(3''-methylbut-2''-enyl) flavanone, (2S)-5,7,4'-trihydroxy-8-(3''-methylbut-2''-enyl) flavanone, and (2S)-5,7,4'-trihydroxy-8-(3'',8''-dimethylocta-2'',7''-dienyl) flavanone	Versian *et al*. (2011)
7	*M. conglomerata*	Kenya	Leaves	Conglomeratin, macarangin, quercetin, 3,3',4' -trimethoxyellagic acid, and 3,3' -dimethoxy ellagic acid	Hashim *et al*. (2022)
			Stem bark	3-acetylaleuritolic acid, 2a-hydroxyaleuritolic acid-3-p-hydroxybenzoate, and scopoletin	
8	*M. conifera*	Indonesia and China	Leaves	5-Hydroxy-4'-methoxy-2",2"-dimethylpyrano-(7,8:6",5") flavanone, 5,4'-Dihydroxy-[2"-(1-hydroxy-1-methylethyl) dihydrofurano]-(7,8:5",4")flavanone, 5,7-Dihydroxy-4'-methoxy-8-(3-methylbut-2-enyl) flavanone, Lonchocarpol A, sophoraflavanone B, 5,7-Dihydroxy-4'-methoxy-8-(2-hydroxy-3-methylbut-3-enyl) flavanone, tomentosanol D, lupinifolinol, isolicoflavonol, (2S)-5,7,3'-trihydroxy-4'-methoxy-8-(3''-methylbut-2''-enyl) flavanone, (2S)-5,7,3',5'-tetrahydroxy-6,8-(3'',8''-dimethylobut-2'',7''-dienyl) flavanone, and 20-epibryonolic acid	Jang *et al*. (2004); Versian *et al*. (2011)
9	*M. constricta*	Malaysia	Leaves	Taraxerone, taraxerol, and β-amyrin	Salleh *et al*. (2017)
10	*M. deheiculata*	China	Fronds	Deheiculatin A, Deheiculatin B, Deheiculatin C, Deheiculatin D, Deheiculatin E, Deheiculatin F, Deheiculatin G, Deheiculatin H, Deheiculatin I, Deheiculatin J, Deheiculatin K, and Deheiculatin L	Qi *et al*. (2017)

Continued

No.	Plant species	Location	Plant part	Constituents	Sources
11	*M. denticulata*	Vietnam	Fruit	6-(8"-hydroxy-3",8"-trimethyl-oct-2"-enyl)-kaempferol, 3'-dehydroxy-solophenol C, denticulatain D, bonannione A, diplacol, macarangin, 3-O-methylmacarangin, 5,7,3',4'-tetrahydroxy-3-methoxy-6-geranylflavone, 3,5,7,3',4'-pentahydroxy-6-geranylflavonol, macarhizinoidin A, robipseudin A, denticulatain E, 8-dimethylallylisosakuranetin, 4'-deprenylmappain, deheiculatin H, poilaneic acid, derivative phaseic acid, taraxerone, and epitaraxerol	Le *et al*. (2021)
		China	Fronds	Denticulatains A, Denticulatains B, Denticulatain C, Denticulatain D, Denticulatain E, 5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-6-(3-methylbut-2 enyl) chroman-4-one, sophoraflavanone A, bonanniol A, diplacol, 5,7,3′,4′-tetrahydroxy 6-geranylflavonol, 5,7,3′,4′-tetrahydroxy-3-methoxy-6-geranylflavone, 3β-hydroxy-7α-e, thoxy-24β-ethylcholest 5-ene, (24R)-6β-hydroxy-24-ethylcholest-4-en-3-one, epitaraxerol, α-tocopherolquinone, boehmenan, dentichalcones A, dentichalcones C, dentichalcones C, (2E)-1-(5,7-dihydroxy-2,2,6-trimethyl-2H-benzopyran-8-yl)-3-(4-methoxyphenyl)-2-propen-1-one, (2E)-1-(5,7-dihydroxy-2,2-dimethyl-2H-benzopyran-8-yl)-3-phenyl-2-propen-1-one, laxichalcone, macarangin, bonanniol A, bonannione A, and cirsitakaoside	Yang *et al*. (2015a); Yang *et al*. (2015b); Zhang *et al*. (2016); Di *et al*. (2020)
		Thailand	Leaves	Macdentichalcone, scopoletin, macarangin, 3-O-methyl-macarangin, denticulaflavonol, sophoraflavanone B	Sutthivaiyakit (2002); Lei *et al*. (2016)
12	*M. gigantea*	Indonesia	Leaves	Macagigantin, Glyasperin A, and Apigenin	Tanjung *et al*. (2009)
13	*M. gigantifolia*	Indonesia	Leaves	5,7-dihydroxycoumarin	Darmawan *et al*. (2012)
14	*M. hemsleyana*	China	Stem bark	3β-O-acetyl aleuritolic acid, canophyllol, β-Sitosterol, Stigmast-4-en-3-one, and Stigmast-4-en-3,6-dione	Wang *et al*. (2008)
15	*M. heynei*	Malaysia	Leaves	Laevifolins A, laevifolins B, Malayheyneiin A, Malayheyneiin B, Malayheyneiin C, Malayheyneiin D, laevifolin A, laevifolin B, macarubiginosin C, eserine, and Trolox	Kamarozaman *et al*. (2018, 2019)
16	*M. hosei*	Malaysia and Indonesia	Leaves	Lupenone, β-sitostenone, 5-hydroxy-7,4'-dimethoxyflavone, 5-hydroxy-6,7,4'-trimethoxyflavone, 4′-O-methyl-8-isoprenyl eriodictyol, and 6-isoprenyl eriodictyol	Salleh *et al*. (2017); Marliana *et al*. (2018a)
17	*M. hurifolia*	Cameroon	Fruit	Macafolias A and macafolias B	Pagna *et al*. (2022)
18	*M. hypoleuca*	Indonesia	Leaves	Dibromo chloropropane, levoglucosan, 2-metoksi-5-propeny, guanosine, Limonene, Lacton acid, trans-5,6-Epoksidekan, d-Nerolidol, n-pentacosane, 1-Siklo leikosan, terakseron, squalene, Alpha-Beta-D-mannoside, and pentatriacontane	Gusmailina and Saputra (2021)
			Sap	Terakseron and Alpha-Beta-D-mannoside	
			Stem	2-propenal, isoeugenol, 1-(4-Hidroksi-3-MET), 4-Metil-2,5-Dimetoksibenzaldehid, Asam homovanillic, acetosyringone, and guaiacol	
			Stem bark	3-(p-hidroksi-m-metoksifenil)-2-propenal, phenol, 3-allyl-2-metoksi-, Eugenol, 2-Propanon 1-(4-hidroksi), dimethoxybenzaldehyde, guanosine, Dekanon, and Sikloheksileikosan	
19	*M. indica*	India and Vietnam	Leaves	Macaflavone I, Macaflavone II, macarindicins I, macarindicins II, macarindicins III, macarindicins IV, broussoflavonol F, vedelianin, schweinfurthin E, vitexin, 2"-rhamnosyl vitexin, isovitexin, (6R,7E,9R)-9-hydroxy-megastigman-4,7-dien-3-one-9-O-b-D-glucopyranoside, (6S,9R)-roseoside, (6S,9S)-roseoside, bridelionoside B, macarindicins D, macarindicins E, macarindicins F, macadenathin B, glyasperin A, kaempferol, quercetin, quercitrin, (+)-isolariciresinol, (–)-woonenoside XI, and (+)-lyoniresinol 4-O-β-D-glucopyranoside	Sultana and Ilyas (1986); Vu *et al*. (2021); Huonga *et al*. (2019)

Continued

No.	Plant species	Location	Plant part	Constituents	Sources
		China	Twigs	Macarindicins A, macarindicins B, macarindicins C, 6-Farnesyl-3',4',5,7-tetrahydroxyflavanone, isolicoflavonol, glyasperin A, broussoflavonol F, broussonol D, macarangin, and ellagic acid	Yang *et al*. (2015b)
20	*M. javanica*	Indonesia	Leaves	Macajavanicin A, Macajavanicin B, Macajavanicin C, laevifolins A, and laevifolins B	Ilmiawati *et al*. (2015)
21	*M. kurzii*	China	Twig	Kurzphenol A, kurzphenol B, kurzphenol C, 3,5-dihydroxy-4-(3-methyl-2-butenyl)bibenzyl, 6,8-diprenylgalangin, licoflavonol, icaritin, 3,4′-di-O-methyl-8-(3-methyl-2-butenyl) kaempferol, 5,7-dihydroxy-6,8-diprenylflavanone, isosakuranetin, 8-prenylnaringenin, glepidotin B, atractylodin, acetylatractylodinol, blumenol A, scopoletin, and salicylic acid	Yang *et al*. (2014)
		Vietnam	Leaves	Macakurzin A, Macakurzin B, Macakurzin C, 5,7-dihydroxy-6-prenylflavanone, Glabranin, Izalpinin, Glepidotin A, 8-Prenylgalangin, Galangin, furanokurzin, Cis-3,5-dimethoxystilbene, Trans-3,5-dimethoxystilbene, and Trans-3,5-dimethoxy-2-prenylstilbene	Thanh *et al*. (2012)
22	*M. lowii*	Indonesia	Leaves	macalowiinin, 4'-O-methyl-8-isoprenylnaringenin, 4'-O-methyl-5,7,4'-trihydroxyflavone	Agustina *et al*. (2012)
23	*M. magna*	Indonesia	Leaves	scopoletin, apigenin, and gallic acid	Minarti *et al*. (2021)
24	*M. mappa*	Hawaii	Leaves	Mappain	Van Der Kaaden *et al*. (2001)
25	*M. monandra*	Cameroon	Stem bark	Kolavenic acid and 2-Oxo-kolavenic acid	Salah *et al*. (2003)
26	*M. peltata*	India	Stem bark	β-Sitosterol, bergenin, 8,10-di-O-methylether, and Tri-O-methyl ether	Ramaiah *et al*. (1979)
27	*M. pleiostemona*	Papua New Guinea	Leaves	*Macaranga* flavanone A, *Macaranga* flavanone B, euchrestaflavanone A, and Bonannione A	Schutz *et al*. (1995)
28	*M. pruinosa*	Indonesia	Leaves	Macapruinosin B, Macapruinosin C, Papyriflavonol A, nymphaeol C, Macapruinosin D, Macapruinosin E, Macapruinosin F, and Macapruinosin A	Syah and Ghisalberti (2015)
29	*M. pustulata*	China	Twig	Deheiculatins M, deheiculatins N, deheiculatins O, deheiculatin I, deheiculatin C, deheiculatin B, poilaneic acid, and 20-hydroxy entcembrene	Syah and Ghisalberti (2015)
30	*M. recurvata*	Indonesia	Leaves	Macarecurvatin A, macarecurvatin B, Di isoprenyl aromadendrin, Glyasperin A, broussoflavonol F, flavestin K, flavestin B, flavestin G, 4-O-methyl-8-isoprenylnaringenin, and 8-isoprenyl-5,7-dihydroxyflavanone	Tanjung *et al*. (2012); Tjahjandarie *et al*. (2019)
31	*M. rhizinoides*	Indonesia	Leaves	Macarhizinoidin A, Macarhizinoidin B, and Methyl 4-isoprenyloxycinnamate	Tanjung *et al*. (2012)
32	*M. rubiginosa*	Indonesia	Leaves	Laevifolins A, laevifolins B, macarubiginosins A, macarubiginosins B, and macarubiginosins C	Tanjung *et al*. (2017)
33	*M. sampsonii*	China	Leaves	Macaranone A, macaranone B, macaranone C, and macaranone D	Li *et al*. (2009)
34	*M. schweinfurthii*	Cameroon	Leaves	Schweinfurthin A, schweinfurthin B, schweinfurthin C, schweinfurthin I, and schweinfurthin J	Beutler *et al*. (1998); Klausmeyer *et al*. (2010)
35	*M. siamensis*	Thailand	Fronds	Macasiamenenes A, macasiamenenes B, macasiamenenes C, macasiamenenes D, macasiamenenes E, macasiamenenes F, macasiamenenes G, macasiamenenes H, macasiamenenes I, macasiamenenes J, macasiamenenes K, macasiamenenes L, macasiamenenes M, macasiamenenes N, macasiamenenes O, macasiamenenes P, macasiamenenes Q, macasiamenenes R, macasiamenenes S, macasiamenenes T, macasiamenenes U, macasiamenin A, macasiamenone A, macasiamenols A, and macasiamenols B	Pailee *et al*. (2015)
36	*M. sinensis*	China	Leaves	3-Desgalloyterchebin, macaranin A, Macaranin B, Macaranin C, Macarinin A, macarinin B, Macarinin C, tergallic acid bislactone, 3,6-O-(R)-hexahydroxydiphenoyl (HHDP)-D-glucose, tercatain, mallorepanin, putranjivain A, and chlorogenic acid	Lin *et al*. (1990)

Continued

No.	Plant species	Location	Plant part	Constituents	Sources
37	*M. tanarius*	Taiwan, Thailand, Japan, Indonesia, China, and Malaysia	Leaves	Tanariflavanone A, tanariflavanone B, (-)-nymphaeol C, tanariflavanone C, Tanariflavanone D, nymphaeol A, nymphaeol B, nymphaeol C, Macaflavanone A, macaflavanone B, macaflavanone C, macaflavanone D, Macaflavanone E, Macaflavanone F, Macaflavanone G, Mallotinic acid, Corilagin, macatannin A, Macatannin B, Chebulagic acid, 1(β)-O-galloyglucose, 4-O-galloyglucose, 6-O-galloyglucose, 2,3-di- O-galloyglucose, 1(β),2,6-tri-O-galloyglucose, 2,4,6-tri-O-galloyglucose, 1(β),3,4,6-tetra-O-galloyglucose, 1(β),2,3,4,6-penta-O-galloyglucose, 1(β),2,4,6-tetra-O-galloyglucose, 3-O-galloyl-(-)-shikimic acid, 5-O-galloyl-(-)-shikimic acid, 4-O-galloyquinic acid, 3,4-di-O-galloyquinic acid, 3,6-(S)-hexahydroxydiphenoyl (HHDP)-D-glucopyranose, punicafolin, furosin, terchebin, geraniin, mallotusinic acid, repandusinic acid A, 1,4-di-O-galloyl-α-D-glucopyranose, 3,4-di-O-galloyl-D-glucopyranose, galloylpunicafolin, galloylgeraniin, 1-O-galloyl-3-O-brevifolincarboxyl-β-D-glucopyranose, macaranganin, tanarinin, (+)-pinoresinol 4-O-[6''-O-galloyl]-β-D-glucopyranoside, macarangioside E, Macarangioside F, mallophenol B, Macarangioside A, Macarangioside B, Macarangioside C, Macarangioside D, lauroside E, Methyl brevifolin carboxylate, Macarangiosides A, Macarangiosides B, macarangiosides C, macarangiosides D, macarangiosides E, macarangiosides F, macarangiosides A, macarangiosides B, macarangiosides C, macarangiosides D, macarangiosides E, and macarangiosides F	Tseng *et al.* (2001); Phormmart *et al.* (2005); Kawakami *et al.* (2008); Gunawan-Puteri and Kawabata (2010); Lin *et al.* (1990); Matsunami *et al.* (2009); Yoshimura *et al.* (2017); Matsunami and Otsuka (2018); Marliana *et al.* (2018b); Rawa *et al.* (2022)
		Hong Kong	Stem bark	macarangonol, kolavenol, blumenol A, blumenol B, annuionone E, and lathyrane	Hui *et al.* (1971)
		Vietnam and Japan	Fruit	Vedelianin, schweinfurthins E, schweinfurthins F, schweinfurthins G, schweinfurthins K, schweinfurthins L, schweinfurthins M, schweinfurthins N, schweinfurthins O, schweinfurthins P, schweinfurthins Q, mappain, methyl-mappain, nymphaeol B, isonymphaeol B, nymphaeol A, 3'-geranyl-naringenin, nymphaeol C, propolin C, propolin D, propolin F, propolin G, propolin H	Peresse *et al.* (2017); Huong *et al.* (2020); Kumazawa *et al.* (2014); Nam *et al.* (2021); Natsume *et al.* (2021); Lee *et al.* (2019)
38	*M. trichocarpa*	Indonesia	Leaves	Macatrichocarpin A, macatrichocarpin B, macatrichocarpin C, macatrichocarpin D, 4′-O-methylmacagigantin, macatrichocarpin F, macatrichocarpin G, Macatrichocarpin H, licoflavanon, flavokawain C, and helichrysetin	Syah and Ghisalberti (2010); Tanjung *et al.* (2018)
		Indonesia and Vietnam	Leaves	3,7,3'4'-tetramethylquercetin, 3,7,3'-trimethylquercetin, 3,7-dimethylquercetin, 2'-hydroxy-macarangaflavanone A, 4',7-hydroxy-8-methylflavan, scopoletin, 3-epi-taraxerol, and Taraxerol	Jang *et al.* (2004); Dinh *et al.* (2006)
39	*M. triloba*	Malaysia	Flowers	6-Prenyl-3'-methoxy-eriodictyol, nymphaeol B, nymphaeol C, 6-Farnesyl-3',4',5,7-tetrahydroxyflavanone, 4,5-dihydro-5'α-hydroxy-4'α-methoxy-6a,12a-dehydro-α-toxicaro, (+)-Clovan-2β,9α-diol, Ferulic acid, abscisic acid, 1β,6α-dihydroxy-4(15)-eudesmene, 3β-hydroxy-24-ethylcholest-5-en-7-one, loliolide, tanarifuranonol, 5,7-dihydroxycoumarin, and malaysianone A	Zakaria *et al.* (2010, 2012)
40	*M. vedeliana*	New Caledonia	Leaves	Macarangin	Hnawia *et al.* (1990)

lipids (Leopoldini *et al*., 2011). Antioxidants inhibit lipid oxidation by reacting with lipids and peroxy radicals and converting them into more stable nonradical products (Lin *et al*., 2018; Petruk *et al*., 2018). Furthermore, antioxidants also help in overcoming inflammation.

Ogundajo and Ashafa (2019) reported that the methanol extract of a popular traditional medicinal plant in west Africa, M. barteri, demonstrated a high antiradical effect against 1,1-diphenyl-2-picrylhydrazyl (DPPH) and nitric oxide (NO) with values of 0.47 and 1.68 mg/ml, respectively. M. tanarius fruit extracts exhibited strong antioxidant activity due to the presence of prenylflavonoids in the seed, pericarp, glandular trichome, and leaf (Kumazawa *et al*., 2014; Kumazawa *et al*., 2008). Chien *et al*. (2022) also reported that M. tanarius new and mature fruit extracts exhibited stronger free radical-scavenging activity and possessed lower IC50 than Taiwanese green propolis extract. Ethyl acetate extract of M. triloba leaves from Central Kalimantan, Indonesia, exhibited a strong ability to neutralize free radicals DPPH (Ardany *et al*., 2018). Kamarozaman *et al*. (2019) reported that new dihydrostilbenes isolated from M. heynei showed some antioxidant activity.

Antimicrobial activity

In cosmetic goods, antimicrobial compounds are used to both inhibit the growth of unfavorable microorganisms in skincare products and increase the shelf life of products (Nowak *et al*., 2021). The skin is the largest organ in the body, and it is exposed to the environment, making it an ideal location for bacteria, viruses, or fungi to grow. In order to protect consumers and stabilize shelf life, especially against potentially harmful bacteria, the formulation of cosmetic products (water based *vs.* oil based) has considered multifunctional antimicrobial ingredients (Hoang *et al*., 2021). This is in line with rising consumer awareness and demands for clean beauty and avoiding artificial ingredients, especially preservatives. It is realized that the use of conventional antimicrobial agents, which are usually loaded with preservatives, has disturbed the balance of skin microflora, so the skin is vulnerable to exposure to harmful microorganisms (Nowak *et al*., 2021).

Methanolic extract of *M. barteri* leaves grown in Nigeria has been reported to inhibit *Pseudomonas aeruginosa*, *Enterococci faecalis,* and *Cryptococcus neoformans* (>80% inhibition (Ogbole *et al*., 2018). Purayil *et al*. (2019) used a combination solvent, chloroform and water (1:10), to extract from the leaves of *M. peltata,* which resulted in a clearance zone of the well diffusion method against *Staphylococcus aureus*. Panda *et al*. (2017) tested acetone, water, and ethanol solvents to extract from *M. peltata* leaves, which had antimicrobial activity against *Escherichia coli*, *S. aureus*, and *Candida albicans*. As described in another report, both the leaves and stem bark of *M. peltata* also had positive activity against four bacterial strains: *E. coli*, *P. aeruginosa*, *Bacillus subtilis*, and *S. aureus* (Verma *et al*., 2009).

Bradacs *et al*. (2010) reported that the inner bark extract of *Macaranga dioica,* commonly used as traditional medicine in the South Pacific Archipelago of Vanuatu, exhibited moderate activity against *C. albicans*. Ogundajo *et al*. (2017) extracted hexane, ethyl acetate, and methanol from *M. barteri* leaves. They found that methanolic extract had the best antibacterial activity against *S. aureus*, *Bacillus pumilus*, *Streptococcus faecalis*, *Listeria* sp., *P. aeruginosa*, *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Shigella sonnei*, *Salmonella typhi*, *Salmonella typhimurium*, *E. coli*, *Proteus vulgaris*, *Proteus vulgaris*, *Enterobacter faecalis*, and *Klebsiella pneumoniae*. The authors also discovered that a hexane extract of the plant was effective against fungi such as *Candida neoformans*, *Trichophyton mucoides*, and *Candida albicans*. Lee *et al*. (2019) isolated five propolins from *M. tanarius*. Among them, propolin D showed the highest inhibition of biofilm formation by strains of *S. aureus*, *Staphylococcus epidermidis*, and *C. albicans,* with MICs of 10–50 µg/ml. Isolated prenylated kaempferol and conglomeratin, from *M. conglomerata,* reportedly showed significant permeation of *P. aeruginosa* (MIC = 7.8 mg/ml) and moderate activity against *S. aureus*, *E. coli*, and *Klebsiella pneumoniae* (MIC = 62.5 mg/ml) (Hashim *et al*., 2022).

Tyrosinase inhibitory effect

Antimelanogenesis activity is one of the most important criteria for determining the suitability of plant compounds for use in skincare agents. It was previously reported by Arung *et al*. (2019) that they isolated glyasperin A, a prenylated flavonoid isolated from *M. pruinosa* that greatly inhibited melanin in B16 melanoma. Another report from Mazlan *et al*. (2013) demonstrated that they had extracted *M. denticulata, M. pruinosa*, and *M. gigantea* using methanol to assess their tyrosinase inhibitory activity. Among them, methanolic extract of *M. denticulata* bark showed the highest inhibition (68.7%). Methanol extract from the leaves and stem bark of *M. hurifolia* has been tested to show their application in tyrosinase inhibition, in which they found appropriate activity with values of 159.42 [mg Kojic acid equivalent (KAE)/g] and 160.95 (mg KAE/g), respectively (Sadeer *et al*., 2019). Lim *et al*. (2009) screened the bioactivity of methanolic extracts of *M. gigantea*, *M. pruinosa*, *M. tanarius*, and *M. triloba*, which resulted in the best tyrosinase inhibition activity obtained by *M. pruinosa* among all the *Macaranga* tested. KAE values and quercetin equivalent were 6.8 and 20.7 mg/g, respectively.

Limitations of natural ingredient in cosmetics

Macaranga extract contains antioxidant, anti-inflammatory, and antimicrobial compounds. Some of these compounds have potential as topical cosmetic preparations. However, it is acknowledged that not all of these natural ingredients are safe because they may be associated with carcinogenic, mutagenic, and reprotoxic chemicals (Hoang *et al*., 2021). As a result, their application as skincare products that protect the integrity of cosmetics and the skin at the same time must be considered wisely. Furthermore, despite their promising effects, validation with clinical results is required. Due to a lack of clinical data and the limited relevance of data, some of the practical significance of the effects mentioned has not been adequately proven. However, these data provide interesting points for dermatologists to consider in the application of natural ingredients in relation to topical therapies (Hoang *et al*., 2021).

Although uncommon, skin contact with cosmetics containing plant extracts can result in allergic responses, contact dermatitis, erythema multiforme, and xanthomatous reactions (Hoang *et al*., 2021). It is possible, due to the lack of separation techniques, that many plant extracts have not been investigated for their compounds (Zorzi *et al*., 2016). Antioxidants may also have a variety of adverse effects, including acute toxicity, skin and eye irritation, skin sensitization, and photosensitization (Hoang *et al*., 2021; Mujtaba *et al*., 2021). In light of this, the application of natural ingredients requires that they are applied in safe concentrations; for instance, the application of essential oils is only recommended at 0.1–0.8%, or diluting with carrier oils (Guzmán and Lucia, 2021; Vostinaru *et al*., 2020). The use of some natural extracts, such as polyphenols, in cosmetics is constrained due to their low stability and sensitivity to heat and light (Hoang *et al*., 2021). Due to this condition, some cosmetic products that contain furocoumarins, compounds that are also present in *Macaranga* extract, should only be applied at night. Sun exposure has phototoxicity effects, causing skin damage.

Natural antioxidants are susceptible to deterioration, and their bioavailability is limited by low absorption. The use of active phytomolecules with the application of nanotechnology in cosmetics has drawn a lot of attention since it can boost absorption by the skin (Salvioni *et al*., 2021). Various types of nanoemulsions, nanoparticles, liposomes, niosomes, and dendrimers have influenced the formulation of cosmetic products (Musthaba *et al*., 2009). According to test results, the application

of nano formulations can minimize hematological toxic effects, boost bioavailability, and lessen other side effects, such as alopecia, nausea, vomiting, diarrhea, exhaustion, and skin rashes (Hoang *et al*., 2021; Saklani and Kutty, 2008; Salvioni *et al*., 2021; Zorzi *et al*., 2016). Recently, major concerns regarding its safety have been raised, and much more exploration is needed to determine its efficacy in delivering active ingredients into the skin. New regulations established by the European Union have passed amendments in its (new regulations) cosmetics directory for safer nanocosmetics to enter the market, safeguarding the beauty and health of consumers (Hoang *et al*., 2021; Musthaba *et al*., 2009). Natural antioxidants are more expensive than synthetic ones in cosmetics, despite the fact that these molecules are safer than synthetic antioxidants.

Other potential uses of *Macaranga* plants

Hendra *et al*. (2017) reported that the extract of *M. tanarius* exhibited positive antihyperlipidemic and hepatoprotective effects. Some active compounds isolated from ethyl acetate extract of *M. tanarius* leaves, i.e., mallotinic acid, corilagin, chebulagic acid, macatannins A and B, can be developed for diabetes treatment agents (Gunawan-Puteri and Kawabata, 2010). Another *Macaranga* species, *M. hurifolia* extract from Nigeria, showed potential for anti-inflammatory and antidiabetic effects (Segun *et al*., 2019b). Ehile *et al*. (2018) reported that the aqueous extract of *M. barteri* exhibited a gastric antiulcer effect at doses ranging from 62.5 to 500 mg/kg b.w. This extract has been reported to be safe for oral medicine due to major toxic anthropometric and hematological effects not being present in tested rats, despite the fact that biochemical and histological studies are needed to ensure safe use of the extract (Ehile *et al*., 2018). Furthermore, as reported earlier, *Macaranga* spp. contains rich prenylated flavonoids (Shahinozzaman *et al*., 2021). These exhibited several potential effects: antivirus activity (Feng *et al*., 2010), antiallergic activity (Quan *et al*., 2008), and larvicidal activity against the fourth-instar larvae of *Aedes albopictus* and *Culex pipiens quinquefasciatus* (Niu *et al*., 2010). Muhaimin *et al*. (2019) reported that ethanolic extract of *M. gigantea* exhibited antiplasmodial activity and can be developed as an alternative agent for controlling malaria. The study also confirmed that M. *denticulata* leaf extract has antinociceptive activity. At doses of 200 and 400 mg/kg, it demonstrated dose-dependent and statistically significant antinociceptive activity in acetic acid and formalin tests. Furthermore, among six major *M. denticulata* compounds, *Macaranga* had the best fitness score of 5.81 with the COX-1 enzyme (Hasanat *et al*., 2017).

CONCLUSIONS

A comprehensive review of the potential of *Macaranga* plants as skincare cosmetics ingredients has been conducted. Macaranga plants contain bioactive compounds which have anti-inflammatory, antioxidant, antibacterial, and tyrosinase inhibitory activity. Therefore, *Macaranga* plants have the potential to be used as skincare cosmetic ingredients.

AUTHORS' CONTRIBUTIONS

Conceptualization is done by E.T.A. and M.T.H.; methodology is carried out by E.T.A., M.T.H., and A.S.P.; investigation is done by E.T.A., I.W.K., H.K., R.A., and E.R.; writing original draft preparation is conducted by M.T.H., I.W.K., H.K., R.A., E.R., Y.Y., W.S., S.P., R.R., D.T., M.I., H.A.A., W.F., A.A., C.R.K., N.I.W.A., Y.K., and E.T.A.; writing review and editing is done by E.T.A., W.F., D.T., and H.A.A.; visualization is carried out by M.T.H., D.T., W.D., H.A.A., and E.T.A.; project administration is done by E.T.A. and W.F.; funding acquisition is done by E.T.A. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no relevant financial or nonfinancial interests to disclose.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this review article.

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