

MALAYSIAN HERBS IN SKIN AGING AND HYPERPIGMENTATION

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ABSTRACT

In the beauty and wellness industries, the association between herbs, skin aging, hyperpigmentation, and cosmeceuticals is gaining significance. The process of skin aging occurs in the epidermal and dermal layers and is primarily associated with the deterioration of the extracellular matrix (ECM). Deterioration of ECM can be due to increased matrix metalloproteinases (MMPs) or decreased transforming growth factor- β (TGF- β). Along with some pigment defects such as hypo or hyperpigmentation, this process can cause skin wrinkles, roughness, and dryness. There is a need to slow down the ECM degradation and inhibition of melanin formation. Herbs have a high potential due to their various biologically active compounds. Malaysia is one of the countries rich in tropical rainforests with its traditional medicinal herbs. However, the use of Malaysian herbs in skin aging and hyperpigmentation is still limited. Thus, this review focuses on selected Malaysian herbs that are traditionally used for various purposes and have potential as anti-aging and anti-hyperpigmentation properties. The information contained in the present review indicates that selected Malaysian herbs can be used in the treatment of skin aging and hyperpigmentation and will assist the cosmetics sectors in the development of herbal anti-aging and anti-hyperpigmentation formulations.

Key words: Aging, herbs, hyperpigmentation, Malaysia

INTRODUCTION

As the famous quote goes ‘Age is an issue of mind over matter. If you don’t mind, it doesn’t matter. However, having said that, aging is an inevitable process that all living organisms have to undergo. The percentage of the population 60 years and above has increased over the years. Currently, 11% of the world’s population is over 60 years of age, with estimates of nearly 22% by 2050, particularly in developing countries (Newgard & Sharpless, 2013). The factors that drive the population aging are improved survival of people at older and younger ages (World Health Organization, 2015). World Health Organization (2015) stated that the underlying changes which tend to occur in all humans to some degree as they age include movement, sensory and cognitive functions, sexuality, immune and skin functions. With age, skin experiences progressive declines resulting from damage caused by physio-

logical processes, environmental factors, particularly sun exposure, and lifestyle that have been shown to promote the development of reactive oxygen species (ROS) and produce oxidative stress (Naidoo & Birch-Machin, 2017).

Of late, the growth of herbal cosmetic products is showing an uptrend due to the current demand and focus on natural products. In recent years, some manufacturers often label their products associated with plant-based or organic ingredients as natural products contain certain amounts of ingredients based on plants and/or organically grown (Belova & Eilks, 2015). World Health Organization has stated that about two-thirds and 50–80% of the population of developed and developing countries use traditional and complementary medicine (TCAM), respectively (Siti *et al.*, 2009). A study by the Ministry of Health found that herbal therapy was the main type of TCAM modality used by the Malaysian populations (Siti *et al.*, 2009). However, there is still a lack of scientific information about the role and application of Malaysian herbs in conditions relating

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to skin aging and hyperpigmentation. Traditional herbs provide fascinating and largely unexplored sources of possible new cosmetic and medicinal products. The trade values of herbal imports and exports in Malaysia recorded in 2014 amounted to US\$ 2077 million and US\$ 441.7 million, respectively with an annual growth rate between 8 to 15% (Zakaria, 2015). The current review article is based on certain salient Malaysian herbs claimed and some proven to have been used in the treatment of skin aging and hyperpigmentation.

By searching some databases such as Google Scholar, Medline, Scopus, PubMed, and PLoS, this review study was prepared using the keywords anti-aging, hyperpigmentation, antioxidant, phytochemical characteristics, *Curcuma longa*, *Andrographis paniculata*, *Ficus deltoidea*, *Cinnamom cassia*, *Clinacanthus nutans*, *Centella asiatica*, and *Morinda citrifolia*. Among these, five herbs that have been identified and proposed for commercialization in the industry by National Key Economic Area include *Clinacanthus nutans*, *Andrographis paniculata*, *Ficus deltoidea*, *Centella asiatica*, and *Morinda citrifolia* (Zakaria, 2016).

Skin aging

Skin aging can be categorized into intrinsic and extrinsic aging. Due to telomere shortening, mitochondrial DNA mutations, oxidative stress, genetic mutations, and strong hormonal changes, intrinsic skin aging can be categorized as normal aging. (Kohl *et al.*, 2011). While extrinsic aging is mainly caused by the exposure of the skin to ultraviolet radiation. Other causes of extrinsic aging are smoking, pollution, and poor diet (Kohl *et al.*, 2011). Aging causes wrinkling, roughness, and dryness of the skin along with certain pigment abnormalities such as hypo or hyperpigmentation (Tobin, 2017).

Molecular pathways show similarities between intrinsic and extrinsic skin aging. Both types of skin aging cause reactive oxygen species, primarily arising from oxidative cell metabolism (Kohl *et al.*, 2011). The process of skin aging occurs in the epidermal and dermal layers and is primarily associated with the deterioration of the extracellular matrix (ECM) (Cole *et al.*, 2018). Matrix metalloproteinases (MMPs) are the enzymes involved in ECM degradation. Due to the impact of ECM degradation by MMPs, the skin loses its tensile strength. These MMPs can be subdivided into several classes, such as collagenase (MMP-1), gelatinase (MMP-2 and MMP-9), stromelysin (MMP-3 and MMP-11), membrane-associated (MMP-17), and recently described MMP-27, respectively (Quan & Fisher, 2015).

In ECM biosynthesis, transforming growth factor- β (TGF- β) plays a core function. It is a cytokine

that promotes collagen production in human dermal fibroblasts (Quan & Fisher, 2015). Natural products that inhibit the MMPs and stimulate the TGF- β production have the potential as an anti-aging agent. Natural products that have antioxidant properties also have the potential to be an anti-photoaging agent since a primary cause of the generation of reactive oxygen species (ROS) in the skin is ultraviolet irradiation.

Hyperpigmentation

Hyperpigmentation is triggered by UV irradiation, female sex hormones, and inflammatory processes with a genetic predisposition (Lee, 2015). Most of the commercially available treatments for hyperpigmentation target tyrosinase. Tyrosinase is a rate-limiting enzyme that transforms tyrosine to melanin (Lee *et al.*, 2016). As skin-lightening agents, tyrosine inhibitors thus play an important role. Other than tyrosinase, oxidative stress also stimulates melanogenesis. Oxidative stress can be triggered by extrinsic and intrinsic factors. Extrinsic factors such as ultraviolet radiation and visible light and intrinsic factors like paracrine regulation of melanocytes influence their response to ultraviolet radiation. A recent study has shown that the antioxidant plays a role as a skin lightening agent as it can downregulate ultraviolet radiation and visible-light-induced hyperpigmentation (Nahhas *et al.*, 2019). In this review, general information about the traditional uses and the potential as an anti-aging and anti-hyperpigmentation of identified Malaysian herbs are reported. The mechanism involved in skin aging and hyperpigmentation is depicted in Figure 1.

Natural herbs

Herbal medicine usage is not only popular among individuals but also primary health care providers in developing countries. The World Health Organization reported that 70 to 80% of the world population relies mainly on herbal sources for their primary medicines (World Health Organization, 2000). Nowadays, the use of herbs is not limited to health or to treat diseases. Cosmetic formulations based on herbs are on the rise as more consumers demand healthier options. Continuous application of synthetic compounds on the skin causes many adverse effects such as skin irritation, allergy, discoloration, rashes along with skin cancer. This review article aims to explore Malaysian herbs that have potential as anti-aging and anti-hyperpigmentation properties.

Labisia pumila

Labisia pumila (*L. pumila*), locally known as Kacip Fatimah, has historically been used by Malay women before and after delivery for generations. A decoction of water from the roots of the entire plant of *L. pumila* is often granted to women who are

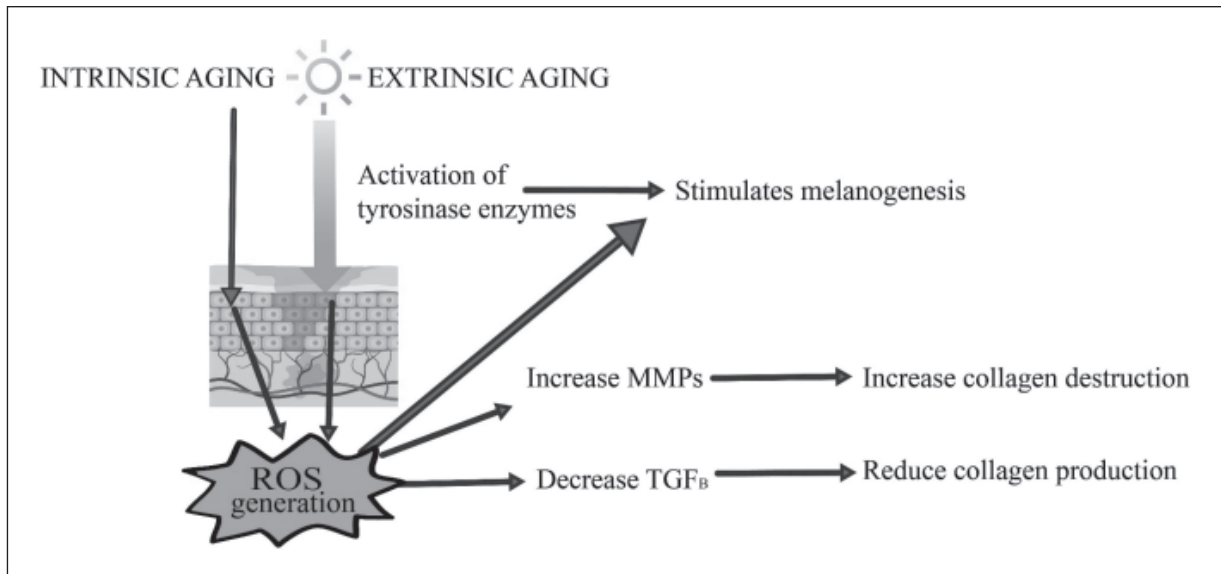


Fig. 1. Mechanism involved in skin aging and hyperpigmentation.

pregnant from one and two months before birth, as this is believed to stimulate and intensify labor. Also, it was mentioned that *L. pumila* can be used after childbirth as it improves uterine contraction, reduces fertility, and restores body strength (Shahrim *et al.*, 2006). Up to now, it has been taken by local individuals to maintain a healthy female reproductive system, treat menstrual abnormalities, and improve sexual function. Other common plant uses include dysentery treatment, rheumatism, gonorrhoea, and removal of gas from the body (Burkill, 1935). A recent study has shown that *L. pumila* has an anti-photoaging effect on the UVB-irradiated skin cells (Choi *et al.*, 2010). The authors found that the water extract of *L. pumila* significantly had an antioxidant effect, decreased the TNF- α level and UVB-induced COX-2 expression, increased pro-collagen type 1 expression, and decreased MMP-1 as well as MMP-9 expression. Although no studies have reported the active compound responsible for the anti-aging properties, previous studies have shown *L. pumila* to be rich in phenolic compounds including phenolic acids and flavonoids (Chua *et al.*, 2011; Karimi & Jaafar, 2011). The anti-aging property might be due to the role of phenolic compounds participating in the antioxidant mechanisms such as scavenging the reactive oxygen species and thus preventing the cells from undergoing oxidative stress. A study by Karimi and Jaafar (2011) found that the leaves of plants showed higher antioxidant activities compared to the roots and stems. The study on its safety in the cosmetic application is still lacking.

***Curcuma longa* L.**

Traditionally in Malaysia, a decoction of the *Curcuma longa* L. (*C. longa* L.) or commonly known

as Kunyit by local people is given to increase blood circulation, relieve abdominal discomfort, remove wind, alleviate muscle and joint pain, and restore body strength (Jamal *et al.*, 2011). Besides that, its other medicinal uses include anthelmintic (Bazh & El-Bahy, 2013), anti-hyperglycemic (Ng & See *et al.*, 2019), neuroprotective (Issuriya *et al.*, 2014), anticancer (Vallianou *et al.*, 2015), and anti-hyperlipidaemic (Maithilikarpagaselvi *et al.*, 2016) effects. A recent study showed that *C. longa* L. had anti-aging properties *in vitro* and *in vivo* (Muta *et al.*, 2018). The authors found that an extract of rhizomes of *C. longa* L. showed an inhibitory effect on gelatinase activity. Furthermore, topical application of a cream containing *C. longa* L. extract improved the elasticity of the facial skin substantially and inhibited the activity of gelatinase in human facial skin. A study of *C. longa* L. showed that its rhizome is rich in curcuminoids, phenolic acids, flavonoids, and iron (Pal *et al.*, 2020). Curcuminoids are known to have anti-wrinkle properties by inhibiting induction of UV-B in keratinocytes and induction of TNF- α in fibroblasts (Jang *et al.*, 2012). The authors found that curcuminoids including desmethoxycurcumin and bisdemethoxycurcumin inhibited UV-B-induced NF- κ B activation in keratinocytes and reduced the expression of MMP-1 in both keratinocytes and fibroblasts. On top of that, *C. longa* L. showed anti-tyrosinase activity (Tamfu *et al.*, 2020), thus having the potential as a skin lightening agent. However, it may cause an adverse effect. Curcumin, the main ingredient in turmeric has been reported to cause contact dermatitis (Chaudhari *et al.*, 2015). Thus, people who have hypersensitivity to turmeric should avoid this herb.

Table 1. Malaysian herbs and their bioactive compounds and mechanisms of anti-aging and anti-hyperpigmentation properties

Species	Local name	Bioactive compounds	Mechanism of anti-aging property	Mechanism of anti-hyperpigmentation property
<i>Labisia pumila</i>	Kacip Fatimah	– phenolic acids – flavonoids	– increase pro-collagen type 1 expression. – decrease MMP-1 as well as MMP-9 expression. – scavenging the reactive oxygen species	
<i>Curcuma longa</i> L.	Kunyit	– curcuminoids (desmethoxycurcumin and bisdemethoxycurcumin) – phenolic acids – flavonoids	– reduce the expression of MMP-1	– anti-tyrosinase activity
<i>Ficus deltoidea</i>	Mas Cotek	– flavan-3-ol monomers and proanthocyanidins	– antioxidant	– anti-tyrosinase activity
<i>Clinacanthus nutans</i>	Belalai Gajah	– terpenoids – phenolics – benzenoids – cerebrosides – glycoylglycerolipids – glycosylglycerides – fatty acids – chlorophyll derivatives – phytosterols – sulfur-containing glucosides	– increase collagen content in the skin of the volunteers (<i>in vivo</i> study)	– anti-tyrosinase activity
<i>Andrographis paniculata</i>	Hempedu Bumi	– diterpenoids (14-deoxyandrographolide and andrographolide)	– increased Type 1 collagen production. – decreased ROS production – enhanced skin hydration, sagging, wrinkling, and dermal density (<i>in vivo</i> study)	– decreased ROS production
<i>Cinnamon cassia</i>	Kayu Manis	– cinnamaldehyde	– activation of insulin-like growth factor-I (IGF-I) signaling in human dermal fibroblasts	– anti-tyrosinase activity
<i>Centella asiatica</i>	Pegaga	– asiaticoside – asiatic acid – madecassic acid	– inhibitory activity against hyaluronidase, elastase, and MMP-1 enzyme	– anti-tyrosinase activity
<i>Morinda citrifolia</i>	Mengkudu	– 3,3'-bisdemethylpinoselinol	– anti-elastase activity	– anti-tyrosinase activity

Ficus deltoidea

Ficus deltoidea (*F. deltoidea*) or commonly known by Malaysian as Mas cotek is a Malay traditional medicine that is very popular due to its good medicinal properties. As a traditional medicine, it has been used to treat diseases like a wound, sores, rheumatism, diabetes mellitus and as an after-birth tonic (Bunawan *et al.*, 2014). The *F. deltoidea* dried leaves have been consumed and sold as herbal tea and capsules among Malaysians

throughout many years. The decoction of the leaves has been reported to possess antidiabetic, antiulcerogenic, antioxidant, anti-melanogenic, anti-inflammatory, analgesic, and antihypertensive properties (Ramamurthy *et al.*, 2014). Another study showed that the water extract of *F. deltoidea* leaves had wound healing and antioxidant properties (Omar *et al.*, 2011; Mustafa *et al.*, 2015). *Ficus deltoidea* has been reported to have a high content of phenolic acids and flavonoids (Soib *et al.*, 2019). The main

phenolic compounds attributed to its antioxidant activity were flavan-3-ol monomers and proanthocyanidins (Omar *et al.*, 2011). There is no study on its anti-aging property has been reported. However, the antioxidant properties of *F. deltoidea* could play a role in anti-aging.

Ficus deltoidea extract has a significant anti-melanogenic effect exerted by direct inhibition of the activity of the tyrosinase enzyme and by downregulation of the expression of genes involved in the pathways of melanogenesis (Oh *et al.*, 2011). no study has reported the active compound responsible for its anti-hyperpigmentation property. However, its scavenging ROS effect due to the high content of phenolic acids and flavanoids in *F. deltoidea* may inhibit melanogenesis production. Similar to *L. pumila*, there is a dearth of information on its safety to topical application.

Clinacanthus nutans

In Malaysia, *Clinacanthus nutans* (*C. nutans*) is called as Belalai gajah. This herb is consumed as herbal tea to treat diseases such as skin rashes, mosquitoes and snake bites, *Herpes simplex* virus lesions, diabetes, and gout (Alam *et al.*, 2016). A study showed that *C. nutans* had potential as an anti-hyperpigmentation agent. Its extract, especially its seeds inhibited the tyrosinase enzyme (Thongmuang & Sudjaroen, 2013). Interestingly, another study showed that *C. nutans* had the potential as an anti-aging agent. The *in vivo* study showed that with the application of *C. nutans* nanoemulsion, the collagen content in the skin of the volunteers increased significantly (Che Sulaiman *et al.*, 2017). Similar to *L. pumila*, there are no studies that have reported the active compound responsible for its anti-aging and anti-hyperpigmentation properties, however, *C. nutans* has been reported to have various bioactive compounds including terpenoids, phenolics, benzenoids, cerebrosides, glycolglycerolipids, glycosylglycerides fatty acids, chlorophyll derivatives, phytosterols, and sulfur-containing glucosides (Kamarudin *et al.*, 2017). The synergistic effect of these compounds contributes to their diverse bioactivities. The safety information of *C. nutans* on the topical application is also lacking.

Andrographis paniculata

Andrographis paniculata (*A. paniculata*) which is also known as Hempedu bumi by local people is commonly used as a health tonic for liver and cardiovascular health and the treatment of common cold, diarrhea, and fever due to various infectious causes. It is also used to boost sexual dysfunction and act as a contraceptive (Hossain *et al.*, 2014). A recent study showed that *A. paniculata* extract had *in vitro* and *in vivo* anti-aging properties (You *et al.*, 2015) and found that *A. paniculata* extract increased

the Type 1 collagen production in normal human fibroblasts. They have also reported that *A. paniculata* extract has greatly enhanced skin hydration, sagging, wrinkling, and dermal density. *Andrographis paniculata* contains diterpenoids called andrographolide responsible for a wide range of biological activities. A recent study showed that methanolic extract of *A. paniculata* and its bioactive diterpenoids include 14-deoxyandrographolide and andrographolide decreased ROS production in dermal fibroblasts and decreased an inflammation marker, IL-6 and TNF- α expression (Mussard *et al.*, 2020). Interestingly, the authors found that *A. paniculata* and its bioactive were non-toxic to keratinocytes.

Cinnamom cassia

The stem bark of *Cinnamom cassia* (*C. cassia*) or called Kayu manis by local people is commonly used as a flavoring agent in various Malaysian cooking. However, the use of *C. cassia* as food should be used with precaution since one of the ingredients in *C. cassia* is coumarin. It is forbidden to use coumarin in food, but the coumarins contained naturally are not (Wang *et al.*, 2013). A previous study of *C. cassia* essential oil showed its main component as cinnamaldehyde, which has strong anti-tyrosinase and anti-melanogenic activities (Chou *et al.*, 2013). Another study showed that cinnamaldehyde promotes type I collagen biosynthesis via activation of insulin-like growth factor-I (IGF-I) signaling in human dermal fibroblasts (Takasao *et al.*, 2012). Takasao *et al.* (2012) showed in an IGF-I-independent manner, cinnamaldehyde substantially increased the phosphorylation levels of the IGF-I receptor and its downstream signaling molecules, such as insulin receptor substrate-1 and Erk1/2. Although cinnamaldehyde has anti-aging and anti-melanogenic properties, few cases of intraoral allergic contact dermatitis to cinnamon flavoring agents have been reported (Isaac-Renton *et al.*, 2015). Thus, the use of *C. cassia* in the topical application should be avoided in certain patients.

Centella asiatica

Centella asiatica (*C. asiatica*) or commonly known as Pegaga by Malaysian is consumed in raw form by Malays as side dishes with rice (Ng *et al.*, 2020a). The plant is beneficial for rheumatism, rising brain capacity by increasing vitality, reducing the level of blood sugar, skin disease, improved circulation, and arthritis. Previous studies showed that *C. asiatica* has both anti-aging and anti-hyperpigmentation properties. The study of methanol extract of *C. asiatica* and its fractions showed that both extracts and its fractions had potent inhibitory activity against hyaluronidase, elastase, and MMP-1 enzyme (Nema *et al.*, 2013). The authors found that

methanol extract of *C. asiatica* showed the highest hyaluronidase inhibitory and elastase inhibitory activities, while the aqueous fraction showed the highest MMP-1 inhibitory activity. On top of that, *C. asiatica* was found as a potent antioxidant (Ng *et al.*, 2020b). The potential of *C. asiatica* in anti-aging could be due to its scavenging ROS effect.

On the other hand, a study on a titrated extract of *C. asiatica* (TECA) containing asiaticoside, asiatic acid, and madecassic acid showed their potential as an anti-hyperpigmentation agent. TECA inhibited melanogenesis via inhibiting tyrosinase mRNA expression (Kwon *et al.*, 2014). Although *C. asiatica* is one of the herbal medicines that have cosmetic potential, some precautions should be undertaken because this herb has been reported to cause contact dermatitis in some cases (Garijo, 1996).

Morinda citrifolia

Morinda citrifolia (*M. citrifolia*) also known as Mengkudu is a tiny evergreen tree. It is native to Southeast Asia and is found in Southeast Asia such as Malaysia, Thailand, Philippines, Indonesia, and some regions in Africa include Samoa, Tonga, and Cuba (Mathivanan *et al.*, 2005). The leaves have a length of 8 or more inches and an oval shape. The diameter of the fruit is 3 to 4 inches with a warty, pitted surface. It seems to have been highly medicinally valued in the tropics. All parts of *M. citrifolia* such as fruit, leaf, bark, and root have been reported to possess medicinal values as antidiabetic, anticancer, and in reducing hypertension (Chan-Blanco *et al.*, 2006). A previous study showed the potential of *M. citrifolia* L as an anti-aging and anti-hyperpigmentation agent (Masuda *et al.*, 2009). The authors found that ethanol extract of *M. citrifolia* seeds had anti-elastase and anti-tyrosinase activities. The other study found that one of the constituents of ethanol extract of *M. citrifolia* seeds which is 3,32 -bisdemethylpinoresinol had MMP-1 inhibitory activity in UVA-irradiated normal human dermal fibroblasts by down-regulation of mitogen-activated protein kinases phosphorylation without cytotoxic effect at 0.3 μ M concentration (Masuda *et al.*, 2012). To date, there are no data available on the topical use of *M. citrifolia* in contact dermatitis. Interestingly, a recent study has shown that oral administration of fermented *M. citrifolia* has the potential to treat atopic dermatitis (Kim *et al.*, 2020).

CONCLUSION

This review article highlights the anti-aging and anti-hyperpigmentation properties of Malaysian herbs. These herbs have been used as medicinal plants over the past few decades and of late, have been found to have cosmetic potential. The information

derived from this review is hoped will assist the cosmetic scientists and other researchers involved in the development of herbal anti-aging formulations using Malaysian herbs in the reduction of wrinkles, skin laxity, and hyperpigmentation. The use of these Malaysian herbs would pave the way in producing more efficient, low toxic, and cost-effective products compared to other synthetic anti-aging formulations that can be exploited in the future. However, the safety of some herbs including *L. pumila*, *F. deltoidea*, *C. nutans*, and *A. paniculata* on the topical application is still lacking. Thus, their safety of application is crucial to be established.

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