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REVIEW PAPER

Potential Dermatological Application on Asian Plants

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Abstract Skin diseases are among some of the most common types of health problems faced in Malaysia, as reported by the World Health Organization (WHO). Correspondingly, research into the use of medicinal plants for skin disease treatment has become important. Through the ages, medicinal plants have been used widely to treat a variety of skin diseases. The demand for plant-based medicines is growing, as they are generally considered to be safer and less harmful than conventional allopathic drugs. This article reviews the potential of Asian plants to be epidermal protecting agents. There are eleven remarkable Asian plants that are known for their skin barrier protecting agent properties. Important studies have shown that natural products offer a rich potential source of epidermal protecting agents. Nevertheless, further surveys and clinical evidence are needed to establish the potential of identified species in contributing to the treatment of skin disease, especially atopic eczema.

Keywords: skin disease, atopic eczema, medicinal plants, epidermal protecting agent

1. Introduction

Human skin is the largest organ in the body that cover its' outer layers, and can be divided into three main layers that include the epidermis, dermis and hypodermis. Its specialized cells and structures have been developed as the body's first line of defense. The outermost layer of the skin is the epidermis, which has varied thickness at different parts of the body. It is the thinnest on the eyelids, at 0.05 mm, and thickest on palms and soles, at 1.5 mm. The primary function of the epidermis is production of stratum corneum [1].

The inner layer of the skin is known as dermis, which also varies in thickness at different regions of the body. The thinnest is on the eyelid, at 0.3 mm, and the thickest is on the back of the body, at 3.0 mm. The dermis is a thick layer of connective tissue that can be divided into two levels. These include the upper level of the dermis, known as the papillary region, and the lower level of the dermis, known as reticular layer. This layer consists of fat and connective tissue, pierced by blood vessels which help to regulate skin and body temperature. The deeper subcutaneous tissue is the hypodermis, which is made of fat and connective tissue.

The skin guards internal organs, gives protection from microbes, regulates body temperature, and permits the sensations of contact, heat and cold [2]. The stratum corneum plays an important role, through serving as a barrier function. A lack of essential nutrients, including beta-carotene and vitamins C and E, can cause the skin to be sensitive, dry, pale, sagging and tired. The skin is a major body protector against pathogens [2,3] and maintains skin hydration when the body interfaces with its environment [3]. Skin also acts as an insulator, vitamin D storage, oxygen and drugs absorber [4] and as water resistance.

1.1. Structure and function of skin barrier

The skin provides a vital barrier structure that protects the body from both routine and extreme environments, including exposure to antigens, solvents, UV light, detergents, microorganisms, toxins, nanoparticles, and a variety of physical activity [5]. Maintaining the epidermal barrier is essential for the body's well-being. Understanding the structure and

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function of the epidermis helps health practitioners to identify and treat various skin conditions. The epidermis, where most of the skin barrier functions reside, is highly stratified and has an outermost layer that is cornified. The epidermal barrier's dysfunction is pathologically involved in a variety of common, antigen-driven skin diseases, including psoriasis and atopic dermatitis.

The outermost layer of skin known as epidermis. The main functions of the epidermis are to help regulate epidermal permeability, and to act as a physical, chemical and antimicrobial protector [6]. The elements of innate response, including antimicrobial peptides, lipids, toll-like receptors, pro-inflammatory cytokines and chemokines production, are also involved in the natural antimicrobial defense action [7]. The integrity and protective functions of the stratum corneum are compromised during stress, when the cutaneous homeostatic permeability barrier is disturbed [6]. Furthermore, psychological stress can cause skin diseases, as well as worsen them, in cases that include atopic dermatitis and psoriasis [8].

Healthy skin protects the body from environmental factors. These include physical factors such as mechanical trauma, thermal injury and radiation, chemical factors such as destructive agents, surface active substances, xenobiotics and allergens, and biological factors such as bacteria, viruses, and others [9]. A major element of the skin's defensive function is to maintain homeostasis, by preventing the uncontrolled loss of water, ions and serum proteins from an organism into the surrounding environment. Schade and Marchionini have identified scientific evidence for the protective functioning of the water-lipid mantle of the skin, and have introduced the concept of the skin barrier [10]. A barrier is defined as an object that separates two distinct spaces, and/or prevents free passage between two environments [11]. In this sense, the skin barrier ensures the integrity of the body and controls the exchange of substances with the environment.

Currently, it is considered that over 90% of skin barrier function resides within the epidermis, and particularly within the outermost layer of the stratum corneum [12,13]. Exploring the morphological and biochemical bases of the epidermal barrier is essential for understanding its main functions. Initially, the stratum corneum (SC) was considered to be inert layer of dead cells formed in the keratopoesis, interconnected through an intercellular lipid layer. The SC, with its main constituents including corneocytes and intercellular lamellar lipid bilayers, are considered to be the main structures that determine the speed of the trans-cutaneous exchange of substances [9,14]. The mechanical resistance of the epidermal barrier is mainly the result of the corneocytes embedded in the so-called cornified envelope. It is composed of proteins, including dynamically-linked loricrin, involucrin and filaggrin [5]. The adjacent lipid layers are responsible for water permeability, and the exchange of substances with the external environment. The main biochemical components of the skin barriers are lipids and proteins.

Many physiological processes directly depend on the hydration of the SC. The degradation of corneodesmosomes is carried out by enzymes, including glycosidase and serine-proteases, which require water to function. In this way, the process of desquamation depends on the water content in SC [3]. Impaired desquamation occurs in diseases and conditions that lead to reduced hydration of the SC, such as ichthyosis vulgaris and xerosis senilis [15].

The enzymatic degradation of filaggrin is also dependent on the water content in SC [16]. The reduced hydration of SC activates the filaggrin degradation of hygroscopic amino acids, reducing the composition of the natural moisturizing factor which serves to retain water within the stratum corneum [17]. The stratum corneum contains pre-formed pro-inflammatory cytokines [18]. A low humidity environment causes a release of pro-inflammatory mediators, including interleukin-1 [19]. This may explain the progression of some inflammatory skin diseases within low-humidity environments, for example as during winter.

The acidic pH of skin surface layers is important for the defensive function of the epidermal barrier, and for the formation and maintenance of its integrity [20,21]. The skin barrier function is effective at birth, when the skin surface's pH is neutral [21,22]. The role of pH is confirmed by the normalization of the recovery process, through the acidification of the environment [21]. The clinical significance of these results is demonstrated through the pathogenetic vicious cycle involved in diaper dermatitis. The insufficient acidity of SC in infants, and the alkaline environment created through the presence of ammonium salts in urine, activates the trypsin and lipase enzymes originating from faeces, and causes further damage and irritation to the skin barrier [23,24].

1.2. Skin barrier disrupting factors

The skin forms a remarkable protective barrier against the external environment, prohibiting harmful microbes and chemicals from entering the body, regulating body temperature and balancing fluids, and providing protection against sunlight. Several environmental factors have been associated with the development of the atopic dermatitis problem, including cleaning with hard water, cleaning with soap and detergents, and exposure to house dust mites and food allergens [25-33]. The prevalence of AD is higher in areas where there is hard water, compared to areas where the water is soft [32]. This may be because of the irritant chemicals present in hard water, and the larger amount of

soap and other detergents used when cleaning with hard water.

Exposure to ultraviolet radiation can result in damage to the skin, and can disrupt the epidermal barrier. Ultraviolet radiation can be classified into three different bands, based on decreasing wavelength and increasing energy. These include UVA (320 ~ 400 nm), UVB (290 ~ 320 nm) and UVC (200 ~ 290 nm). These different wavelengths can have different effects on human tissue. The acute effects of UVA and UVB exposure are both short lived and reversible. UVA rays cause light brown tan to the skin while UVB rays cause long term tan due to melanin synthesis [34]. Acute exposure to UVB can cause edema, erythema and pigmentation, consequently causing delayed tanning, thickening of the epidermis and dermis, and vitamin D synthesis. UVC rays have sterilization and biocidal properties that harmful especially for the eyes and give effect on living beings [34]. On the other hand, chronic exposure can result in immune suppression, photo ageing and photo carcinogenesis [35,36].

A study undertaken by Aberg and colleagues has proved that psychological stress disturbs the stratum corneum structure and function, by down-regulating the epidermal and adnexal expression of antimicrobial peptides. Cutaneous infections can be caused by increases in glucocorticoid production, which mimic systemic glucocorticoid administration, and can be reduced through the administration of the CRF1 antagonist antalarmin [37]. It also has an adverse effect on the function of epithelial tissues, including the epidermis, where it perturbs both epidermal permeability barrier homeostasis [38, 39] and cutaneous wound healing [40-44].

The effect of cosmetic/personal care products usage in everyday life may be a factor in epidermal barrier disruption. There are various chemicals used in the preparation of cosmetic/personal care products, which can have harmful effects and be toxic to the skin if not used with caution. The chemicals can also result in immediate reactions on overly sensitive skins, especially for people who suffer from skin diseases including psoriasis and atopic dermatitis. Dangerous chemicals including formaldehyde, mercury, parabens and sodium lauryl sulfate (SLS) are commonly used as ingredients in cosmetic/personal care products formulations [45]. These chemicals may cause skin irritation, as well as allergic reactions and drying effects, which can lead to adverse effects on the skin. An overdose of the use of these chemicals over a long period of time may result in serious health impacts [45].

Skin diseases such as psoriasis and atopic dermatitis are another factor in epidermal barrier disruption. AD is a chronic or relapsing inflammatory skin disease, often preceding asthma and allergic disorders [46,47]. AD patients have a higher susceptibility to allergic sensitization, microbial colonization and infections [47,48]. Filaggrin is structural protein that aggregates the keratin cytoskeleton, and facilitates the collapse and flattening of keratinocytes in the outermost skin layer. Filaggrin represent the most significant genetic factor for AD identification [48]. The most immediate result of filaggrin deficiency in AD sufferers is a reduction of stratum corneum hydration, and an increase in transepidermal water loss [48].

2. Atopic Dermatitis

Atopic dermatitis (AD) is a relapsing-remitting condition, which flares-up periodically, and is often triggered by allergens, irritant chemicals and stress. It is frequently associated with elevated serum IgE levels, and a family history of AD, allergic rhinitis and asthma. A combination of genetic, immunologic, and environmental factors can have an effect on AD incidence risk. Evidence suggests that AD is a cutaneous manifestation of a systemic disorder, that also gives rise to other atopic conditions. In fact, AD is often the initial step in the 'atopic march', or the sequential development of allergic disease manifestations during early childhood, which leads to asthma and allergic rhinitis in the majority of afflicted patients [49].

Impaired barrier function can also be observed in atopic dermatitis patients. This is manifested in the breaking down of skin barriers, the loss of skin moisture, and the invasion of bacteria into the body [12]. The dehydration of skin among atopic dermatitis patients can cause the skin to become sensitive, dry and easily cracked. Regular scratching at sensitive areas can result in inflammation to the skin. Scratching is induced by an itch at a sensitive area, thereby stimulating nerve fibers and leading to more scratching reactions [50]. Severe scratching associated with eczema can ultimately cause infections, as a result of broken skin [51].

Environmental factors including soaps, fabrics, deodorants and excessive sweating, low humidity, certain foods and stress also can induce flare-ups [50]. When these irritants irritate the skin, the sufferer feels itchy and begins to scratch the affected area, in turn worsening the skin damage, and causing additional inflammation [51]. The sensation of the itch is enhanced through the long term itching and scratching of skin. The frequently-scratched skin will become thick and leathery, and there will be red or darker patches on the skin.

Frequent scratching can cause permanent changes in skin color. Scratching also causes undesirable changes in skin, including lichenification and prurigo nodule formation [52]. Allergens are more subtle trigger factors. An allergen does not irritate, but may trigger an AD flare-up in those

who have become allergic to it from prior exposure. Allergens are usually animal or vegetable proteins that originate from foods, pollens or pets [50]. When people with AD are exposed to an irritant or allergen to which they are sensitive, inflammation-producing cells come into the skin [52]. There, they release chemicals that cause itching and skin redness, which can lead to skin damage. Fig. 2 shows the atopic dermatitis cycle, in regards to the skin barrier function.

2.1. The pathophysiology of atopic dermatitis

The pathogenesis of atopic dermatitis is unknown, but the disease seems to be the result of genetic susceptibility, immune dysfunction and epidermal barrier dysfunction [54]. This can be caused by many factors, and involves a complicated immunologic cascade, including interruptions to the epidermal barrier, dysregulation of IgE, deficiency in cutaneous cell-mediated immune responses, and genetic factors. Langerhans' cells, inflammatory dendritic epidermal cells, monocytes, macrophages, lymphocytes, mast cells and keratinocytes are the main elements of immune dysregulation that can lead to a predominance of Th2 cells over Th1 cells, by interacting through a complex cascade of cytokines [55].

Compromised skin barriers that maintain the skin's water balance can cause patients with atopic dermatitis to have dry and sensitive skin. Linolenic and linoleic acid, which are essential fatty acids (EFAs), play a significant role in the epidermal barrier. A reduction of linoleic and linolenic acid metabolites in atopic dermatitis patients is caused by a deficiency of desaturase [56]. High transepidermal water loss and subsequent xerosis (dryness) can be caused by a loss of EFAs. The substrate of inflammatory mediators (prostaglandins and leukotrienes), which are produced from EFAs, can lead to a secondary reduction of prostaglandin E_1 (PGE_1).

Defects in the epidermal barrier can make the skin more prone towards atopens, which include atopic allergens such as house dust mites, grass and pollen. There will be an increase of IgE production, due to the stimulation of Th2 lymphocytes to produce cytokines that include IL-4, IL-5 and IL-13 [57]. High levels of IgE antibodies that appose house dust mites and other allergens can be observed in atopic dermatitis patients. In order to improve atopic dermatitis, these allergens need to be eliminated from the environment.

Previous studies have shown that the barrier-disrupted dry skin of AD patients is mainly attributable to significantly decreased levels of ceramides, evaluated as lg ceramide/ weight or protein, within the stratum corneum (SC) [58]. Ceramide acts as a water modulator [58] and a permeability barrier, by forming multi-layered lamellar structures with other lipids between cells in the SC layers [58-60].

The ceramide deficiency in the SC of AD skin has been substantiated in many studies [51,61-65]. The significance of the deficit in ceramides that impairs the cutaneous permeability barrier of the SC is evidenced through the clinical observation that trans-epidermal water loss (TEWL) assessed in AD non-lesional skin increases inversely with decreased levels of ceramides in the SC, from the same skin site of AD patients [66,67]. Epidermal barrier function is measured according to the degree of TEWL, which is usually increased in AD patients, due to decreased skin capacitance and hydration [68,69].

2.2. Atopic dermatitis prevalence around the globe and in Malaysia

Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic, inflammatory, pruritic skin disease of increasing prevalence, which effects approximately 15 ~ 30% of children, and 2 ~ 10% of adults [52]. More than 50% of children with AD will develop asthma and allergies within the first few years of life [70]. The prevalence of AD appears to be steadily increasing, at least in developing countries. AD has a genetic background strongly influenced by environmental factors, including urbanization, diet, climate, infections and aeroallergens [71]. AD is a very common disease, but it is impossible to know the exact prevalence of AD in each country. In nearly all regions, information regarding atopic eczema has been collected through questionnaire-based studies like be used in International Study of Asthma and Allergies in Childhood (ISAAC) [72,73].

Phase three of ISAAC surveyed 385,853 children aged within the 6 ~ 7 year age group, and 663,256 children aged within the 13 ~ 14 year age groups, in regards to the prevalence of current symptoms of eczema. From this survey, Mallol *et al.* (2013) reported that for the younger age group, the lowest prevalence values of eczema were in the Eastern Mediterranean and the Indian Subcontinent, while the highest values were in Latin America and Oceania [53]. For the older age group, the lowest prevalence values of eczema were reported in Asia Pacific, Eastern Mediterranean, the Indian Subcontinent, and Northern and Eastern Europe, while the highest values were reported in Africa. The global prevalence percentage of current symptoms of eczema reported simultaneously by children is shown in Fig. 1. This report summarizes that eczema symptoms appear more commonly in girls compared to boys, for both the 6 ~ 7 year and 13 ~ 14 year age groups, although this ratio varied across regions [53].

In Malaysia, the study on atopic eczema was conducted only in Kota Bharu, Kelantan. The prevalence of atopic eczema was at 13.7% in the 5 ~ 7 year group, 9.9% in the 12 ~ 14 year group [74], and 17.6% in primary school children [75]. Although atopic disorders are common in

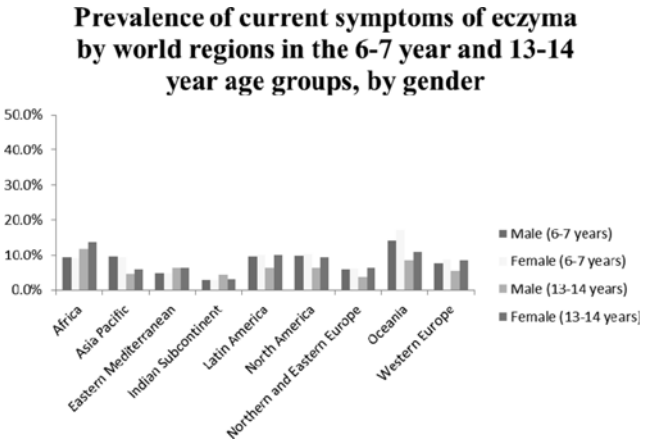

Fig. 1. Global variations in the prevalence percentage of eczema symptoms in children within the 6 ~ 7 and 13 ~ 14 age groups, by gender. Reproduced data from Mallol *et al.* (2013) [53].

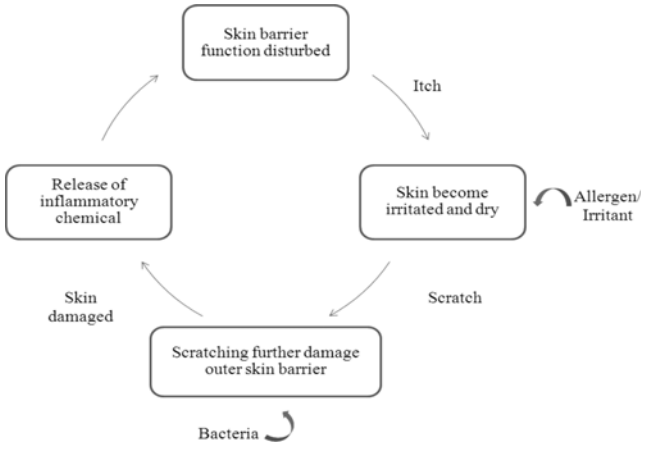

Fig. 2. The atopic dermatitis cycle.

this country, the results revealed no major changes in the prevalence rates of these diseases over a period of six years. These prevalence data are comparable with previous reports regarding Malaysian children, but are considerably lower than those reported for most developed countries. Written and video questionnaires were used as part of the Phase I International Study of Asthma and Allergies in Childhood [74,75].

2.3. Plants traditionally used to treat skin problems

Plants and their extracts are becoming more popular, due to their active compounds that give numerous benefits to human body. These include fewer side effects, better patient tolerance, lower cost, and cultural and social acceptance resulting from long traditional use. In addition, many incurable diseases which cannot be treated with other medicines can be cured through herbal medicines. In order to gain this benefit, several investigations and studies have been conducted on plants that can treat skin diseases, which range from itching to skin cancer. Due to the easy availability, economic benefits and minimal side effects of medicinal plants, when compared to the allopathic system of medicines, the World Health Organization (WHO) estimates that about 80% of the world's population still depend on herbal remedies from plants for the treatment of diseases.

Herbal remedies have formed the foundation of modern pharmacology. These natural remedies have been used for centuries to treat skin conditions and a wide variety of dermatological disorders, including inflammation, photo-toxicity, psoriasis, atopic dermatitis and alopecia areata. Although these remedies are currently widely accepted by patients, their scientific respect among dermatologists in particular is limited. Alternative medications seem to be promising, although their true effects are unknown, and so further investigations must be performed in order to assess their clinical benefits. Herbal drugs for topical application also deserve consideration, because of their widespread use and their ill defined benefit/risk ratio [76]. Table 1 shows the list of medicinal plants reportedly used to treat skin diseases, including psoriasis and atopic dermatitis.

3. Overview of Studies Regarding Plant's Herbs as Epidermal Protecting Agents

3.1. *Cocos nucifera* L. (virgin coconut oil)

Coconut, *Cocos nucifera* L of the family Arecaceae (Palmae) is the source of virgin coconut oil (VCO). VCO can be defined as oil obtained from the fresh, mature kernel of the coconut by mechanical or natural means, with or without the use of heat, without undergoing chemical refining, bleaching or deodorizing, and which does not lead to the alteration of the nature of the oil [116]. Virgin coconut oil is produced from fresh coconut milk. Coconut milk is rich in vitamins, antioxidants, amino acids and essential fatty acids. Coconut flesh has the most valuable component which is oil, and a high total lipid content that includes tocotrienols.

Coconut oil is a highly saturated oil with medium-chain fatty acids, including capric (7%), lauric (49%), myristic (18%), palmitic (9%), stearic (2%), and small percentages of unsaturated oils that include oleic (6%) and linoleic acids (2%) [117]. Virgin coconut oil is colorless and clear, and cold press oil has the aroma of fresh coconut. VCO contains lauric acid, which has antimicrobial, anti-viral, anti-fungal and antibacterial properties [118]. A few studies have reported the benefits of lauric acid as an antimicrobial and anti-inflammatory agent that can help to address skin problems. Huang *et al.* (2014) has reported that lauric acid exerts bactericidal and anti-inflammatory

Table 1. Plants reported to treat skin diseases

Species	Family	Local/Common Name	Part(s) used	Phytochemical compounds	Activities	References
Achyranthes aspera	Amaranthaceae	Prickly Chaff Flower	Whole plants		Antioxidant	[77]
Allium cepa	Amaryllidaceae	Onion	Bulbs		Antibacterial	[78,79]
Allium sativum	Amaryllidaceae	Garlic	Bulbs	Allicin, alliin	Antibacterial	[80]
Aloe barbadensis	Aloaceae	Aloe Vera	Leaves	Aloin	Antioxidant, Antimicrobial, Antifungal, Wound healing, Anti inflammatory	[81-85]
Azadirachta indica	Meliaceae	Neem	Leaves		Antioxidant, Anti inflammatory, Antimicrobial, Antifungal	[86-89]
Bangiales	Bangiaceae	Porphyra	Whole plants	Mycosporine	Photo protective activity	[81]
Beta vulgaris	Amaranthaceae	Beetroot	Fruits		Antioxidant	[90]
Borago officinalis	Boraginaceae	Borage Oil	Seeds	Gamma linoleic acid (GLA)	Anti inflammatory	[81]
Brassica oleraceae	Brassicaceae	Red Cabbage	Leaves		Antioxidant	[91]
Calendula officinalis	Asteraceae	Marigold	Flower	Narcissin	Wound healing, Antioxidant	[92]
Camellia sinensis	Theaceae	Green Tea	Leaves	Epigallocatechin gallate	Antioxidant	[93]
Crocus sativus	Iridaceae	Saffron	Seeds, flower		Antioxidant	[94,95]
Curcuma longa	Zingiberaceae	Turmeric	Rhizome	Curcumin	Antioxidant	[96]
Daucus carota	Apiaceae	Carrot	Fruits		Antioxidant	[97]
Echinacea angustifolia	Asteraceae	Purple Cone Flower	Flower	Echinaforce®	Wound healing, Antioxidant, Anti inflammatory	[93,98,99]
Eucalyptus globulus	Myrtaceae	Blue Gum, Camphor Oil	Stem barks		Antimicrobial	[100,101]
Ficus carica	Moraceae	Fig	Stem barks		Antimicrobial	[86,102]
Lavendula officinalis	Lamiaceae	Lavender	Flower	Cineole, Linalool	Wound healing, Antioxidant, Antibacterial, Antimicrobial	[103]
Lawsonia inermis	Lythraceae	Henna	Leaves		Anti inflammatory, Antimicrobial	[104,105]
Mangifera indica	Anacardiaceae	Mango	Gum	Mangiferin	Anti inflammatory, Antimicrobial	[86,106]
Matricaria chamomile	Asteraceae	Chamomile	Flower		Antioxidant, Anti inflammatory	[107-109]
Mirabilis jalapa	Nyctaginaceae	Four O'clock Flower	Flower		Anti inflammatory	[110]
Momordica charantia	Cucurbitaceae	Bitter Gourd	Fruits		Antioxidant	[111]
Oenothera biennis	Onagraceae	Evening Primrose Oil	Seeds	Gamma linoleic acid (GLA)	Anti inflammatory	[81]
Prunus persica	Rosaceae	Peach	Flower		Anti inflammatory, Antibacterial, Wound healing	[112]
Rosmarinus officinalis	Lamiaceae	Rosemary	Flower	Caffeic acid	Photo protective activity	[113-115]
Thyme vulgaris	Lamiaceae	Thyme	Leaves		Antimicrobial, Anti inflammatory	[93]

activities against *Propionibacterium acnes*. *P. acnes* is a common bacteria that causes the skin disease acne vulgaris, besides, this bacterium can induce inflammation and excessive sebum production in human skin [119].

Lauric acid also has the potential to be used as alternative to the antibiotic therapy of acne vulgaris, as reported by Nakatsuji *et al.* (2009). Lauric acid has effectively reduced inflammation and swelling in the mouse ear model, as caused by *P. acnes* [118]. There is limited research about VCO's effect on the human skin cellular model. The latest study about the antinociceptive and anti-inflammatory activities of VCO was undertaken by Zakaria *et al.* (2011).

VCO has shown significant ($p < 0.05$) antinociceptive dose-dependent antinociceptive activity within the acetic acid-induced writhing test, and both phases of the formalin and hot-plate tests [120]. Meanwhile, the VCO have exhibited anti-inflammatory activity in an acute, carrageenan-induced paw edema test. These results prove that the lauric acid of VCO has an anti-inflammatory property.

VCO also contains antioxidants. In the previous study conducted by Nevin and Rajamohan (2006), the effect of VCO on antioxidant activity and lipid peroxidation was identified through a test on a rat model [121]. The results showed that VCOs are effective in preventing the peroxidation of lipids, and increasing the levels of antioxidant enzymes. Research has been conducted regarding the healing properties of VCO. The treatment of wounds with VCO has led to their faster healing, as indicated by the decreased time required for complete epithelization, and the higher levels of various skin components [121]. Thus, VCO has been shown to support wound-healing activity on human skin.

Previous research conducted by Evangelista *et al.* (2014) has shown that the topical application of VCO over eight weeks to a group of pediatric patients with mild and moderate atopic dermatitis (AD) resulted in more prominent results than those resulting from the use of mineral oil [122]. Although VCO predominantly has saturated fats, and contains 62% medium-chain fatty acids, it may still provide better permeation for AD patients because of their impaired skin barrier [123]. This study was conducted based on SCORAD (SCORing of Atopic Dermatitis) index values, transepidermal water loss (TEWL) and skin capacitance in pediatric patients with mild to moderate AD. A randomized, controlled trial design was used in this study, in which the participants who were blinded to codes allocated the treatments randomly using the list, and dispensed the packaged bottles. The codes were not disclosed to the investigators until the end of the study, in order to avoid bias. As well as improving barrier function, VCO may also address the chronic inflammation characteristics of AD [122].

3.2. *Gynura procumbens* (*Sambung Nyawa*)

Gynura procumbens is a scientific name for a traditional herb known as *Sambung Nyawa* within Malay society. Other vernacular names for *G. procumbens* include *kecam akar, akar sebiak, daun dewa* and *bai bing cha* [124]. The herb belongs to the Asteraceae (Compositae) plant family. This plant grows to be around 10 ~ 25 cm tall [125], and its leaves which are commonly used as folk medicine, are fleshy, hairy on both surfaces, and vary in shape to be either ovate or oblong-elliptic. There shapes feature a rounded or cuneate base, and also an obtuse or acute, often attenuated apex [79]. This herb was originally from Africa, traded widely to China, South East Asia, Australia and Sri Lanka [126].

G. procumbens is also widely used as a traditional medicine in Asian countries, including Malaysia, Thailand and Indonesia. In Malaysia, *G. procumbens* leaves are used to treat diabetic patients while in Thailand, the aerial part of this herb is commonly used to treat inflammation, rheumatism and viral infections of the skin [127]. In Indonesia, citizens use this herb to treat fevers, skin rashes, and it can also act as a tonic for ringworm infection [127]. From previous studies it has been successfully proven that the leaves of *G. procumbens* exhibit beneficial properties, including the ability to counter the herpes simplex virus [128], while also having anti-hyperglycemic [18], anti-inflammatory [18], anti-hyperlipidemic [19], anti-allergy agent and antihypertensive properties [129]. Other research has found out that *G. procumbens* leaf contents do not cause any toxic effects [130]. The leaves contain flavonoids, unsaturated sterols, terpenoids, polyphenols and essential oils.

G. procumbens leaf extract has also been tested as a wound healing agent. Zahra *et al.* (2011) had investigated the effect of this herb on wound healing, and the histology of sound areas [131]. The wound healing ability of 0.2 mL of this extract has been compared to that of vehicle (gum acacia) and Intrasite gel. The results show that rats' wounds treated with Intrasite gel and *G. procumbens* leaf extract heal quicker than those treated with vehicle gel. A histological analysis of wound areas show that wounds treated with *G. procumbens* leaf extract show comparatively less scar width at wound closure, and granulation tissue contained less inflammatory cells and more collagen with angiogenesis, when compared to wounds dressed with vehicle gel [131].

In cosmetic products, *G. procumbens* leaf extract is added to formulations in order to protect the skin against ultraviolet (UV) radiation. UV radiation can damage the skin and cause intrinsic and extrinsic skin aging, which can be seen identified through the appearance of wrinkles, sagging and laxity [7]. Junoh *et al.* (2011) investigated the effect of the *G. procumbens* ethanolic leaf extract in inhibiting UV-B-induced MMP-1 and MMP-9 expression in human dermal fibroblasts, through the inhibition of pro-inflammatory cytokine mediators and ROS scavenging [132]. The results showed that a treatment of 20 μg/ml of the ethanolic leaf extract of *G. procumbens* inhibited MMP-1 in up to 70 ~ 73% of MMP-9 expressions induced through UV-B irradiation, *via* the inhibition of pro-inflammatory cytokine mediator release and ROS production [132].

3.3. *Clinacanthus nutans* (Sabah Snake Grass)

Clinacanthus nutans, known as Sabah Snake Grass (Belalai Gajah), is a small shrub from the Acanthaceae family. It

has been used in folk medicine to cure various kinds of ailments, including snake bites, kidney failure and cancer. The name of the plant has quickly achieved great fame throughout Asia. This well-known plant has been categorized as an essential medicinal plant for primary healthcare by the Thai Ministry of Public Health [133]. Previously, *C. nutans* leaves have been traditionally used to treat inflammation, including infective and non-infective inflammation [134] and viral infection [135,136]. The use of this herb has also been adopted by clinics, in order to treat herpes infections in Thailand [137].

Previous research by Pannangpetch *et al.* (2007) reported that the ethanolic leaf extract of *C. nutans* has an antioxidant activity, and a protective effect against free radical-induced haemolysis [138]. The free radical (1,1-diphenyl-2-picrylhydrazyl; DPPH) scavenging activity, the ferric reducing antioxidant power (FRAP) and the intracellularly antioxidant activity of the leaf extract have been identified. This is evident through the fact that the leaf extract could scavenge DPPH with a maximum scavenging activity of 67.65 ± 6.59%, and with IC_{50} of 110.4 ± 6.59 μg/mL. The FRAP value was 17 mg ascorbate, equivalent to one gram of the leaf extract. The leaf extract demonstrated a significant inhibition of peroxide productio±n in rat macrophages, stimulated by phorbol myristate acetate (PMA) and the protected red blood cell against 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) induced hemolysis, with an IC_{50} of 359.38 ± 14.02 mg/mL. The ethanolic leaf extract of *C. nutans* had an antioxidant activity, and a protective effect against free radical-induced hemolysis [138].

Panthong *et al.* (2008) identified the anti-inflammatory activity of *C. nutans* whole plant's extracts, using two neutrophil-dependent acute inflammatory models [134]. The methanolic crude whole plant's extract of *C. nutans* was studied for its anti-inflammatory activity, in models of ethyl phenylpropiolate (EPP) induced ear oedema and carrageenan-induced paw oedema in rats. EPP-induced ear oedema has a good predictive value for the screening of anti-inflammatory agents, and these whole plant's *C. nutans* extracts have dose-dependently and significantly inhibited oedema formation within this model, at all time points examined. The whole plant's *C. nutans* extract also significantly inhibited myeloperoxidase (MPO) activity in the rat ear, indicating the likely involvement of neutrophils in the cellular mechanism of the action. These findings suggest that the powerful anti-inflammatory properties of *C. nutans* whole plant's extracts are mediated, in part, by the inhibition of neutrophil responsiveness [134].

3.4. *Piper betle* L. (Sireh)

The betle (*Piper betle*) is the leaf of a vine belonging to the *Piperaceae* family, which also includes pepper and kava. It is valued both as a mild stimulant, and for its medicinal properties. *P. betle* leaf is mostly consumed in Asia and elsewhere in the world by some Asian emigrants, as betle quid or *paan*, with or without tobacco. The *P. betle* plant originated from South and South East Asia. *P. betle* leaf is notable for its effect of staining the teeth of regular users. The roots and fruits are well-known as a treatment of malaria and asthma [139]. The *P. betle* plant is an evergreen and perennial creeper, with glossy, heart-shaped leaves and white catkin.

In research undertaken by Majumdar *et al.* (2003) it was shown that the ethanolic extract of the leaf of the *P. betle* vine exhibited a significant healing effect on peptic ulcers induced by non-steroidal, anti-inflammatory drugs (NSAID) in albino rats [140]. Before treatment with the extract, through the use of microscopic observation, a number of deep ulcers were observed throughout the glandular stomach on the first day of the study. Continuous treatment with the leaf extract resulted in the gradual healing of the NSAID-induced gastric lesion by the 3rd day, and no ulcer spot was found on 10th day. Tissue peroxidised lipid levels, and malonyl dialdehyde (MDA) showed gradual lowering during the testing of the experiment [140]. Based on the study of the NSAID-ulcer as an experimental model, the gastric mucosal barrier, primarily the hexosamine and mucus content, gradually increased. This indicated the *P. betle* leaf extract's significant protective and healing actions. The healing action is a result of the antioxidative mechanism of the *P. betle* leaf extract [140].

A study undertaken to determine the antimicrobial activity of four different extracts (water, methanol, ethyl acetate and petroleum ether) of *P. betle* leaves at five different concentrations (5, 10, 25, 50 and 100 mg/mL), against four different types of bacteria, namely *Streptococcus pyogens, Staphylococcus aureus, Escherichia coli* and *Proteus vulgaris*, was conducted by Devjani and Barkha (2011) using the agar well diffusion method [141]. The test microorganism were spread over on solidified plates and wells, then were bored using sterile cup borer of 1 mm diameter. This study revealed that increasing the concentration of *P. betle* leaves extracts results in a significant increase in the zone of inhibition of all types of bacteria [141]. The maximum inhibition of an aqueous *P. betle* leaf extract was obtained against *Escherichia coli*. Meanwhile the maximum inhibition of methanolic *P. betle* leaf extract was determined against *Staphylococcus aureus,* the ethyl acetate leaf extract promoted a clear zone of inhibition against *Escherichia coli*, and a maximum inhibition of ether leaf extract was obtained against *Proteus vulgaris.* In addition, another study also reported that *P. betle leaves* extracts containing a high concentration of fatty acids, including palmitic acid, stearic acid and hydroxy fatty acid esters, may result in antimicrobial

activity on against diverse pathogenic microorganisms [142]. All the *P. betle* leaves extracts showed clear zones of inhibition against all the bacteria involved in the present study, due to the high concentration of sterols [141].

3.5. *Ficus deltoidea* (Mas cotek)

In Malaysia, *Ficus deltoidea* or Mas cotek is widely known for its beneficial effect for women and it is predominantly consumed orally as a tea by local women, before and after giving birth [143]. The University Malaya and Malaysian Planting Research Institute (MARDI) cooperated together in order to scientifically investigate *F. deltoidea*. From this research, it was determined that *F. deltoidea* contains five bioactive components essential to the human body, including flavonoid, tannins, triterpenoids, proanthocyanins and phenols. The *F. deltoidea* extract exhibits strong radical-scavenging activity, therefore allowing it to act as antioxidant, and at the same time it has hypoglycemic and antinociceptive properties [144].

Abdullah *et al.* (2009) reported the presence of a high content of total polyphenols, flavonoids and tannins within the extracts of the leaves of three varieties of the plant, which have been shown to have strong antioxidant activity [145]. Polyphenols have been shown to have antibacterial, anti-carcinogenic, anti-inflammatory, anti-viral, anti-allergic, estrogenic and immune-stimulating properties. Abdullah *et al.* (2009) has evaluated anti-inflammatory activities using three *in-vitro* assays, including lipoxygenase, hyaluronidase and 12-O- tetradecanoylphorbol-13 acetate (TPA)-induced oedema [145]. The result shows that the anti-inflammatory activities of methanol leaves extracts were more present in the TPA model. TPA-induced mouse ear oedema inhibitory assay was used in the determination of anti-inflammatory activity. TPA in acetone (20 μL of 0.05 μg/μL) was applied topically to the right ear of each mouse. The results of this study indicated that extracts of the leaves of *F. deltoidea* possess anti-inflammatory properties [145].

From previous research by Oh *et al.* (2011), five different concentrations of *F. deltoidea* leaves extracts were observed using the DPPH assay, to determine their antioxidant activity [146]. It was determined that the *F. deltoidea* leaf extract has a strong antioxidant activity, as the absorbance of the free radical DPPH decreased when measured by IC_{50} percentage of inhibition. 35.191 g/mL was the 50% of free radical scavenging (FSC_{50}) value for *F. deltoidea*. Anti-photo ageing and anti-melanin synthesis can be promoted primarily through reactive oxygen species (ROS) scavenging activity, and ROS scavenging activity of ascorbic acid is thought to be a primary factor of its anti-melanogenic activity. From previous studies it was also determined that the antioxidant activity of *F. deltoidea* was greater than ascorbic acid, and therefore *F. deltoidea* leaves extracts also have great potential for use in whitening cosmetic materials [146].

Hasham *et al.* (2012) investigated the effects of the *F. deltoidea* leaves extracts in terms of its anti-photoageing activity, using cultured human dermal fibroblasts and immortalized human keratinocytes (HaCaT) [147]. The results of this study illustrated the efficacy of the *F. deltoidea* leaf extract in alleviating UVB-induced photoageing and inflammation of the skin, by modulating the expression of pro-inflammatory cytokines, COX-2, MMP-1 and type 1 pro-collagen. Treatment with the *F. deltoidea* leaf extract has dramatically inhibited the UV-induced TNF-α, IL-1α, IL-6, and COX-2 expression. Therefore, the *F. deltoidea* leaf extract may exert a protective effect against UVB-induced damage to skin, useful in anti photo-ageing cosmetic products [147].

3.6. *Labisia pumila* (Kacip Fatimah)

Labisia pumila is a flowering plant of the Primulaceae family native to Malaysia. This plant is known as the 'queen of plants' of all Malaysian herbs, as this plant has been broadly used for centuries by women in Malaysia in order to ease childbirth, as well as to treat post-partum illness [148,149]. *L. pumila* is an herbaceous plant that grows in low clusters, with solitary or rarely branching stems, and fine, hairy roots. The leaves are oblong-shaped, hairy on their undersides, and can grow up to 20 ~ 40 cm in length. Various extracts of *L. pumila* have antioxidative activity when compared to Silymarin, an extract from the European milk thistle plant (*Silybum marianum*) [150-152].

Wrinkle formation in human skin, as stimulated by collagen reduction within the dermis, is primarily the result of UVB exposure [153,154]. Two main causes of collagen reduction in dermis include the degradation of collagen, mainly through the action of MMP-1, and the down regulation of type 1 pro-collagen expression. Pro-collagen is reduced by 61%, the result of UVB irradiation, when compared to an untreated control group [155]. However, the synthesis of pro-collagen can be restored with a treatment using *L. pumila* leaves extracts, for increasing the expression of type 1 pro-collagen. The *L. pumila* leaf extract increased the expression of type 1 pro-collagen to a level commensurate with UVB untreated control. Therefore, *L. pumila* leaf extract can be used as an anti-ageing agent for cosmetics [152,155-157].

Cell disruption can be caused by a certain level of UV irradiation. An increase in ROS within the cells, as initiated by UVB irradiation, is the primary reason for cell death. This cell death can eventually lead to a variety of photo-damage instances, through DNA oxidative damage [152,158]. UVB irradiated fibroblasts with a 52 mJ/cm^2 UVB exposure was treated through *L. pumila* extract, and it was observed that recovered cell viability is significant to untreated cells, in

which cell viability sits at around 70%. This data clearly shows that *L. pumila* leaf extract has a strong protective activity against cell damage initiated by UVB irradiation. Norhaiza *et al.* (2009) reported that the active components that contribute to the antioxidant properties of *L. pumila* leaf extract include β-carotene and flavonoids, as these components might scavenge the ROS generated by UV irradiation [151]. β-carotene and flavonoids could also directly or indirectly affect the expression of pro-inflammatory cytokine, and thereby reduce inflammation initiation caused by UV irradiation.

L. pumila leaf extract has been proven to have strong antioxidant activity, compared to that of ascorbic acid, by analyzing their antioxidant activities using the DPPH (2, 2-diphenyl-1- picrylhydrazyl) methods [155]. UVB induced-TNF-α can be reduced, when treated with an *L. pumila* leaf extract. Previous studies have shown that UVB induced-TNF-α production was increased by four to five folds, when compared to treated cells. The elevated TNF-α secretion of the UVB-irradiated HaCaT cells was significantly reduced when treated with *L. pumila* leaf extract for 24 h. Dexamethason is a potent anti-inflammatory agent, and was used as a positive control. The treatment of dexametason 1 μM reduced TNF-α secretion by approximately 40%, while the level of UVB-induced TNF-α secretion was almost completely inhibited by 92%, with a 0.01% *L. pumila* leaf extract. This study shows that the *L. pumila* leaf extract could be used as an anti-inflammatory agent [155].

3.7. *Andrographis paniculata* (Hempedu Bumi)

Andrographis paniculata is an herbaceous annual that belongs to the Acanthaceae family, native to Southeast Asia, and specifically to China, India, and Sri Lanka. This herb has been traditionally used in Ayurvedic medicine, otherwise known as Indian traditional medicine. It is most used to treat and prevent infectious diseases, as it is thought to strengthen the immune system [159]. *A. paniculata* has been reported to have beneficial properties, including antibacterial, antifungal, antiviral, choleretic, hypoglycemic and hypocholesterolemic properties [160].

Andrographolide is the primary bioactive phytochemical of *A. paniculata* [161], and it is found in the plant's leaves at a concentration of >2% [41]. Das *et al*. (2009) reported that the nicotine-induced inhibition of a resultant increase in nitric oxide (NO) to different parts of rats' brains can be prevented through the simultaneous treatment with water and ethanol leaves extracts of *A. paniculata* or andrographolide [94]. Through the use of phytochemical analysis, it was observed that the water leaf extract of *A. paniculata* contains a higher quantity of flavonoid, but a lower phenol content, when compared to an ethanol extract [162].

Andrographolide pretreatment has significantly limited the accumulation of the phorbol-12- myristate-13-acetate (PMA)-induced formation of ROS, and the N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced adhesion of rat neutrophils [163]. Andrographolide can cause iNOS activity to decrease, by reducing the expression of the iNOS protein [164,165]. Besides that, andrographolide can also perfectly reestablish the maximal contractile response of thoracic aorta to phenylephrine, after incubation with LPS, and can prevent the mean arterial blood pressure of anesthetized rats from falling as a result of LPS [165].

A. paniculata has been widely used as a traditional medicine to treat a variety of infections. Modern research also has examined the activity of *A. paniculata* on various parasites, bacteria and viruses. Singha *et al.* (2003) reported significant antibacterial activities of in an aqueous extract of *A. paniculata,* and attributed this to the combined effect of andrographolides and arabinogalactan proteins [166]. A similar conclusion was reached by Zaidan *et al.* (2005) who found that a crude aqueous extract of leaves exhibits significant antimicrobial activity against gram positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and gram-negative *Pseudomonas aeruginosa*, but had no activity on *Escherichia coli* or *Klebsiella pneumonia* [167].

3.8. *Orthosiphon stamineus* (Misai kucing)

Orthosiphon stamineus, from the Lamiaceae family, is a plant native to South-East Asia. The word Orthosiphon is derived from two Latin words, namely orthos and siphon, which mean straight and cylindrical, respectively. It is an herbaceous shrub which grows to a height of 1.5 meters [168]. In traditional medicine, an extract of *O. stamineus* is usually created through a boiling process, and is used to treat hypertension, liver and kidney pains, and to promote excretory functions. Its common name is 'Java tea', as this plant is primarily grown in Java, and it is also referred to as 'cat's whiskers' because of its great stamina. It is believed to have antiallergenic, antihypertensive and anti-inflammatory properties. It is also reported to possess antifungal qualities, and it exhibits considerable antibacterial properties [169, 170].

A study conducted by Vogelgesang *et al.* (2011) has determined that the aqueous extract leaves of the *O. stamineus* exhibits anti-seborrhea properties, as it can improve the shiny appearance of skin and reduce pore size, and thus has the potential to be used in cosmetic formulas [168]. In the *in-vitro* study, *O. stamineus* has the ability to reduce mRNA expression of the 5α reductase type 1 in normal human epidermal keratinocytes (NHEK), and this correspondingly helps to minimize the oily appearance of skin. In the ex-vivo study, it was confirmed that the *O. Stamineus* leaf extract can also reduce the production of the chief components of sebum, which is squalene [168].

Previous research by Akowuah *et al.* (2004) reported on the antioxidant properties of *O. stamineus* leaf extract [171]. The DPPH assay has been used to test the free radical scavenging ability of *O. stamineus*. Antioxidants interrupt free radical chain oxidation, by donating hydrogen from hydroxyl groups to form a stable end-product which does not commence or proliferate the further oxidation of lipids within the human body [172]. The findings of the current study are in agreement with those indicating that the leaves extracts of *O. stamineus* are free radical inhibitors, and that primary antioxidants that react with free radicals and polar extracts have the highest free radical scavenging activity. However, Akowuah *et al*. (2004) investigated for the first time the antioxidant activities of *O. stamineus* leaves extracts fractions [171].

3.9. *Aloe Barbadensis* Miller (*aloe vera*)

Aloe Barbadensis Miller belongs to the Asphodelaceae (Liliaceae) family, and is a shrubby or arborescent, perennial, xerophytic, succulent, pea-green color plant [173]. *Aloe vera* has a positive impact on skin diseases, and it is usually taken as a health drink. The name *aloe vera* is derived from the Arabic word Alloeh, meaning shining bitter substance, while vera in Latin means true. It is also found to be effective in treating wrinkles, stretch marks and pigmentations. *Aloe vera* can also improve blood circulation, and prevent cell death surrounding wound areas, and therefore it can be used to accelerate wound healing processes [173].

Aloe vera exhibits healing properties by significantly increasing collagen synthesis, which is important for wound contraction after the topical and oral intake of *aloe vera*, as this plant contains a mannose-rich polysaccharide called glucomannan. Glucomannan acts as a growth hormone which is able to interact with growth factor receptors in the fibroblast around the wound area, thus initiating fibroblast activity and proliferation [174]. Despite encouraging increases in collagen synthesis, *aloe vera* gel also promotes changes in collagen composition, and can increase degrees of collagen cross-linking. These two factors can simultaneously stimulate wound contraction, and increase the breaking strength of the resulting scar tissue [175]. A previous study has also claimed that hyaluronic acid and dermatan sulfate within the granulation tissue of the healing wound can be increased through treatment with *aloe vera*, either topically or orally [174].

Aloe vera also exhibits a moisturizing effect, as it contains mucopolysaccharides that are able to bring moisture into the skin. In addition, *aloe vera* activates fibroblasts, cells which are responsible for producing collagen and elastin fibers, thereby encouraging the skin to be more elastic and less wrinkled. *Aloe vera* also contains amino acids that encourage the softening of hardened skin cells, and zinc which can be used to help tighten pores. A study has also been conducted to determine the treatment of dry skin associated with occupational exposure, and it has been identified in the study that *aloe vera* gel gloves both recover and enhance skin integrity, reduce the appearance of fine wrinkles, and reduce erythema [176]. It also has an anti-acne effect [173].

The skin plaque appearance caused by psoriasis can be reduced by applying a cream containing 0.5% *aloe* for 4 weeks, as *aloe vera* has the ability to destroy bacteria and fungi [82]. The application of *aloe vera* gel can also improve the partial thickness of a burn on the skin [83], promote skin recovery from frostbite injuries [85], delay the formation of skin damage due to radiation treatment, [84] and inhibit fungi, viruses and bacteria. *Aloe vera* contains six antiseptic agents, including lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur [173].

3.10. *Zingiber officinale* (ginger)

Ginger is derived from the root of *Zingiber officinale*. It is a flowering plant within the family Zingiberaceae, which originated in South-East Asia, and was then used in many countries as a spice and condiment for adding flavor to food [177]. In addition, the *Z. officinale* rhizome has also been used in traditional herbal medicine. The health-promoting aspects of *Z. officinale* have been attributed to its rich phytochemistry [178]. Fresh and dried *Z. officinale* contains relatively large amounts of volatile oils, including camphene, p-cineole, alpha-terpineol, zingiberene, and pentadecanoic acid [179,180]. Kikuzaki and Nakatani (2006) reported that 12 out of the 5 gingerol-related compounds and 8 diarylheptanoids isolated from *Z. officinale* rhizomes, exhibit higher antioxidative activities than α-tocopherol [181].

Z. officinale is a strong antioxidant substance, and which may either mitigate or prevent the generation of free radicals. It is considered to be a safe herbal medicine, with only a few insignificant adverse/side effects [181]. *Z. officinale* rhizome extract has been shown to have an antioxidant activity almost equal to that of synthetic antioxidants, including BHA and BHT [182]. Jung *et al.* (2009) indicated that the rhizome hexane fraction extract of *Z. officinale* inhibits the excessive production of NO, PGE [178], TNF-alpha, and IL-1beta [183]. Because of the potent compounds in *Z. officinale* rhizome utilized for inhibiting allergic reactions, it may be useful for the treatment and prevention of allergic diseases [184]. A study conducted by Habib *et al*. has determined that the elevated expression of NF-κB and TNF-α in rats with liver cancer can be decreased through the application of *Z. officinale* rhizome extract [185]. The activation of NF-κB is linked to a variety of inflammatory diseases, including cancer, atherosclerosis,

myocardial infarction, diabetes, allergy, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock and acquired immunodeficiency syndrome (AIDS) [186].

Further research undertaken by Khaki and Khaki (2010) has established that *Z. officinale* rhizome extract must have reduced the oxidative stress that Pb could cause. *Z. officinale* is the source of antioxidants that reduces the oxidative stress that Pb exposure can cause in *Z. officinale*-treated animals [187,188]. There was no significant (P-value > 0.05) difference in both the plasma and tissue MDA concentration of the control, and those of the animals treated with *Z. officinale* rhizome extract, along with Pb, whereas animals treated with Pb only showed a significant (P-value < 0.05) increase in plasma MDA concentration. This confirms that *Z. officinale* can reduce the oxidative stress that Pb exposure could have caused in *Z. officinale*-treated animals. *Z. officinale* rhizome extract can decrease damage to liver cells, specifically from the oxidative damage induced by Pb, and it is dependent on their antioxidant effects [189]. A similar conclusion was reached by Hasan (2015), who found that *Z. officinale* rhizome extract significantly decreased the adverse harmful effects of lead acetate exposure on the liver, while *Z. officinale* may also exert its protective actions against Pb-induced histopathological changes in liver tissue [190].

A previous study conducted by Azu and Onyeagba (2007) has found that *Z. officinale* and its constituents can exhibit anti-microbial activity against *E coli, Salmonella typhi* and *Bacillus subtilis*, while the largest zone of inhibition was observed when *Salmonella typhi* was treated with an ethanolic rhizome extract of *Z. officinale* [191]. In addition, earlier studies have determined that *Z. officinale* also has a broad antibacterial activity. An example of this is the effectiveness of a treatment of an ethanol rhizome extract of *Z. officinale* in destroying *Candida albicans* [192-194]. Another study has also reported that the gingerol component in *Z. officinale* has anti-fungal properties [192,195]. Chief constituents such as gingerol [196], as isolated from the *Z. officinale* rhizome, has shown antibacterial activity against the periodontal bacteria [197], and has been reported as an active inhibitor of *Mycobacterium avium* and *M. tuberculosis in-vitro* [198].

3.11. *Nephelium lappaceum* L. (rambutan)

Nephelium lappaceum is a medium-sized tropical tree in the family Sapindaceae. *N. lappaceum* is a tropical fruit, whose peel possesses antioxidant properties. It is commonly known as rambutan, and is widely distributed in South East Asia, specifically in the eastern and southern regions of Thailand. *N. lappaceum* is believed to have originated in Indonesia, and is now widely found in the Philippines, Malaysia, Cambodia, Sri Lanka, India, Ecuador, Australia and America.

From a previous study, Nont *et al.* (2010) performed antioxidant analyses based on lipid peroxidation inhibition and DPPH scavenging assays [199]. The results showed that the methanolic extract of *N. lappaceum* peel contains significant amounts of phenolic compounds (542 mg/g dry extract), and has exhibited obvious antioxidant activity. *N. lappaceum* peel extract can serve as a potent antioxidative agent, possessing much more antioxidant activity than synthetic antioxidants (BHT) [199]. There are many types of compounds that possess antioxidant activities in higher plants, and the phenolic compounds were highlighted as potential antioxidants [200]. Phenols are very important plant constituents, because of their scavenging ability in regards to free radicals, due to their hydroxyl groups [201].

Previous research by Ton Mohamed (2015) has determined that DPPH-antioxidant assays and *in-vitro* fibroblast growth stimulation are tests that will be conducted on the leaf extract of *N. lappaceum,* in order to evaluate wound healing abilities [202]. The migration rate of human skin fibroblast was assessed through the use of a scratch wound assay, which can measure the expansion of a cell population on surfaces, as described by Fronza *et al.* (2009) [203]. Confluent monolayers of human skin fibroblast were scratched and then allowed to re-epithelialize for 24 h at 37ºC, wither in the presence or absence of *N. lappaceum* leaf extracts of various concentrations. The test samples of water extracts achieved cells migration rates of up to around 30.99 ± 8.39%, at a concentration of 50 μg/mL. This finding confirmed the potential of *N. lappaceum* water leaf extract to facilitate dermal repair. Saponins are known to promote wound healing processes, due to their antioxidant and antimicrobial activity [204].

The proliferation of microbial pathogens in a wound, causing tissue damage and eventually resulting in an inflammatory response, can be defined as an infection. The typical micro-organisms that can cause wound infections are *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Clostridium perfringens, Clostridium tetani,* Coliforms, *Enterococcus faecalis* and *Enterococcus* spp. [205]. In order to prevent the infections that have become the main causes of morbidity and mortality in wound patients, and the prolonged inflammation that can lead to sepsis, *N. lappaceum* leaves extracts can be used to treat these infections [206,207].

4. Summary

Plants from which extracts have been prepared and tested, in regards to their ability to act as epidermal barrier protecting agents, have been listed in this review study. The list consists

of eleven plant species that show a high tendency towards skin barrier protector, and that can serve as alternative medications for the treatment of skin diseases including psoriasis and atopic dermatitis. The plants shown in Table 1 need to be studied further, in order to identify and isolate potential bioactive compounds.

5. Conclusion

This review has covered only a few potential plants that could be used as epidermal barrier protecting agents. The available research highlighted the available information for various parts and extracts from medicinal plants, used for skin disease treatment. Plants have various active compounds that can provide safer and cost-effective treatment. They also have a great potential to treat various kinds of skin diseases. They are also effective in providing UV radiation protection from the sun, and preventing the side effects of harmful UV radiation on skin. Furthermore, medicinal plants have numerous ingredients that are useful for skin care. However the potential of many plants have been undefined, and therefore more research trials and clinical evidence is needed. Compared with conventional allopathic drugs, medicinal plants are easily, lower cost and safer, while allopathic drugs are more expensive and have harmful side effects on human health. Therefore the use of products based on plants has good prospects, especially in regards to their use in health care products. The market for medicinal plants is growing faster in developed countries, compared to that for pharmaceutical products. Therefore, both the government and industry sector should ensure the availability of a high quality standard of medicinal plants, in order to fulfil market demands.

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