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A Review on Herbal Skincare Creams

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Abstract

Skin is the largest organ of the human body which has been outlined to have more than 20 vital physiological functions. Skin acts as a protective barrier against pressure and trauma. It also acts as a barrier for external environments including pollution, sunlight, radiation, harmful microbes, and chemical. Skincare products are medicinal formulations prepared to be used on external parts of the human body to produce therapeutic topical effects and shield the deteriorated skin. Herbal skincare creams have been widely used by many generations for centuries for the purpose of skincare. Nowadays, these herbal skincare creams are becoming more popular and prevalent among people due to their mindset and concerns about synthetic or chemical substances that may lead to adverse effects. The main factors that lead to the usage of herbal ingredients in skincare creams are their outstanding antioxidant, antimicrobial, and tyrosinase inhibition properties. The studies on the potential pharmacologically active herbs for skincare creams allow us to understand their importance. In this review, several examples of herbs being used and still undergoing clinical studies were identified according to different skin conditions includes hyperpigmentation, skin aging, and acne. This detailed work might contribute to accomplishing consumer demand.

Keywords: Herbal; Acne; Aging Hyperpigmentation; Antimicrobial activity

Introduction

Skin care creams are defined as a semi-solid emulsion containing mixtures of oil and water which can be used to moisturizes the skin of the face and any other parts of the body(1). Skin is the organ with the largest surface area in human body, having two main layers, the epidermis which protects our body and prevents water loss, and the dermis containing various glands, blood vessels, and receptors(1). The integrity of skin damage by various factors, including advanced age, stressful lifestyle, exposure to ultraviolet lights, usage of inappropriate skin cleansing agents, hormonal changes, and others(2, 3). As a result, many people exhibit mild signs and symptoms of deteriorated skin such as wrinkles and dry skin. A regular skin care is required to prevent inflammation and infections such as acne vulgaris and ulcerations(2).

Good skincare practice does not only help to enhance protective functions of skin, but also impart beneficial cosmetic effects on us. With the increasing aging population of the world and aggressive marketing by cosmetic companies, the demand for skincare products surged. Skin health and beauty has also been suggested as an important indicator in people's perception of wellness(4). Furthermore, the increased exposure to environmental pollution and ultraviolet lights may quicken the skin deterioration process. Thus, the search for new and more effective skincare products remains a lucrative aspect.

Skincare products generally produce a localized effect on the affected part of our skin. Despite its function in preventing entry of foreign materials, epidermis is not impermeable to all substances. The hydrophobic nature of the keratinized cells at stratum corneum makes skin a good barrier against ionic compounds, but lipophilic substances may still penetrate through the stratum corneum, albeit at varying speed.

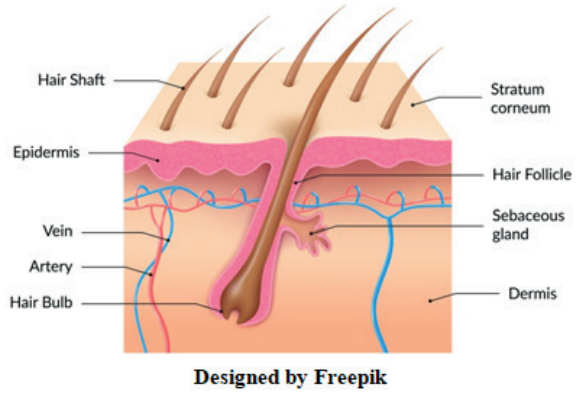

Figure 1. Structure of the skin.

The structure of the skin is presented in Figure 1. Most of the target sites for topical skincare products are located at lower layers of skin, hence, these products need to be able to penetrate through stratum corneum and to reach below. This is further complicated by the remaining layers of epidermis, which are hydrophilic in nature. Hence, if a substance is too lipophilic it might remain at stratum corneum, unable to be distributed further into deeper layers of the skin(5). The drug molecules may still enter the skin via hair follicles, which

by itself form a natural gap at stratum corneum layer. Due to the limited surface area of follicular route on skin, traditionally the follicular pathway was not considered as the main absorption pathway for transdermal drugs. However, newer studies are now being carried out to review the significance and potential of this pathway(6).

Main factors affecting the substances' penetration includes the integrity of skin barrier, the polarity and molecular weight of the substance, and temperature of the penetration site. Increased skin hydration via perspiration or elevated humidity also enhances the penetration of drugs through transdermal route(7). The use of permeation enhancers may disrupt the integrity of skin barrier or increase hydration of the skin to improve transdermal absorption(5, 8). Due to the nature of stratum corneum and viable epidermis, substances which exhibit both hydrophilic and hydrophobic characteristics may penetrate better into the skin. Hence, a proper vehicle is generally used to endow such properties to the pharmacological agent. Thus, the solubility of the substance in vehicle, and the release rate of substance from the vehicle affects the transdermal absorption greatly(7). The various thickness of skin at different body sites, along with the number of follicles at different body parts also affects the rate of absorption at the skin.

Due to the complex nature of the skin, the development of topical products needs to factor in the site of application, the biophysical properties of the skin on that site, and the suitable vehicle or permeation enhancer compatible with the active ingredients.

Natural ingredients in skincare products

Skin care products are the medicinal preparations intended to be placed in contact with the various external parts of the human body that manifest beneficial topical actions and provide protection against degenerative skin conditions(9). The preparations of natural ingredients have been traditionally used for skin care purposes in past centuries. Anti-inflammatory, anti-allergy, moisturizing, pro-collagen, anti-aging, anti-hyperpigmentation, wound healing and free radical scavenge action of herbal ingredient have been discovered by clinical studies(10). Most of the herb-based creams demonstrated superior effectiveness on various therapeutic use as compared to placebo. Nowadays, these preparations are becoming more popular in modern formulations due to consumers' concerns about synthetic ingredients/chemical substances includes sulphide, alcohol, paraben and sodium lauryl sulfate (SLS). Consumers also favor herbal or natural-based products over synthetic products, due to the long history of herbs used in the community without major toxic effects.

One of the most commonly used skincare products are skin lightening creams. The natural skin lightening agents obtained from plant extracts are more effective, safer, non-toxic and cost effective than the chemical agents such as mercury and hydroquinone, which can lead to adverse effects(11). Mercury may cause adverse effects since it can be absorbed through intact skin(12), leading to systemic side effects. The adverse effects of mercury on kidney and neurological functions have been well established in previous studies(13, 14). Chronic adverse events related to exposure to hydroquinone include ochronosis, nail discoloration, conjunctival melanosis and corneal degeneration(15), with ochronosis being the most common chronic complication related to long-term use of hydroquinone(16). For many years, hydroquinone also has been known to be highly cytotoxic to melanocytes and potentially mutagenic to mammalian cells(17).

Natural skin care products improve skin tone, texture, and appearance by delivering nutrients that are essential for healthy skin. Furthermore, phytochemicals have been found to inhibit or prevent the physiological mechanisms leading to many common skin conditions, includes hyperpigmentation, acne, and skin aging. These herbal extracts are primarily added to the skincare formulations due to several associated properties such as antioxidant capacity, pigmentation inhibition, and antimicrobial activity, which can also be beneficial for attenuation and prevention of various skin conditions(9, 18).

However, in the current market, very few creams were prepared using the natural, protected, organic, and herbal ingredients. Most of the creams exist now in the market used synthetic polymers, emulsifiers, perfuming agents, pigments, surfactants and thickeners to form the base. There is a wide and crucial need to substitute these toxic synthetic agents from base by using natural agents instead.

Potentially active pharmacological herbs for skincare products

To understand the potential herbs for skin care, we have identified and focused on three skin issues commonly faced by public: hyperpigmentation, acne, and skin aging.

Hyperpigmentation

Melanin is a pigment molecule that determines the color of a skin. Melanocytes produce melanin which protects the tissues and organs from infections and external forces such as ultraviolet radiation, through a complex process called melanogenesis. However, hyperpigmentation only occurs when excessive melanin is produced. Hence, controlling the production of melanin is an important treatment for pigmentation-related disorders(19). In melanogenesis, the enzyme tyrosinase plays a crucial role in the conversion of L-dopa to melanin via tyrosinase activity. This activity is a rate-limiting process which regulates the production of melanin. Phytochemicals which can inhibit the actions of tyrosinase can help to reduce the rate of melanin

production and thus produces skin whitening effects. The mechanism for skin hyperpigmentation is summarized

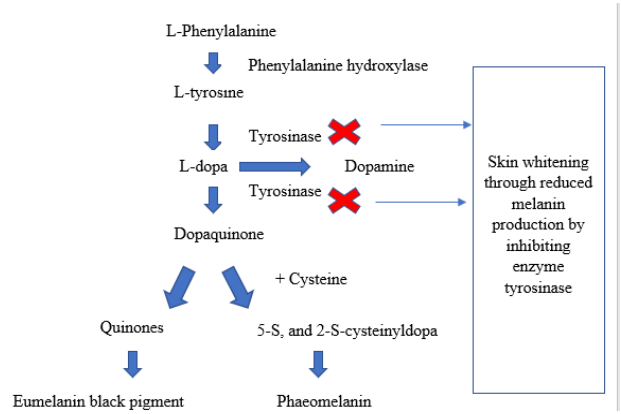

Figure 2. Mechanism of hyperpigmentation.

The consumption of soy rich products may reduce the risk of cardiovascular diseases, diabetes mellitus and breast cancer. Due to the advancement in science and technology, soy extract was found to have depigmentation effect on the skin. Serine protease inhibitors present in soy extract inhibit protease-activated receptor-2 (PAR-2) mediated phagocytosis of melanosome by keratinocytes. Furthermore, the isoflavones content in soy extract shows antioxidant property which subsequently protect the skin from ultraviolet radiation and provides photoprotection(20). On the other hand, orange peel (*Citrus aurantium*) extract and mulberry (*Morus alba*) extract were effective as whitening agent in cosmetics due to their anti-tyrosinase action(21, 22). In addition, mulberry extract was also having antioxidant property(22). In contrast, enzyme such as lignin peroxidase (derived from *Phanerochaete chrysosporium*) was proved to decolorize melanin and provide skin whitening effect(23). Lignin peroxidase acts by breaking down melanin instead of lignin due to their similarity in molecular structure (24, 25).

Another study formulated *Hippophae rhamnoide s* and *Cassia fistula* cream for skin whitening effect. The study showed significant reduction in melanin content over time. This is attributed to the activity of flavonoids present in *Hippophae rhamnoides* and *Cassia fistula* that inhibits tyrosinase, the rate limiting enzyme for melanogenesis(26, 27). Zhang Q et al. (28) formulated a polyherbal cream consists of Yunnan camellia, sanchi, *Prinsepia uti lis* oil and *Portulaca oleracea* for the management of melasma. Among all the herbal extracts, Yunnan camellia works by inhibiting melanogenesis, whereas sanchi works by promoting microcirculation. In addition, *Prinsepia ut ilis* oil helps to maintain skin hydration and repair skin barrier, while *Port ulaca oleracea* acts as anti-inflammatory agent(29, 30). Despite of the inhibition of melanogenesis, camellia extract showed to have antioxidant property which is beneficial for pigmentation control(31). Hence, the combined effects of all the four herbal extracts simultaneously reduced the MASI scores among the study subjects(28).

Rambutan (*Nephelium lappaceum* L.), also commonly known as 'hairy litchi', is a tropical fruit belonging to the family *Sapindaceae*. Due to the potential anti-tyrosinase activities of rambutan fruit extract, the rambutan fruit cream has previously been developed as a potential skin whitening product(32). In the previous study, crude methanol extract flesh (CMEF), successive methanol extract flesh (SMEF), crude methanol extract peels (CMEP) and successive methanol extract peels (SMEP) of rambutan fruits were the components of antiaging cream. CMEP and CMEF exhibited potent tyrosinase inhibition activity with IC_{50} values of 38.88µg/ml and 43.80µg/ml respectively. SMEP, SMEF, CMEP and CMEF exhibited more potent antioxidant activity with IC_{50} values of 38.88µg/ml, 93.85µg/ml, 103.84µg/ml and 98.71µg/ml respectively. The results concluded that the rambutan fruit creams show good potential for cosmetic product development(32).

Another study formulated *Phaleria macrocarpa* cream for skin whitening effect. *Phaleria macrocarpa* is a fruit-bearing plant commonly found in tropical countries including Indonesia and Malaysia. Also known as 'Mahkota Dewa' in Malay language, its fruit contains large amounts of mangiferin. Mangiferin cream exhibits potent tyrosinase inhibition activity with a percentage of inhibition rate of 93.40 ± 2.10 at 1000µg/ml. Mangiferin showed potentantioxidant activity with a percent inhibition rate of 92.28 ± 2.92 at 62.5µg/ml by DPPH method. The study found that *Phaleria macrocarpa*cream formulation is an effective anti-tyrosinase preparation for the skin, and have a good chance in improving the cosmetic product development(33).

Skin aging

The signs of aging become clearer as life progresses. Changes in skin appearance and texture are one of the first evidences which indicates the beginning of aging process. Aging is caused by combination of endo-native factors (such as genetic alterations, cellular metabolism, and hormonal environment) and external factors (such as chemicals, toxins, pollution, UV radiation, and ionizing radiation). UV-irradiation, for example, induces the transcriptional activity of the elastin gene by a fourfold causing increase in elastin promoter activity, while reducing the fibrillin-1 expression leading to greater elasticity of the elastic fibers(34). These aging processes are accompanied by phenotypic changes in cutaneous cells and the systematic and functional changes in the extracellular matrix components (such as collagens, elastin, and proteoglycans) which are required to provide minimal strength, elasticity and hydration to the skin, respectively(35).

Figure 3 shows the basic mechanism of skin aging. Anti-aging and anti-wrinkle processes may be done by reducing the activities of hyaluronidase,

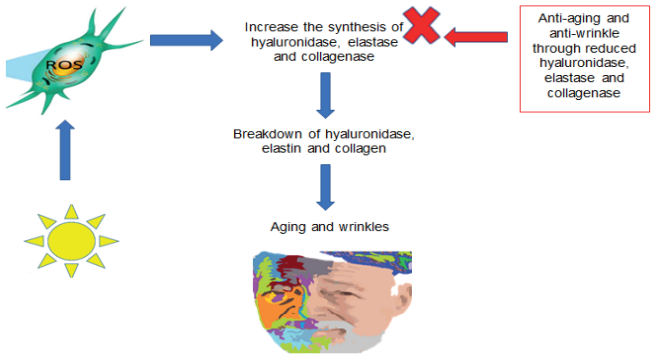

Figure 3. Basic mechanism of skin aging.

elastase, or collagenase. Some of the naturally occurring photo-protective compounds may also help to reduce the irradiation effect and hence reduces aging process. Creams containing herbal extracts with reported anti-aging activities have been successfully developed in various studies.

Herbal extracts with antioxidant activities and UVB protection have also been studied on its skin anti-aging effect. In the recent years, topical creams containing *Coptisteeta* with *Trichosant hes rost hornii, Scut ellaria baicalensis* and *Raphanus sativus*were developed by Korean researchers to be tested on its anti-wrinkle properties (36, 37). *Coptisteeta* (Family: *Ranunculaceae*) is a traditional Chinese medicine commonly used for internal (gastrointestinal diseases) and external ailments (skin diseases). It was documented that its ethanolic extract and berberine, one of the component from its rhizome, contributed to its antioxidant activity (38). *Trichosant hes rost hornii*(Family: *Cucurbitaceae*) is widely used to treat coughing. Both of these plants claimed to be useful against symptoms of skin disease such as itching and numbness. Meanwhile, *Scut ellaria baicalensis* (Family : *Lamiaceae*) and *Raphanus sativus* (Family : *Brassicaceae*) are effective in treating skin diseases such as urticaria and acne (37). Studies with RCT documented that both the creams possessed good anti-wrinkle and anti-collagenase activities several weeks after application in addition to their great protection against UVB irradiation. Hence, these creams can effectively improve naturally aging skin conditions and preventing the skin from extrinsic aging mainly caused by photo damage (36, 37).

Besides, *Panax ginseng* (Family: *Araliaceae*) has been found to be a promising natural anti-aging candidate to be incorporated in cosmetics. Researchers had identified that a number of ginsenosides (Rb1, compound K, F1) are the major contributor to its anti-aging properties. Enzyme-modified *Panax ginseng* (EG) cream was developed and it had significantly improved crow's feet conditions by inhibiting extrinsic skin aging induced by UVB rays. Its application on mouse skin also showed significant improvement in reversing thickening of skin and loosening of collagen fibres caused by UVB irradiation. In addition, EG cream also effectively improved skin roughness and hydration in human after application. Thus, these findings suggested that the enzyme-modified *Panax ginseng* is a great anti-aging natural ingredient to be considered in the formulation of cosmetic products(39).

Another herbal extract, *Grammat ophyllum speciosum* pseudobulb extract (GSE), is known to aid in anti-aging according to a study in Thailand. *Grammato phyllum speciosum* (Family: *Orchidaceae*), also known as giant orchid, is widely found in tropical rainforest in Southeast Asia. Its ethanolic pseudobulb extract (GSE) was found to be effective in the regeneration of skin by increasing human keratinocytes stem cell phenotypes. Gastrodin, which is the polyphenols found in GSE, acts as a great antioxidant that can protect the keratinocytes from superoxide-induced apoptosis. It can be concluded that GSE can be a good choice to be incorporated in skin care products for its dermatologic benefits (40). Further more, jasmine rice panicle extract had been used traditionally in a number of countries to treat skin diseases such as in skin aging, skin whitening and often used for skin rejuvenation. It was proved to have great antioxidant properties after testing on human fibroblast cells against hydrogen peroxide-induced oxidation. Besides, it was found to have synergistic anti-tyrosinase properties that reduces melanin formation and promotes skin whitening as shown in B16 melanoma cells(41).

The polyherbal cream of curcumin, quercetin, resveratrol and safranal was previously developed by Donglikar et al.(42). This polyherbal cream showed synergistic antioxidant activity, and the efficient topical product has reported SPF value of 22.60. The researchers concluded that this topical product is a stable natural photo protective formulation with antioxidant potential, high SPF and more importantly with uniform UVA/UVB protection (42).

Similarly, polyherbal cream with cocoa polyphenol, *Aloe vera* and *Euchema cottoni* (seaweed) has also been developed with anti-aging properties(43). The researchers found that combination of extracts from these three ingredients allowed good skin protection towards UVB lights. The anti-aging properties was determined by investigating number of wrinkles caused by UV light exposure on rat's limb, and the skin with this polyherbal exhibited fewerwrinkle and erythema after exposing to UVB lamp. Polyherbal cream with cocoa polyphenol, *Aloe vera* and *Euchema cottoni* was shown to produce good UV protection to skin in the study(43).

Certain herbal extract helps to increase the collagen content in skin, and thus reducing wrinkles. The leaves of *Clerodendrum paniculatum* (Family: *Lamiaceae*) also been reported in the treatment of skin ailments. Meanwhile,*Murraya koenigi* leaves (Family: *Rutaceae*) and *Rosa damascena* flowers (Family: *Rosaceae*) were commonly reported for their antioxidant activities. The polyherbal cream formulation of *Rosa*

damascena, *Clerodendrum paniculatum*, *Murraya koengii* and *Annona squamosa* showed stimulation of collagen gene I expression in *in-vitro* study. The researchers found increased collagen content in the skin and thus improved formation of collagen matrix. Hence, the polyherbal cream can repair damaged skin caused by various clinical conditions for skin elasticity and skin regeneration(44).

Other formulations help to exhibit anti-aging properties by inhibiting the activities of elastase. For example, the polyherbal creams containing the leaves of *Nyctanthes arbor-tristis*, ripe fruit of the *Aegle marmelos* wood, and the terminal meristem of *Musa paradisiaca* flower in the ratio 6: 2: 1: 1 and 1: 1: 1 respectively were found to exhibit antioxidant activities and anti-elastase activities in fibroblast cells(45). The results concluded that formulation 6: 2: 1 could be used as a potential agent to prevent skin aging and restore skin elasticity(45).

Herbal extracts with antioxidant activities have also been studied on its skin anti-aging effect. *Annona squamosa* is one of the important medicinal plants (Family: *Annonaceae*), and is commonly called 'custard apple'. *Annona squamosa* leaves are sometimes used as folk medicine in treatment of wound in different parts of the world. Presence of acetogenins, polyphenols in leaves of *A. squamosa* play a role as an effective free radical scavenger. Leaves extract of *Annona squamosa* anti-aging cream shows maximum percentage inhibition of DPPH of about 78%, as compared to ascorbic acid which shows maximum 61% inhibition (50µg/ml) and concluded it helps in decrease oxidative damage due to its high antioxidant effect to our skin(46).

In another study, Ilomuaya and team focused on *Ocimum gratissimum* and *Tetracarpidium conophorum*'s anti-aging properties(47). *Ocimumgratissimum* is an herbaceous which belongs to the family *Lamiaceae*. It is commonly known as scent leaf. *Tetracarpidium conophorum* , also known as African walnut, belongs to the family *Euphorbiaceae*. The formulated polyherbal cream of both plants showed concentration-dependent antioxidant activity in the study, with the highest antioxidant activity with IC_{50} value of 80.1µg/ml and 83.2µg/ml, respectively. The study concluded that the polyherbal oil-in-water cream showed excellent antioxidant properties. It can be used to protect the skin from reactive oxygen species created by UV radiation and environmental toxin, thus protecting the skin from photo aging(47).

The antioxidant effect of other plant extracts in skincare products have also been evaluated(48). Green tea extract with EGCG, pomegranate extract, amla extract, *Rhodiolarosea* extract, mango extract, bearberry extract, kakadu plum extract, tetrahydrocurcuminoid, resveratrol, oleuropein 40%, showed more than 90% inhibition in ABTS assay. The mango extract had a synergistic effect on the base of the cream with higher antioxidant activity compared to the extract alone (48).

Another common plant with potential skincare properties is papaya (*Carica papaya*). Its plant extract helps to increase collagen production in the skin, making the skin soft and firm. Papaya latex showed the highest antioxidant activity (32.01%). The tyrosinase inhibitory activities of papaya latex, papaya fruit extract and yam bean tuber extracts were 68.42%, 36.80% and 52.63% respectively and it shows as the potential natural skin lightening agent(49). Ethyl acetate fraction and xylene extract of *Carica papaya* were also reported to have high reducing power and free radical scavenging properties which could protect the skin and avoid aging of skin(50).

Acne

Acne is one of the most common skin disorders, and its occurrence is closely related to many factors, including sebum secretion, hormone levels, bacterial infection, and inflammatory reactions. Acne generally develops due to blockage of follicles, hyperkeratinisation, keratin plug formation and sebum. *Propionibacterium acnes*, a type of aerotolerant anaerobic Gram-positive bacteria, is a normal component of the cutaneous flora. It may invade the pilosebaceous unit using lipid rich sebum as a nutrient source and grow in the presence of increased sebum production leading to inflammation via complement activation and the release of metabolic byproducts, proteases and neutrophil-attracting chemotactic factors(51). When comedones ruptures, the contents of the pilosebaceous unit spread into the adjacent dermis and it leads to development of inflammatory acne vulgaris lesions such as cysts, nodules, papules and pustules(52). Acne may also be caused by fungal infection on skin.

Jantaratet al.(53)have formulated a gel preparation from herbal ball of *Androgra phispaniculata*, *Centella asiatica*, the Benchalokawichian remedy, plus the stem bark powder of *Hesperethusa crenulate*. The resulting gel exhibited antimicrobial activity against *Propionibacterium acnes*, and have the potential to be further formulated into commercial skincare products(53).

The garlic oil cream (sourced from *Allium sativum*) has also been investigated for usage in the treatment of fungal acne. Its medicinal property is linked with various components such as allicin, copper, zinc selenium and vitamin C in the garlic oil. The resulting cream formulation consisting showed good effects on microbial growth (zone of inhibition for C*andida albicans* was 42.32mm). The study concluded that the formulated garlic oil cream may be an effective preparation for the treatment of fungal infections (54). Another potential acne herbal preparation is from *Samadera indica,* a plant traditionally used for many diseases including itching, skin diseases, oedema, constipation, arthritis and general debility (Family: *Maroubaceae*). *Samadera indica* (5% w/w) in a carbopol gel base formulation showed activity against *Candida*

albicans, and could be a potential gel formulation for topical delivery of fungal acne infections(55). Besides anti-aging formulation, *Aloe vera* extract has also been studied as a component of polyherbal gel for fungal acne treatment. The combination of both *Catharanthus roseus* and *Aloe vera* extracts in herbal gel topical formulation was reported to have antifungal inhibition zone comparable to that of fluconazole(56). As a part of their self-defense mechanism, many plants produce bioactive phytochemicals with antifungal activities and it will be interesting to see if extracts from other plants can be formulated into similar preparations.

Studies demonstrated that tea tree oil and *Cassia fistula* was effective for the management of acne due to its antibacterial and anti-inflammatory effect(57, 58). High facial sebum level causes pilosebaceous duct obstruction that finally leads to acne formation. In addition, increased sebum is favorable for the growth of *Propionibacterium acne*. The formulation of *Hippophae rhamnoides* emulsion was shown to inhibit Type 1-α reductase and subsequently regulates sebum production(59–61). The anti-sebum effect of *H. rhamnoides* is attributed to the rich content of polyphenols, oleic acid and linoleic acid(62). Hence, *H. rhamnoides*is having anti-acne effect by reducing the sebum production(63).Studies have shown that theaflavin and its gallate present in black tea extract contributes to greater antimicrobial action(64, 65). Furthermore, the tannins and alkaloids present in black tea extracts possess both anti-inflammatory and 5α-reductase inhibitory effects which are beneficial for acne control(66, 67).

Nakamura CV et al.(68) reported that *Ocimum gratissimum* essential oil showed antibacterial activity due to the presence of a compound named eugenol. On the other hand, Lima ED et al. (69)demonstrated that *Ocimum gratissimum* essential oil was effective as an antifungal agent. Both antibacterial and antifungal actions of *Ocimum gratissimu*m essential oil are effective for the treatment of acne vulgaris(68, 69). Parveen S et al. (70) formulated an unaniherbomineral cream and supported that *Irsa* and *Baboona* was having anti-inflammatory action; *Neem* was having antiseptic property, while *Nagamortha* was having anti-inflammatory, antiseptic and healing effects which are beneficial to treat acne vulgaris.

Moghimipour E et al.(71) formulated a topical polyherbal cream consists of *Calendula officinalis*, *Rosa canina*, *Zataria multiflora* Boiss and *Trigonellafoenum-graecum* that demonstrated antimicrobial, anti-inflammatory and antioxidant effects. Furthermore, the inclusion of *Glycin max* in the formulation showed phytoestrogenic effect. The combined effects of the herbs are beneficial in reducing the severity of acne vulgaris(71). Shafiq Y et al.(72) demonstrated that 5% *Casuarina equiset if olia* herbal cream was having antibacterial, antifungal, anti-inflammatory and antioxidant effect which are typical for acne control. This is attributed to the amino acids, gallic acid, sitosterol and other active constituents present in *Casuarina equisetifolia*extract(73–75). Propolis was found to have antibacterial, antifungal, antioxidant and anti-inflammatory effect due to the presence of polyphenols, pinocembrin and apigenin(76, 77). On the other hand, *Aloe vera* showed antioxidant, anti-inflammatory and soothing effects during the course of acne treatment(71, 76, 78).

Herbal products with clinical trialevidences

Pigmentation Control / Skin Whitening

Mercury and hydroquinone-containing whitening agents were commonly used in the management of hyperpigmentation and melasma. However, they caused harmful effects on human health such as kidney damage, contact dematitis and onchronosis. Thus, the development of herbal-based face creams that possess anti-tyrosinase and whitening effects was widely studied by researchers. Mexameter was utilised to measure skin melanin content and observe for the improvement of skin tone after application of herbal cream.

Topical herbal creams commonly used in the management of hyperpigmentation had beensummarized in Table 1. Soy moisturizer and two (2%) w/w orange peel extract (*Citrus sinesis* L.) have more significant whitening effect and skin melanin reduction than cream base (control). The depigmenting property of soybean was attributed to the presence of antioxidants, soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI) in the extract(21, 79). Lignin peroxidase (derived from *Phanerochaete chrysosporium*) cream showed more rapid and significant skin lightening effect than 2% hydroquinone cream and placebo. This was attributed to the similarity in molecular structure between lignin and melanin that enable lipid peroxidase to break down melanin for skin whitening effect(24).

Mulberry (*Morus alba*) extract cream showed significant reduced in melanin level and improvement in melasma due to the existence of anthocyanin and flavonoid moiety that believed to inhibit tyrosinase activity as well as producing skin whitening effect(80, 81). In addition, emulsion containing *Hippophae rhamnoides* and *Cassia fistula* extract showed significant reduction in melanin level and improvement in pigmentation among all melasma patient in contrast to placebo(26). Polyherbal cream containing Yunnan camellia, sanchi, *Prinsepia utilis* oil and *Portulacaoleracea* was more effective than positive control and placebo in improving the condition of melasma(28).

Anti-aging / Anti-wrinkles

Several topical herbal creams have been investigated for their effectiveness towards wrinkle reduction by conducting randomized controlled trials (RCT) on human subjects. Five wrinkle parameters are

Table 1. Clinical trials of topical herbal creams.

No.	Cream	Study design	Efficacy	Side effects	Reference
1.	Moisturizer containing stabilized soy extracts	Randomized double-blind vehicle- controlled study	Soy extracts moisturizer improved blotchiness, mottled hyperpigmentation, dullness and skin tone.	No side effects.	(79)
B.	**Skin whitening**				
2.	Cream containing 2% w/w orange peel (*Citrus sinesis L.*) extract	Randomized controlled trial	Cream containing orange peel extract had more skin whitening effect than cream base (control).	No skin irritation.	(21)
3.	Lignin peroxidase cream	Randomized double-blind placebo-controlled, spilt-face study	Lignin peroxidase cream had more significant skin whitening effect than 2% hydroquinone cream and placebo.	Not reported.	(24)
4.	4% Mulberry fruit (*Morus alba*) extract cream	-	4% Mulberry fruit extract cream significantly reduce skin melanin content compared with cream base.	Skin drying effect.	(81)
C.	**Melasma**				
5.	Topical 75% Mulberry Extract Oil	Randomized single-blind placebo-controlled, full-face trial	75% Mulberry extract oil had better skin lightening property than placebo.	Mild itching in 4/25 subjects.	(80)
6.	Emulsion containing *Hippophae rhamnoides* and *Cassia fistula* extract	Single-blind, placebo-controlled study	Both *Hippophae rhamnoides* and *Cassia fistula* extract showed significant whitening effect as compared with placebo.	Mild itching/irritation in 4/25 volunteers (both plant extracts) Moderate erythema in 2/25 volunteers (*H. rhamnoides*); 4/25 volunteers (*C. fistula*).	(26)
7.	Polyherbal cream (containing Yunnan camellia, sanchi, prinsepia utilis oil and *portulaca oleracea*)	Randomized controlled clinical trial	More effective than arbutin cream and placebo in reducing the severity of melasma. Density of inflammatory cells decreased significantly.	No adverse event.	(28)
D.	**Wrinkle reduction**				
8.	Topical herbal cream of *Coptis teeta* and *Trichosanthes rosthornii*	Randomized double-blind placebo-controlled study	More effective than placebo cream in term of decreasing skin roughness and maximum roughness.	Not reported.	(36)
9.	Topical herbal cream of *Scutellaria baicalensis* and *Raphanus sativus*	Randomized double-blind placebo-controlled study	More effective than placebo cream in term of decreasing skin roughness, maximum roughness, average roughness, smoothness depth and arithmetic average roughness.	Not reported.	(37)
10.	Topical cream containing enzyme-modified *panax ginseng* (EG)	Single-center randomized double-blind placebo-controlled study	EG is significantly more effective than placebo in decreasing global photo-damage score, total roughness, smoothness depth, and arithmetic roughness average of the skin.	No side effects.	(39)

E.	**Anti-aging**				
11.	Topical serum containing pseudobulb ethanolic extract of *Grammatophyllum speciosum*	Randomized double-blind placebo-controlled split-face study	0.5% GSE is significantly more effective than serum base in improving skin distensibility, decreasing skin viscoelasticity and wrinkle volume.	No side effects (86.45%). No significance between control and GSE serum.	(40)placebo-controlled trial was conducted with 24 subjects for 56 days after facial application to evaluate efficacy. The results were measured with Visioface® and Cutometer® MPA 580 as well as by visual observations. Results: The total content of the antioxidant polyphenols in G. speciosum ethanolic extract (GSE
12.	No7 Protect & Perfect Intense Beauty Serum (Alliance Boots Ltd, Nottingham, UK)	Randomized double-blind placebo-controlled study	Test serum was significantly more effective than vehicle in reducing facial wrinkles and able to stimulate the deposition of fibrillin-1 in the treated skin area.	Not reported.	(84)
F.	Anti-aging, anti-wrinkle, skin lightening and firming				
13.	Topical cream containing jasmine rice panicle extract	Randomized double-blind placebo-controlled study	0.1% and 0.2% mL cream had significant and comparable effect on enhancing skin hydration, skin tone, firmness, smoothness and reduced wrinkle volume as compared to cream base.	No side effects and skin irritation.	(41)
G.	Acne vulgaris				
14.	5% topical tea tree oil gel	Randomized single-blind controlled study	Effective in relieving acne vulgaris but slower onset than 5% benzoyl peroxide lotion.	Skin dryness, pruritus, stinging, burning and redness.	(85)
15.	5% topical tea tree oil gel	Randomized double-blind	(86)	No skin irritation.	(21)
16.	Topical emulsion containing Hippophae rhamnoides and Cassia fistula	Randomized single-blind	(86)	Not reported.	(24)
17.	2% tea extract (Swan brand mark) lotion	Randomized	(88)	Skin drying effect.	(81)
18.	Topical Preparations of Ocimum gratissimum Linn Leaf Essential Oil	Preliminary clinical test	2% Ocimum oil was more effective than 10% benzoyl peroxide in acne vulgaris.	Mild 'burning' sensation on skin.	(90)
19.	Unani herbomineral cream (Irsa root, Neem leaves, Nagarmotha root, Harsinghar stem, Anzroot, Sibr extract)	Randomized single-blind controlled trial	Unani herbomineral cream was effective in the treatment of acne vulgaris.	Not reported.	(70)

20.	Topical polyherbal cream (containing extracts of Calendula officinalis, Rosa canina, Zataria multiflora, Trigonella foenum and Glycin max)	Placebo-controlled clinical trial	More effective than placebo in reducing number of papules, inflammation and severity index of acne vulgaris.	Not reported.	(71)
21.	Topical herbal cream (containing 5% of Casuarina equisetifolia extract)	Randomized controlled clinical trial	Effective in relieving acne vulgaris based on Cook's acne grading.	No adverse event.	(73)

commonly used to evaluate skin wrinkle, which are skin roughness (Rt), maximum roughness (Rm), average roughness (Rz), smoothness depth (Rp) and arithmetic average roughness (Ra)(82).

As shown in Table 1, cream containing *Coptisteeta* with *Trichosanthes rosthornii, Scutellaria baicalensis* and *Raphanus sativus* were shown to be effective to reduce skin roughness as compared to placebo(82, 83). It was proven to be able to inhibit collagenase by inhibiting matrix metalloproteinases (MMP-1), in which its expression is caused by UVB irradiation. Due to the increase in the subcutaneous tissues elasticity after application of the cream, it was able to reduce skin wrinkles as well as to achieve good anti-aging effect(82, 83). Besides, topical cream with enzyme-modified *Panax ginseng* (EG) also shown to have significantly decreased global photo-damage score, smoothness depth, and arithmetic average roughness as compared to placebo after 12 weeks of application. It was also documented that it gives remarkable hydrating properties to the trial participants despite low humidity setting was employed (39). Visual assessment had been conducted for the creams. Wrinkles around eyes were significantly improved after application of the topical herbal cream as compared to placebo. The creams were applied twice daily for the subject, which is very user friendly and convenient to apply(39, 82, 83).

Besides, biological activity and clinical efficacy studies on topical creams containing *Grammat ophyllum speciosum* pseudobulb extract (GSE) and jasmine rice panicle extract had been conducted in the recent years. It was shown that both the extracts were able to contribute significantly to the enhancement of skin properties related to anti-aging (skin distensibility, wrinkle volume, skin viscoelasticity, hydration level , skin tone, firmness and smoothness) in contrast to placebo(40, 41). Their effectiveness on skin were mostly contributed by the phenolic content in the extract itself. Questionnaires regarding consumer's preference on the creams physical properties and effectiveness were used and both the creams received good feedback from the subjects(40, 41).

A marketed product in the UK which contains plant extracts with anti-aging properties (*Panax ginseng*, *Morus alba*, *Lupinus alba*, *Medicago sativa*) and several functional peptides were tested on human subjects with facial wrinkles(84). As fibrillin-1 is the major glycoprotein component of fibrillin-rich microfibrils, increase in fibrillin-1 indicates increase in skin elasticity and firmness. In this study, it significantly reduced facial wrinkles at 6 and 12 months with fibrillin-1 deposition shown in immuno-histological test on dorsal wrist biopsies as compared to those treated with vehicle only(84).

Anti-acne

Topical herbal creams commonly used in the management of acne vulgaris had been summarized in Table 1. All the herbal cream preparations reviewed were effective in relieving acne in terms of reducing comedones and accelerating the healing of skin. Out of nine formulation reviewed, three of the herbal cream contained tea oil 5% topical tea tree oil gel demonstrated excellent effectiveness in relieving acne as compared to placebo, but slower onset as compared to conventional treatment (5% benzoyl peroxide lotion) (85, 86). In addition, Kim S et al. (87) demonstrated that the blend of tea tree oil and Palmarosa essential oil was more effective than tea tree oil alone. Multiple clinical trials were conducted for general treatment of acne vulgaris. However, different conventional treatment was used for different severity of acne vulgaris. There was no standard conventional treatment used in clinical trials for the comparison of effectiveness with herbal cream. Therefore, indication of herbal cream based on severity of acne vulgaris must be established for optimal management of acne vulgaris.

Topical emulsion containing *Hippophae rhamnoides, Cassia fistula* and 2% tea extract showed significant improvement in facial acne, compared with placebo (66, 88, 89). Furthermore, topical preparation containing 2% *Ocimum gratissimum Linn* leaf essential oil was more effective than 10% benzoyl peroxide and placebo in the management of acne vulgaris(90). Orafidiya L.O et al. (91) demonstrated that the combination of *Ocimum gratissimum* Linn leaf essential oil and *Aloe vera*gel showed greater anti-acne property than *Aloe vera* gel alone. In addition, it was more effective than 1% Clindamycin solution.Aqueous gel base incorporated with synthesized nanoparticles containing

of *Ocimum gratissimum* leaf extract was formulated for the treatment of acne vulgaris due to its superior anti-bacterial effect(92). Unani herbomineral cream was compounded using the extracts of *Irsa* root, *Nee*m leaves, *Nagarmotha* root, *Harsinghar* stem, *Anzroot* and *Sibr*. Various essential oils such as *Baboona*, *Khus*, *Mur-makki*, *Kundur* and *Chameli* were also included in the formulation. This cream showed significant improvement in the acne severity score in contrast to the control group(70). Furthermore, topical polyherbal cream (containing extracts of *Calendula officinalis*, *Rosa canina*, *Zataria multiflora*, *Trigonella foenum* and *Glycin max*), herbal cream (containing 5% of *Casuarina equisetifolia* extract) and topical cream (containing extracts of propolis, tea tree oil and *Aloe vera*) were reported to be effective in the treatment of acne vulgaris(71, 72, 93). Plant extract containing phenolic compounds was having antimicrobial and anti-inflammatory effects that contribute to the effectiveness of herbal cream in the management of acne vulgaris. However, the safety profile of herbal cream for long-term treatment was not well established and requires close monitoring. Contact sensitization should be recommended before application to avoid severe skin reaction such anaphylaxis in patient (70).

Status of clinical studies for herbal skincare creams

According to the afore mentioned literatures, a number of potential cosmetic formulations had been developed and proved to be pharmacologically effective. However, out of these formulations only a few clinical studies were identified.

The increased utilization of *in-vitro* studies for cosmetic products is attributed to their relatively time-saving and cost effective nature as compared to clinical trials. In addition, *in-vitro* testing reduces the need for *in-vivo* experiments, the recruitment of respondents as well as the risks towards human volunteers(94). Although randomized controlled trial is the gold standard for effectiveness study, issues with generalizability and follow-up have restricted its application in the cosmetics industries(95).

Besides, approval for cosmetic products and ingredients (except for colour additives) are not required from FDA before such products being introduced to the market. In the current regulations, cosmetics may be marketed as long as they are labelled in a proper manner and the ingredients used are proved to be safe according to the safety data obtained from the ingredient supplier or reported by the Cosmetic Ingredient Review (CIR) after they are being reviewed(96). According to Guidelines for Control of Cosmetic Products in Malaysia, the submission of clinical trial data is not a requirement in the application for notification ofcosmetic products(97). Hence,clinical trial for cosmetic products is often not taken into the consideration by various cosmetic companies prior to marketing.

Although animal testing is widely implemented in the last decade, genetics and physiological variations between animals and human beings might lead to under or overestimation of the actual effects and hazards towards the society. The results obtained from animal testing mightnot be fully applicable to humans. Thus, the safety and efficacy of cosmetic products to human remain questionable(98, 99).

In fact, extensive safety and efficacy assessment of cosmetic products on human are essential to minimize post market local or systemic adverse effects. Apart from that, both *in-vitro* testing and clinical studies should be conducted in order to assess the compatibility and acceptability of cosmetic products. The results of clinical studies may act as an important marketing tool that attracts and guides the consumers on brand selection and procurement(100–102).

In addition, natural ingredients might be a good candidate to replace chemical substances in the formulation of cosmetic products. Most of the natural ingredients are proven to be relatively safe with minimal side effects and more cost effective as compared to synthetic cosmetics. Hence, researchers and cosmetic industries are encouraged to focus more on the development of herbal-based cosmetics with extensive evaluations of their safety and efficacy through randomized control trials in order to assure their superiority to the consumers(103).

Advantages and limitations of herbal skin care creams

Herbal cosmetic creams are generally more tolerable and have multiple beneficial effects on the skin due to the presence of various phytochemicals that work synergistically. If the source of the herb is available in abundance then the cost of the final product will also be lower. However, they also come with some limitations due to the technical components.

Standardisation of a herbal extract is a system to ensure that every component of the medicinal plant, is finger printed to contain the correct amount/ratio/ percentage and will induce its therapeutic effect. These process although is very good quality assurance tool can also be quite tedious depending on the type of major therapeutic component present. The identification, extraction and quantification of herbs are challenging and time consuming. For instance, standardization and quality control of herbs should be conducted through High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), Thin Layer Chromatography (TLC), Mass Spectrometry (MS) or combination of both GC and MS(104, 105).However, this is restricted by the availability of analytical instruments and standard references.

Besides, the content of active constituents in herbs is often affected by light, temperature, atmospheric

humidity, altitude, rainfall and soil, which eventually lead to the inter-batch variation in the herbal cosmetics. The age, part of plant, collection time, method of collection, processing and storage may also affect the quality of the herbs (106). Hence, Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Supply Practice (GSP) and Good Manufacturing Practice (GMP) should be implemented to ensure the safety, efficacy and quality of herbal cosmetics(107). In addition, extra measures should be performed to minimize the presence of microbes, heavy metals and contaminants (107, 108).

Despite having natural plant-derived ingredients which are of the best quality, microbial contamination might be one of the biggest challenges faced by the manufacturers. The herbal skin care creams usually will have shorter life span/expiry as compared to chemically-derived creams if more natural preservatives are selected instead of the chemical ones(109).This is most likely due to the unavailability of broad spectrum natural preservatives in the market which is able to protect the herbal cosmetics against the contamination by a wide range of bacteria, viruses and fungi(110).Of late trend, for herbal cosmetics creams is going organic and natural, they excludes many skin irritants such as phthalates, SLS, parabens, synthetic colorings/fragrance and etc. The more natural options being selected which are skin- friendly and such the preservation dates will be slightly lower than synthetic creams. However, this seems unimportant as compared to immense benefits gained by going natural and skin friendly.

In addition, clinical evidence from randomized clinical trials for the present herbal cosmetics is scarce since clinical trial data is not a requirement in the application for notification of cosmetic products(97). The safety and efficacy of herbal cosmetics on human remained questionable even with favorable results obtained through *in-vitro* and pre-clinical animal studies(98, 99).Hence, manufacturers of herbal cosmetics are encouraged to conduct well-designed randomized control trials for their newly developed products in order to ensure its effectiveness and safety before they are being introduced to the market to the society.

Conclusion

The market demand for quality skincare products is increasing. Although there were few limitations identified, the positive aspects and the advantages of herbal skin care creams overweighed chemical-based products. In addition, the rising reports of adverse effects from synthetic ingredients in skincare creams have renewed the interest on natural/herbal skincare creams, especially on its anti-aging, whitening, and anti-acne properties. The benefits of certain bioactive phytochemicals have long been researched, and this review identified that many cream formulations have been developed from varieties of natural products. However, many such formulations did not proceed to clinical studies. This may be due to the resource-intensive aspect of clinical trials and the loose regulations on cosmetic products. Proper clinical trials are important to safeguard consumers' interest and well-being, and researchers should be encouraged to develop and evaluate herbal skincare creams via clinical trials.

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Disclosure of Interest

The authors report no conflict of interest.

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