Chapter

Chalcones in Dermatology

Jumina, Harizal and Yehezkiel Steven Kurniawan

Abstract

The human skin is pivotal for protecting the body from various stresses and diseases, regulating several physiological aspects, and sensing any signal changes around the environment. To work and function optimally, the skin should be protected and cared regularly by using some treatments. Chalcone, as a privileged structure, exhibits wide and unique bioactivities related to several skin disorders such as in preventing and treating pigmentation disorders (melasma and vitiligo), cutaneous leishmaniasis, rashes (acne vulgaris, seborrheic dermatitis and dandruff, psoriasis and atopic dermatitis), and rosacea. In this chapter, the role of chalcone derivatives in treating several skin disorders as mentioned above is discussed to provide a brief and comprehensive perspective regarding the role of chalcone in dermatology including in vitro, preclinical, and clinical assays.

Keywords: chalcones, dermatology, skin disorder, bioactivity, skin treatment

1. Introduction

In the human body, the skin is the outermost and largest organ with three basic functions, i.e. protecting from various stresses and hazards, regulating some physiological aspects, and sensing any conditional changes in the environment. While conducting its functions, the skin works with other internal systems and forms a rigid network with nervous, immune, and endocrine systems [1]. On the other hand, the skin also interacts with the environment around [2] such as microorganisms living on the skin surface [3] to maintain the function of the human body. Any imbalances between these factors often lead to various multifactorial skin disorders [4]. Based on their main cause, skin disorders can be classified into six groups including tumor and cancer, trauma, pigmentation disorders, microbial (viral, bacterial, fungal, and parasitic) infections, rashes, and miscellaneous conditions [5]. Therefore, treatment of skin disorders requires systematic attention in the medical field.

The treatment of skin disorders is usually conducted in topical, systematic, or combinatorial modes using bioactive compounds to relieve any formed defects in nervous, immune, and endocrine systems. Various bioactive compounds have been evaluated through a long clinical assay [6]. In the development process of these compounds, many parameters should be considered such as economical aspect, bioavailability, stability, toxicity, and metabolism of drug molecules in both topical and systematic therapies [7].

Chalcone is a class of organic compounds with 1,3-diaryl-2-propen-1-one (**Figure 1**) as the backbone structure that is obtained either through an isolation and purification process from natural samples [8], semisynthesis process from existing natural products [9], or total synthesis process [10]. Chalcone is considered

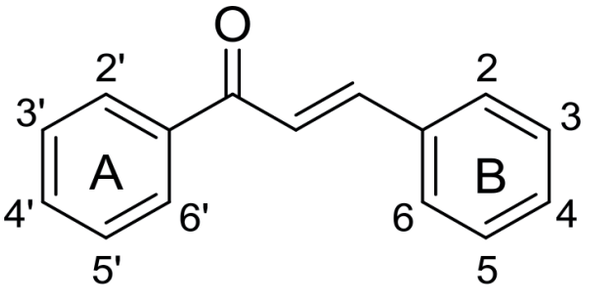

Figure 1.
Backbone structure of chalcones.

as privileged scaffold since it exhibits broad biological activities [10]. Many pieces of study have used chalcone as a lead compound to find more potent drugs for diseases due to the ease and convenience in synthesizing and functionalizing chalcone structure. In treating skin disorders, the efficacy of chalcone derivatives is related to several biological activities including antioxidant [11], anti-inflammation [12], immunomodulation [13], anti-angiogenesis [14], antimicrobial [15], and enzyme modulator [16]. The usage of chalcone derivatives in dermatology has been developed over the past several years to obtain the most active ingredient in either for maintaining skin health or treating skin disorders. Licochalcone A, isoliquiritigenin, and xanthohumol are examples of well-known chalcone derivatives with low toxicity and side effects on treating skin disorders and disease. In this chapter, these applications are described and discussed to provide a broad and comprehensive perspective regarding the role of chalcones in the dermatology field.

2. Dangerous impacts of ultraviolet irradiation

The ultraviolet (UV) light is the electromagnetic radiation with a wavelength range from 200 to 400 nm. In general, based on the wavelength range, UV radiation is divided into four regions including UVC, UVB, UVA2, and UVA1 at 200–280, 280–320, 320–340, and 340–400 nm, respectively. This hazardous radiation causes various acute and chronic negative effects on the human skin. Clinical manifestations that occur usually depend on the wavelength and intensity of UV radiation, part of the body exposed, and type of skin (based on Fitzpatrick's classification of skin). Acute effects of UV radiations, in general, involve various forms of inflammations such as erythema, local immunosuppression, phototanning, and epidermis thickening [17]. Mechanistically, acute effects are initiated by suitable interactions between several chromophores (either on the epidermis or dermis layers) and UV irradiation [18]. These interactions trigger the structural changes that modulate various biochemical and immunological processes [19] such as releasing several pro-inflammatory cytokines, damaging various cell biomolecules [20], generating various reactive oxygen species (ROS) [21], and producing several inflammatory mediators such as prostaglandins, histamine, and leukotrienes [22, 23]. Meanwhile, chronic effects usually lead to photoadaptation or photoprotection effects through the formation of photoaging, immunosuppression, and photocarcinogenesis [17].

2.1 Chalcones as sunscreen active ingredients

Chalcone has been found as one of the bioactive compounds that is able to reduce negative effects from UV radiation such as hesperidin methyl chalcone, licochalcone A, etc. Chalcones as antioxidant and anti-inflammatory agents are

used in topical or systemic methods, while the sunscreen agent is used in topical applications. In general, the sunscreen activity of chalcones is generated by high UV absorbance on the UVB-UVA region [24], which corresponds to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electronic transition from HOMO to LUMO energy levels in chalcones' conjugated electronic system. The absorbance region of chalcones can be shifted by introducing electron-donor substituents (bathochromic shift) or electron-withdrawing substituents (hypsochromic shift) in both of the chalcone aromatic rings. However, the effects of these groups are more significant if present in A ring compared to B ring [25].

The main problem in using chalcone derivatives as sunscreen active compound is relatively poor photostability and transformations into various by-products [26–28]. Several reports have investigated the utilization of chalcone derivatives as sunscreen active compounds and also prepared sunscreen formulations with high compatibility on the skin. However, the photostability of chalcone derivatives used has not been evaluated yet [25, 26].

2.2 Chalcones as photoprotective agents

Several chalcones exhibit strong protection on UV-induced deleterious effects such as *trans*-chalcone, butein, monspermoside, licochalcone A, phloretin, and hesperidin derivatives. Unsubstituted *trans*-chalcones showed a potential activity in reducing inflammation effect and oxidative stress in mice [27, 28]. A formulation containing 1% unsubstituted *trans*-chalcone has been applied to protect the skin from UVB radiation by inhibiting inflammation through reducing tumor necrosis factor alpha (TNF-α) levels and improving antioxidant and detoxification systems through enhancing heme oxygenase 1 (HO-1) and nuclear factor erythroid 2-related factor 2 (Nrf2) messenger ribonucleic acid (mRNA) expressions [28]. Systemic administration of *trans*-chalcone could inhibit UVB-induced skin inflammation and prevented oxidative stress by targeting nicotinamide adenine dinucleotide phosphate H (NADPH) oxidase and cytokine production [27]. Butein and monspermoside compounds were also used as photostabilizer for UVA-absorbing compounds such as dibenzoylmethane [29].

Licochalcone A, isolated from *Glycyrrhiza inflata*, is the most well-studied chalcone derivative related to its activity as UV photoprotector. Either in vitro or in vivo studies showed that licochalcone A had a strong protective effect against UVB-induced oxidative stress and inflammation. Licochalcone A attenuated UVB-induced inflammation by inhibiting prostaglandin E2 (PGE2), cyclooxygenase (COX-2), lipoxygenase, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Nrf2 [30–32], while in vivo assay showed that topical formulation containing licochalcone A caused a significant reduction in UV-induced erythema, irritation, and oxidative process in the skin [31–33].

Similar to their flavanone analog, hesperidin [34], hesperidin methyl chalcone, and hydrolyzed methylhesperidin compounds as semisynthetic products also exhibit high UV protective effect. Topical and systematic administration of hesperidin methyl chalcone in hairless mice inhibited UVB-induced oxidative stress by reducing free radicals and ROS, enhanced endogenous antioxidant systems, and inhibited inflammation by reducing the production of cytokines [35]. The hydrolysis product of methylhesperidin, 4′,6′-dihydroxy-3,4,2′-trimethoxychalcone and 4′-hydroxy-3,4,2′,6′-tetramethoxychalcone compounds, also induced cytoprotective gene expression and reduced oxidative stress by promoting Nrf2 nuclear translocation and antioxidant response element (ARE) luciferase activity in UVB-irradiated keratinocytes [36].

Phloretin is a natural dihydrochalcone that exhibited a strong inhibition of several matrix metalloproteinases. The isolated 3-hydroxyphloretin and phloretin from *Malus doumeri* var. *formosana* showed high inhibition of MMP-1 production in fibroblast cells [37]. A combination of phloretin, ferulic acid, and vitamin C as antioxidants had a high protective effect on UV damage in the human skin by preventing erythema formation and inhibiting MMP-9 and thymine dimerization reaction. In this case, phloretin acted as an antioxidant and synergized with other antioxidants by stabilizing and enhancing the bioavailability of ferulic acid and vitamin C in the skin [38].

3. Pigmentation disorders

Melanogenesis is a complex process of production and distribution of melanin by melanocytes. In this process, melanins (in form of eumelanin, pheomelanin, or trichochrome) are synthesized and stored in melanosomes (an organelle in melanocytes) and then transported to nearby keratinocytes to act as photoprotector in the skin and lead to chronic pigmentations [39]. The synthesis of melanin involves several reaction steps and is catalyzed by phenylalanine hydroxylase (PAH), tyrosinase (TYR), tyrosine hydroxylase isoform I (THI), tyrosinase-related protein 1 (TRYP1), and tyrosinase-related protein 2 (TRYP2) [40] enzymes. The rate-determining step of this process is hydroxylation of L-tyrosine to L-dopaquinone catalyzed by tyrosinase enzyme [41]. The final products of this process include black-brown eumelanin, yellow-reddish brown pheomelanin, and trichochrome [42].

There are many internal (endocrine, immune, inflammatory, and central nervous systems) and external (ultraviolet radiation and drugs) factors that affect the melanogenesis process [41]. Any disruptions from these factors will cause different types of pigmentation disorders including various skin conditions with strange melanocyte density, melanin concentration, or both that change pigmentations in the skin [43]. In general, pigmentation disorders can be divided into two main groups including hyperpigmentation and hypopigmentation that related to the amount of changes of normal melanin pigmentation, respectively. Both of these groups include several diseases with different clinical manifestations, but the most common forms of these are melasma (hyperpigmentations) and vitiligo (hypopigmentations) [42, 43].

3.1 Melasma

Melasma is a multifactorial skin disease indicated by the presence of symmetrical hyperpigmented area in a certain part of the face including centrofacial, malar, and mandibular parts. This disease is affected by UV, visible, and infrared exposure, by inducing reactive oxygen species and promoting melanogenesis [44], hormonal conditions [45], and genetics [46]. Chalcone derivatives are extensively used in medical therapy as photoprotective described in Sections 2.1 and 2.2, and hypopigmenting agents. Various studies showed that either natural or synthetic chalcones exhibited strong activity in inhibiting cellular tyrosinase and reducing cellular melanin formation [47]. However, the action mode of chalcone derivatives in this study is unknown since most of these studies used mushroom tyrosinase that is different from human tyrosinase [48]. Other studies conducted by Kim and coworkers showed similar results with additional parameters. In these studies, chalcones containing cyclohexylmethoxy group not only attenuated cellular melanin production and tyrosinase activity, but also reduced the expressions of

several melanogenesis-related genes (transcriptional activity of tyrosinase and microphthalmia-associated transcription factor/MITF) and proteins (TRP1, TRP2, and MITF) [49, 50].

Table 1 shows several in vitro assays that use Murine B16 melanoma cell lines (B16F10), melanoma cells, and human melanocyte (G361) cells in determining chalcone derivatives' efficacy for hypopigmenting agent. In vivo studies also showed that licochalcone A and isoliquiritigenin-containing licorice extract cream can improve melasma and increase skin brightness [51]. Loading the licorice extract into solid lipid nanoparticles has been formulated and applied in a clinical trial for melisma [52].

3.2 Vitiligo

Vitiligo is an acute skin disease characterized by unilaterally distributed depigmented areas in the skin due to the systematic degradation of melanocytes [56]. The mechanism triggering this disease has not completely elucidated yet; however, there are several theories proposed to explain it including genetics (mutations of certain genes cause autoimmunity) [57], autoimmunity (instable melanocytes induce immune system activation), oxidative stress (endogenous and exogenous stress-induced reactive oxygen species that cause internal damage of melanocytes)

Chalcone derivatives	Source	Types of cells	Effects (ref.)*
Isoliquiritigenin	*Glycyrrhiza glabra* L.	G361	↓Cellular melanin formation (IC_{50} 4.73 μg/mL) [53]
2,4,3′,4′-Tetrahydroxychalcone	Synthetic	G361	(M = 5 μM) ↓cellular melanin content (62.5%) [54]
2,4,2′,4′-Tetrahydroxychalcone	Synthetic	G361	(M = 5 μM) ↓cellular melanin content (55.0%) [54]
3-Hydroxyphloretin	*Malus doumeri* var. *formosana*	HEMn**	(M = 100 μM) ↓cellular tyrosinase (80.5%) and cellular melanin content (18.3%) [55]
2′-Cyclohexylmethoxy-6′-hydroxy-4-hydroxymethylchalcone	Synthetic	B16F10	↓Cellular melanin production (IC_{50} = 6.2 μM) and cellular tyrosinase activity (IC_{50} = 6.8 μM); ↓TRP1, TRP2, and MITF expression; ↓transcriptional activity of tyrosinase (IC_{50} = 6.0 μM) and MIRF (IC_{50} = 5.8 μM) [49]
4-Acetamido-2′-cyclohexylmethoxychalcone	Synthetic	B16F10	↓Cellular melanin production (IC_{50} = 0.54 μM) and cellular tyrosinase activity; ↓MITF, TRP1 and TRP2 expression; ↓phosphorylation of ERK1/ERK2 and CREB; ↓transcriptional activity of MITF and CRE [50]

**IC50, half maximal inhibitory concentration; ERK1/ERK2, extracellularly regulated kinase 1 and 2; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein.*
***HEMn: Primary skin melanocyte cells from neonatal foreskin.*

Table 1.
Chalcone derivatives activities in inhibiting cellular melanogenesis.

Chalcone derivatives	Source	Types of cells	Effects (ref.)
Chalcone-containing Kaliziri extract	*Vernonia anthelmintica* (L.) Willd.	B16F10	↑Tyrosinase, TRP-1, TRP-2, and MITF expression [64]
4′-(3-(3,4-Difluorophenyl)isoxazol-5-yl)methoxychalcone	Synthetic	B16F10	(M = 50 μM) ↑cellular melanin content (463%) [62]
4-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)isoxazol-5-yl)methoxychalcone	Synthetic	B16F10	(M = 50 μM) ↑cellular melanin content (438%) [62]
4′-Methoxy-4-dimethylaminochalcone	Synthetic	B16F10	(M = 40 μM) ↑cellular melanin content (75%); ↑cellular tyrosinase activity (30%) [65]

Table 2.
Chalcone derivatives' activities in activating cellular melanogenesis.

[58], melanocyte growth and defective melanocyte adhesion (repeated pressure and friction cause detachment of melanocytes to surrounding structures) [59], viral infections (certain viruses cause vitiligo) [60], and neural mechanism (neuropeptides elevate in vitiligo lesions) [61].

Improvement of skin appearance in vitiligo can be approached either by pigmentation or depigmentation. Chalcone derivatives are able to act as hypopigmenting (as described in Section 4.1) and hyperpigmenting agents. Several chalcone derivatives acted as hyperpigmenting agent by activating tyrosinase enzyme and elevating melanin production (**Table 2**). The presence of certain electron-withdrawing substituents such as halogen and trifluoromethyl substituents on the chalcone structure exhibited a significant effect in activating tyrosinase [62]. Chalcones also showed strong absorption in UV regions with low toxicity and have been formulated as broad-spectrum sunscreen protecting the affected skin from UV radiations and photofilter used in narrow-band UVB (NB-UVB) phototherapy [63].

4. Cutaneous leishmaniasis

Leishmaniasis is one of the vector-borne diseases generated by *Leishmania* spp. protozoans and transmitted to mammals through infected female sandflies (*Phlebotomus* and *Lutzomyia*) [66]. In general, certain *Leishmania* species can cause different clinical features with different degree of severity as the result of the interplay between *Leishmani*a species characteristics, biological vector, and the responses of host immune system [67]. In this section, the explanation is focused on the cutaneous leishmaniasis as the most well-known form [68].

Cutaneous leishmaniasis is identified by the presence of skin lesions (ulcers) in the biting spot of *Leishmania* spp.-infected sandfly. Almost all pathogenic *Leishmania* spp. could cause cutaneous leishmaniasis (18 from 20 species) [69] with 24 species of *Phlebotomus* spp. and 40 species of *Lutzomyia* spp. acting as a vector or potential vector [70]. At first, after biting by the infected female sandfly, the spot will form small erythema developing into a papule and then a nodule and ulcerate to become skin lesion. In the human body, promastigotes of *Leishmania* parasites injected by sandfly will be phagocytosed by macrophages [71]. Promastigotes manipulate macrophages to develop and multiply promastigote into amastigotes that infect another sandfly by biting infected human [72]. These processes cause

Species	Compounds	Source	Activity (IC_{50}) and mechanism*
L. major	Licochalcone A**	*Glycyrrhiza uralensis*	↓Intracellular amastigoten (0.5 μg/mL) by damaging amastigote mitochondria and disturbing its function [73] and inhibiting fumarate reductase [74]
L. amazonensis	4-Fluoro-2′-hydroxy-4′,6′-dimethoxychalcone**	Synthetic	↓Promastigote (0.8 μM), ↓intracellular amastigoten (4.3 μM). Mechanism is not related to the inhibition of fumarate reductase [78]
	3′,4′,5′-Trimethoxy-3-nitrochalcone in nanoemulsions	Synthetic	↓Intracellular amastigoten (0.32 μM) [79]
	trans-chalcone	Synthetic	↓Axenic amastigoten (10.3 μM), ↓promastigote (10.3 μM) by ↑ROS production and ↓mitochondrial integrity, phosphatidylserine exposure, and damaging the membrane. Immunomodulator by ↓ TNF-α, TGF-β, IL-10, ROS and NO, ↑ Nrf2, heme oxygenase, and ferritin [80]
	2′,4′-Dihydroxychalcone**	Synthetic	↓Promastigotes (0.4 μM) by inhibiting glycerol-3-phosphate dehydrogenase [77]
	Lonchocarpine/4-hydroxylonchocarpine (3:1)**	*Dorstenia mannii*	↓Intracellular amastigotes (6.64 μg/mL). Activity comes from synergistic effect from two compounds [81]
	2′-Hydroxy-4′,6′-dimethoxy-3-nitrochalcone	Synthetic	↓Intracellular amastigotes (7.2 μg/mL) [82]
L. braziliensis	*trans*-chalcone	Synthetic	↓Promastigotes (1.58 μM) [83]
	4-Methoxy-3-(*N*-phenylsulfamoyl)chalcone	Synthetic	↓Promastigotes (3.50 μM) [84]
	3-Chloro-2′,4′,6′-trimethoxychalcone	Synthetic	↓Promastigotes (2.70 μM) [85]
L. infantum	*(E)*-3-(5-nitrofuran-2-yl)-1-(4-(piperidin-1-yl)phenyl) prop-2-en-1-one**	Synthetic	↓Amastigotes (6.2 μM) by inhibiting cysteine proteases such as procathepsin L [76]
	(E)-3-(3-(3,5-di-tert-butyl-4-hydroxyphenyl) acryloyl)-4-hydroxyquinolin-2(1H)-one**	Synthetic	↓Intracellular amastigotes (1.3 μM) [86]
L. panamensis	*(E)*-1-(4-chlorophenyl)-3-(3-((7-chloroquinolin-4-yl)amino)phenyl) prop-2-en-1-one**	Synthetic	↓Amastigotes (0.79 μg/mL) [87]

**TGF-β, transforming growth factor beta; IL-10, interleukin-10.*
***Been reviewed by de Mello and coworkers [88].*

Table 3.
Several chalcone derivatives with high activity and selectivity against Leishmania *spp*.

the complex inflammatory responses that mediate and determine the appearance of clinical features and the severity degree.

Various investigations have been conducted and showed that several chalcone (natural and synthetic) derivatives have high activity (IC_{50} < 10 μg/mL or IC_{50} < 5 μM) and selectivity against *Leishmania* parasites in vitro and in vivo. However, the mode of action and molecular target of these chalcone derivatives have not been well elucidated yet. Licochalcone A showed strong activity against *L. major* (IC_{50} = 2.4 μg/mL) by damaging ultrastructure of promastigote and amastigote mitochondria of the parasite selectively and disturbing its function as respiration organelle [73]. Several studies also showed that fumarate reductase [74], nucleoside hydrolase, dihydroorotate dehydrogenase, oligopeptidase B and methionyl-*t*RNA synthetase in *L. major* [75], cysteine proteases in *L. infantum* [76], and glycerol 3-phosphate dehydrogenase (G3PDH) of *L. mexicana* [75, 77] can be targeted to kill the parasite. Chalcone derivatives strongly inhibiting these enzymes showed high activity in killing the parasite (**Table 3**). When the sunscreen activity of chalcones is generated by their conjugated electronic system, the antimicrobial activity of chalcones is caused by the presence of halogen, methoxy, hydroxy, and other functional groups.

5. Rashes

5.1 Acne vulgaris

Acne vulgaris, one of multifactorial acute inflammatory diseases, affects the pilosebaceous unit (hair follicles) in the skin. This disease is commonly found in the area with high-density pilosebaceous units (face, neck, upper chest, shoulders, and back) and characterized by the presence of seborrhea (excessive grease production), noninflammatory lesions (open comedones/blackhead and closed comedones/whitehead), inflammatory lesions (papules and pustules), and various degrees of scarring [89].

Pathogenesis of acne involves the interplay between four main factors including hyperseborrhoea (excessive sebum production) mediated by certain androgens and alterations in sebum fatty acid composition, hyperkeratinization within the follicle that lead to the formation keratin plug (microcomedone), pilosebaceous unit colonization by *Cutibacterium acnes* (aerotolerant anaerobic bacterium) colony, and the release of inflammatory mediators in response to the presence of *Cutibacterium acnes* [90]. It was shown that *Staphylococcus epidermidis* (facultative anaerobic bacterium) also had a beneficial role by limiting the colonialization of *Cutibacterium acnes* and inflammation [91].

Several chalcone derivatives exhibited anti-acne activity with mainly as antibacterial and anti-inflammatory agents. Licochalcone A as a potent anti-inflammatory agent [31] has been studied and combined with other active compounds in several anti-acne formulations. Skin care formulation containing licochalcone A, L-carnitine, and 1,2-decanediol can reduce pustule lesions, popular lesions, total lesions, and sebum levels [92]. A combination of 0.1% adapalene gel and moisturizer containing licochalcone A, L-carnitine, and 1,2-decanediol also showed synergistic effect in reducing inflammatory lesions without interfering the efficacy of each active ingredient [93]. Another combination between 0.1% adapalene gel and moisturizer containing licochalcone A, glycolic acid, salicylic acid, and gluconolactone even showed better results than monotherapy using only adapalene [94]. Licochalcone A, in another report, had antibacterial activity against *Cutibacterium acnes* and inhibited *Cutibacterium acnes*-mediated NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) inflammasome activation in the skin [95].

Antibacterial effects against *Cutibacterium acnes* have been shown by phloretin, xanthohumol, panduratin A, isopanduratin A, and some chalcone derivatives. Phloretin, a natural dihydrochalcone derivative, showed both antibacterial effects by inhibiting the growth of *Cutibacterium acnes* (MIC = 0.5 mg mL^{-1}) by blocking the activity of KAS III [beta-ketoacyl-(acyl-carrier-protein) synthase III] in *Cutibacterium acnes* and anti-inflammatory effect by attenuating COX-2 and PGE_2 expressions and inhibiting c-Jun N-terminal kinases (JNK) via toll-like receptor 2 (TLR2)-mediated inflammatory signaling in *Cutibacterium acnes*-induced inflammation of the skin [96, 97]. Four natural chalcone derivatives, xanthohumol isolated from *Humulus lupulus* L. (minimum inhibitory concentration/MIC = 0.003 mg mL^{-1}) [98], panduratin A and isopanduratin A isolated from *Kaempferia pandurata* Roxb. (MICs = 0.002 and 0.004 mg mL^{-1}) [99], and 2′,6′-dihydroxy-3′-methyl-4′-methoxydihydrochalcone isolated from *Eucalyptus maculata* (MIC = 0.002 mg mL^{-1}), also exhibited antibacterial activity against *Cutibacterium acnes* [100]. Different mode of action was shown by two synthetic chalcone derivatives, 2,2′-dihydroxychalcone and 2′-hydroxy-2,3,5′-trimethoxychalcone, to reduce sebum secretion and pore size on the skin [101].

5.2 Seborrheic dermatitis and dandruff

Seborrheic dermatitis is a skin illness mainly influencing skin area with high amounts of sebaceous glands (such as the face, scalp, central chest, and anogenital) and characterized with the presence of erythematous patches with superficial scaling. The mildest form of seborrheic dermatitis that only affects the scalp area with no overt inflammation is usually considered as dandruff or pityriasis capitis. In general, seborrheic dermatitis affects adolescents during puberty to adulthood; however, another form of this disease is considered as infantile seborrheic dermatitis affecting babies and young children [102].

The main mechanism triggering this disease remains unknown; however, it is probably caused by the imbalance of three factors: sebum oversecretion by the sebaceous gland that is affected by certain hormonal [103] and environmental [104] conditions, sebum metabolism by *Malassezia* spp. that accumulate linoleic acid, and individual susceptibility to the penetration of the unsaturated fatty acids that mediate pain and itch [105, 106]. The lipid layer of *Malassezia* spp. also stimulated keratinocytes to produce anti-inflammatory (IL-4, IL-10) and pro-inflammatory (IL-1α, IL-6, IL-8, IL-12, TNF-α) cytokines [107, 108].

Licochalcone A is an active anti-inflammatory drug used in several formulations in treating seborrheic dermatitis. Tonic containing urea, lactate, polidocanol, and licochalcone A-containing *Glycyrrhiza inflate* root extract improved dry, itchy, and inflamed scalp condition which is often associated with seborrheic dermatitis. A combination of rinse-off shampoo (containing piroctone olamine and climbazole) and leave-on tonic (containing piroctone olamine and licochalcone A) significantly reduced dandruff and relieved its microinflammation. Treatment using this combination also significantly decreased some cytokines including IL-1ra/IL-1α and IL-8, compared to placebo shampoo [109]. In another report, a moisturizer containing licochalcone 0.025% also had a comparable cure rate with hydrocortisone 1% moisturizer in treating infantile seborrheic dermatitis [110].

5.3 Psoriasis

Psoriasis is a multifactorial skin disease characterized by the presence of red, dry, itchy, and scaly plaques due to chronic hyperproliferative keratinocyte cells and

inflammatory cell infiltration [111]. Pathogenesis of this disease includes several steps triggered by environmental [111] and genetic [112] factors: (1) secretion of TNF-α by keratinocyte cells triggered by certain environmental and genetic factors, (2) TNF-α-induced dendritic cell activation and production of IL-23, (3) IL-23-induced T-helper 17 (Th17) cell differentiation, and secretion of IL-17A that cause hyperproliferation of keratinocyte cells [113]. Moreover, IL-17A also synergizes with IL-36 secreted by keratinocytes to amplify and support chronic characteristic of this disease [114]. Several molecular targets have been identified with drug candidates being tested in clinical stages such as cytokines (TNF-α, IL-17A, IL-17E, IL-17F, and IL-23 p19 subunit), phosphodiesterase 4, A_3 adenosine receptor, and Janus kinases (JAK1-JAK3) signaling pathways [115].

Recent studies report that chalcones are efficient in improving some psoriasis models. Intraperitoneal injection of isoliquiritigenin compound remedied mouse with psoriasis-like skin predisposition and decreased several pro-inflammatory cytokines (IL-6 and IL-8) as well by inhibition of NF-κB on in vitro and in vivo assays [116]. The isolated licochalcone B and echinatin compounds from *Glycyrrhiza glabra* also exhibited higher activity than isoliquiritigenin compound in relieving psoriasis-like inflammation induced by several pro-inflammatory agents such as 12-*O*-tetradecanoylphorbal-13-acetate (TPA), adenosine diphosphate (ADP), and UVB radiation [117]. In other targets, several α-bromo- and α-tetrafluoromethyl-2′,3,4,4′-tetramethoxychalcones showed anti-inflammatory and immunomodulatory activities through inhibition on IL-3 and interferon-α (IFNα)-induced JAK2/STAT5 (signal transducer and activator of transcription 5) [118] and STAT1 and STAT2 [119] signaling pathways. Furthermore, both compounds were also able to inhibit NF-κB and to activate Nrf2 transcriptional activity [120].

5.4 Atopic dermatitis

Atopic dermatitis (atopic eczema) is a complex inflammatory skin disease characterized by the presence of skin dryness with intense itching sensation, younger/early-onset, and atopy [121]. There are three main factors that contribute to pathogenesis of atopic dermatitis, i.e., (1) genetic and immune factors on the defect of physical and chemical barrier in the skin [122], (2) hyperactive immune cells due to a biological response (mutation on caspase recruitment domain family member 11/CARD11 gene) because of the incoming pollutants and pathogens [123], and (3) environmental factors that contribute in triggering and enhancing severities of atopic dermatitis process [124].

Chalcone-containing formulations have been prepared and evaluated in treating atopic dermatitis. These chalcone derivatives were combined with other active ingredients, and it was found that they acted as anti-inflammatory and antioxidative agents. It was also reported that licochalcone A-containing moisturizer showed slightly lower effect than hydrocortisone lotion in treating mild-to-moderate atopic dermatitis in children [125]. Another study also found that oil-in-water formulation containing *Glycyrrhiza inflata* root extract (licochalcone A), decanediol, menthoxypropanediol, and ω-6-fatty acids had quite similar efficacy compared to hydrocortisone lotion (standard medication) in a 1-week clinical study with significant improvement in skin conditions, which is remarkable [126]. Using 0.02% triamcinolone acetonide cream as a reference, a combination of 4-*t*-butylcyclohexanol and licochalcone A compounds in moisturizer formulation showed a slower improvement rate, but better result in relieving erythema and increasing skin hydration [127]. Meanwhile, water-in-oil emollient containing licochalcone A, ω-6-fatty acids, ceramide 3, and glycerol formulation could serve a preventing effect on reducing atopic dermatitis flares even after stopping the treatment [128].

Other compounds such as isoliquiritigenin and 3′-isopentenyl-2,2′,4,4′-tetrahydroxy-6′-methoxychalcone (ITC) showed similar effects on atopic dermatitis skin. Evaluation of isoliquiritigenin in relieving atopic dermatitis-like lesion in mice caused a significant improvement in skin condition and attenuated several pro-inflammatory parameters such as Immunoglobulin E (IgE), Th2 cytokine upregulation, TNF-α, IL-6, and IL-4 [129]. ITC isolated from *Sophora flavescens* Aiton also ameliorated atopic dermatitis-like model in mice by inducing HO-1 expression which leads to suppression of Th2 chemokine expressions [130].

6. Rosacea

Rosacea is a multifactorial chronic inflammatory skin disorder characterized by the presence of persistent or periodical redness and several kinds of changing in phymatous in the central facial skin (cheeks, chin, nose, and central part of forehead) [131]. Based on the appearance of certain major phenotypes, rosacea is divided into erythematotelangiectatic rosacea, papulopustular rosacea, glandular/hyperplastic rosacea, ocular rosacea, and other special forms such as rosacea conglobata, rosacea fulminans, gram-negative rosacea, steroid-induced rosacea, granulomatous (lupoid) rosacea, Morbihan's disease, and rosacea in children [132]. Pathogenesis of rosacea has not been fully comprehended yet, but there are several factors that involve including (1) genetics, Haber's syndrome with rosacea as one of clinical feature can be inherited; (2) environment, certain environmental factors can trigger rosacea including extreme air temperature, sudden temperature changes, food (caffeine, alcohol, hot and spicy food), sunlight (UV and IR radiation), etc.; (3) overproduction of antimicrobial peptides (AMPs) by congenital immune system such as LL-37; (4) ROS-induced inflammation produced by adaptive immune cells; (5) overexpression of toll-like receptors (TLRs); (6) *Demodex folliculorum*-induced inflammations; and (7) neuroinflammation and vascular hyperactivity [132, 133].

Hesperidin methyl chalcone, licochalcone A, and tetracarboxymethyl naringenin chalcone exhibit significant activity in improving the skin with rosacea. Clinical studies showed that hesperidin methyl chalcone-containing topical formulations could improve infected skin condition by decreasing the proportion of dilated vessels, total vessel area, and IL8 productions. These formulations showed a complementary effect between each active ingredient in relieving inflammation and reducing the redness [134]. Another study reported that hesperidin methyl chalcone had anti-inflammatory and anti-analgesic activities which are two targets in treating rosacea by inhibiting transient receptor potential vanilloid type 1 (TRPV1), oxidative stress, TNF-α, interleukin (IL) production (IL-1β, IL-6, and IL-10), and NF-κB activity [135].

Licochalcone A is a natural product from *Glycyrrhiza inflate* that shows potent activity in treating especially in mild and moderate symptoms. In vivo studies showed that skin care formulations containing licochalcone A provided various activities such as UVA/UVB protecting, moisturizing, and redness concealing abilities that improved skin appearance with rosacea. These formulations exhibited high compatibility with sensitive skin and could be combined with other treatments such as metronidazole treatment [136]. Licochalcone A-containing moisturizer formulation also increased skin hydration and reduced transepidermal water loss [137]. The most recent chalcone derivative used as anti-rosacea is a stabilized form of naringenin chalcone, i.e., tetracarboxymethyl naringenin chalcone (TNC). TNC was obtained from naringenin chalcone by total etherification reaction of methylchloroacetate. In vitro study showed that TNC significantly reduces LL-37, calcitriol, and several LL-37-induced inflammatory mediators in keratinocytes. Clinical test also showed that formulation containing TNC as a single active ingredient reduced the redness of the skin with rosacea compared to untreated skin areas [138].

7. Conclusions

Most of the skin diseases involve any defects in the skin due to its interaction with UV irradiation, pollutant, and/or other internal and external factors. Because of that, several skin diseases such as pigmentation disorders (melasma and vitiligo), cutaneous leishmaniasis, rashes (acne vulgaris, seborrheic dermatitis and dandruff, psoriasis, and atopic dermatitis), and rosacea have been reported and investigated for better medical treatment. Chalcones, a group of privileged molecules with 1,3-diaryl-2-propen-1-one backbone, exhibit high efficacy in treating those skin diseases. These efficacies are strongly related to the good activity of chalcones as antioxidant, anti-inflammation and immunomodulation, anti-angiogenesis, antimicrobial agents, as well as their ability in modulating various enzymes. Even though chalcones are really potential to be used as a photoprotective agent, the utilization of designed synthetic chalcones is still limited due to their low photostability and medium to high toxicity and also because of unknown protein targets of those skin diseases as for today reports. Development in these fields is still required to obtain more potent drugs with excellent biocompatibility and other desired properties.

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Conflict of interest

The authors state that there is no conflict of interest.

Author details

Jumina[1*], Harizal[2] and Yehezkiel Steven Kurniawan[3]

1 Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Gadjah Mada, Yogyakarta, Indonesia

2 Department of Pharmacy, Faculty of Health Sciences, Universitas Esa Unggul, Jakarta, Indonesia

3 Ma Chung Research Center for Photosynthetic Pigments, Universitas Ma Chung, Malang, Indonesia

*Address all correspondence to: jumina@ugm.ac.id

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