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Review

Polyphenol chrysin for management of skin disorders: Current status and future opportunities

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ABSTRACT

The polyphenol chrysin is a frequent food component. It has been demonstrated to have a number of favorable benefits on a variety of skin ailments and disorders. It's anti-inflammatory and antioxidant properties are high. It has been demonstrated to protect skin from UV exposure by neutralizing reactive oxygen species that cause cutaneous damage and skin cancer. In acne, psoriasis, wound healing, and cutaneous leishmaniasis, chrysin has shown promising therapeutic advantages. It is increasingly being used in anti-aging skin cosmetics especially those for reducing under-eye dark circles. However, chrysin is not yet clinically translated as a drug. This present review highlights the potential and future scope of chrysin as a therapeutic agent in skin disorders and also as a cosmeceutical.

Contents

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1. Introduction

Our body's largest defensive organ is our skin. The physical barrier of skin keeps damaging UV rays out, protects against viruses, and serves as the human body's first line of defense. Therefore, any kind of stimuli that compromises the integrity of the skin's barrier affects its function (Yu et al., 2019) Skin diseases can be caused by a variety of factors, including genetics, environmental factors, and psychological factors. Since it is the most visible organ of our body, skin disorders may often cause problems in social acceptance. It is therefore essential to develop novel strategies to fight various factors that result in skin disorders (Ndiaye et al., 2011).

Polyphenols comprise a huge collection of phytochemicals such as flavonoids, stilbenes, lignan, and phenolic acid (Fraga et al., 2019) Flavonoids are naturally occurring phytoconstituents with promising health benefits. There are a plethora of flavonoids that are present in our daily dietary foods, plants, and fruits. Flavonoids are associated with several pharmacological activities depending on their chemical structures and attached chemical entities or functional groups. The first flavonoid rutin was isolated from orange in 1930, and since then, scientists have identified more than 4000 flavonoids to date that are associated with several human health benefits (Kumar and Pandey 2013).

Recently several researchers have been exploring the therapeutic and beneficial effects of one such flavonoid, ''Chrysin''. Chrysin (5,7-di-OH-flavone) has the ubiquitous 1 flavone backbone. Its IUPAC name is 5,7-dihydroxy-2-phenyl-4H-chromen4-one and 5,7-dihydroxyflavone. Chrysin is a common bioactive constituent in passion fruits, vegetables, honey, propolis, and mushrooms. The hydroxyl and keto groups' presence on the structure of chrysin makes it a good candidate for further research of synthesizing cocrystals with this flavonoid (Mani and Natesan 2018, Naz et al., 2019).

Chrysin is a naturally occurring antioxidant related to a number of health benefits. It is reported to have anticancer, (Samarghandian et al., 2016, Lima et al., 2020, Yeo et al., 2020, Lee et al., 2021) cardioprotective, (Farkhondeh et al., 2019) anti-inflammatory, (Xiao et al., 2014) hepatoprotective, nephroprotective, (Pingili et al., 2019) antidiabetic and antihyperlipidemic (Ramírez-Espinosa et al., 2017) antidepressant,(Cueto-Escobedo et al., 2020), anti-allergic (Wang et al., 2020) and anxiolytic effects (Rodríguez-Landa et al., 2021).

Recently, researchers have been studying its effects on inflammatory skin disorders. Studies are being carried out to understand the exact mechanistic pathways involved in treating skin conditions such as psoriasis, (Li et al., 2020) atopic dermatitis (AD) (Song et al., 2019) skin irritation and inflammation (Yu et al., 2019) However, because to a lack of research in this area, the biological effects of chrysin have not yet been standardized for clinical translation. In this review, we aim to know more about the health effects of chrysin and its role in the management of skin disorders. We will also explore the future scope of using this polyphenol to treat skin disorders.

2. The human skin and its disorders

Most of us often regard the skin as a static barrier that shields us from all the invasions from the environment surrounding the skin. However, the skin is involved in several physical and mechanical functions and is a dynamic tissue. The physical appearance of the skin is affected by a variety of events such as trauma, injury, age, and skin diseases (Wong et al., 2016) Several factors also affect the skin microbiome. The skin's microbiome is the collection of different microorganisms that reside in the skin and maintain a balance between them to maintain skin homeostasis (Schommer and Gallo 2013).

A network of blood arteries, nerves, ligaments, and lymphatics connects the epidermis to the underlying connective tissue, enveloping our bodies. The human skin comprises three different layers epidermis, dermis, and hypodermis. All three layers are involved in different functions (Wong et al., 2016).

The epidermis is the uppermost dynamic biologically active layer of the skin. It is made up of keratinocytes, corneocytes, ceramide, and collagen. Additional cells include melanocytes (pigment-producing cells), Langerhans cells (antigen-presenting cells), and Merkel cells (cells with both neuroendocrine and epithelial features that are sensitive to mechanical stimuli, especially pressure). It also hosts the hair follicles and the eccrine and apocrine glands that are responsible for thermoregulation of the body. It serves to protect the skin from extremes of weather and is a waterproof covering of the body (Fore 2006) The dermo-epidermal junctions adhere the epidermis to the dermis and form a junction that keeps away the pathogens. Blood arteries, lymphatic ducts, and nerve endings abound throughout the dermis (Breitkreutz et al., 2013, Wong et al., 2016) While the hypodermis consists of connective tissue and adipose tissue that is responsible for insulating and protecting the skin. It also acts as a fat reserve of the skin. It also consists of the microvacuolar tissue that stores the interstitial fluid.

Any insult to the skin layers results in skin disorders and infections. Microorganisms such as viruses, bacteria, and fungi are common causes of skin infections. The infections may be superficial that cause redness and lesions on the epidermis, while other severe infections such as cellulitis may even go deeper till the dermis. Oral and topical treatment with antibacterial, antivirals, and antifungal agents is a common treatment modality to treat skin infections (Clebak and Malone 2018) Furthermore, there are several chronic inflammatory diseases such as acne, (Fox et al., 2016) psoriasis, (Greb et al., 2016), and atopic dermatitis (Kim et al., 2019) that may cause damage to the skin. Aging results in several skin changes that include sagging of skin, loss of fatty tissue, and appearance of fine lines that later appear as wrinkles (Bonté et al., 2019) Skin cancer is another threatening skin disorder of high incidence and needs appropriate and prompt treatment (Sajadimajd et al., 2020).

Although conventional medicine has been used to treat skin infections, chronic skin inflammatory diseases, and severe conditions such as skin cancers, researchers are considering polyphenols and other plant extracts as a part of treatment for skin conditions (Reuter et al., 2010).

3. Skin disorders and the role of chrysin in its treatment

There has been a dynamic development in the research of polyphenols as a treatment modality in various disease conditions. The researchers have explored the pharmacological effects of chrysin, its source, and different delivery systems to make this polyphenol available for treatment (Stompor-Gorący et al., 2021) Let us

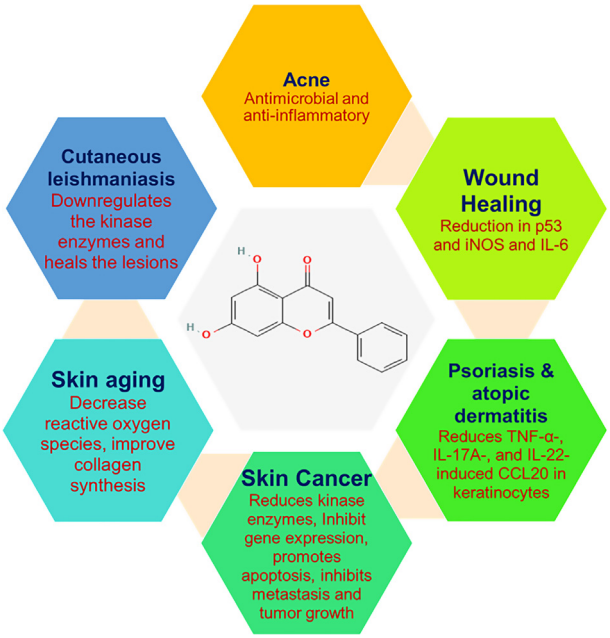

Fig. 1. Application of chrysin in various skin diseases and the mechanism of action responsible for the therapeutic benefits.

review the studies that involve chrysin for treating various skin conditions. Fig. 1 summarizes all the skin diseases and disorders for which chrysin has been explored and also the mechanism of action of chrysin that was found to be responsible for the benefits in that particular disease.

3.1. Acne

Acne vulgaris is a skin disorder that affects people of all ethnicities and ages all over the world. The androgen hormones are responsible for the first appearance of acne during puberty. The condition is characterized by chronic inflammation of the pilosebaceous gland (Soleymani et al., 2020) Although not life-threatening, the condition affects the confidence of the individuals having the acne outbreaks and makes them avoid social appearances as in many cases it leaves your skin scarred, it results in loss of self-esteem and has a negative psychosocial impact (Darji et al., 2017) *Propionibacterium acnes* are the key pathogen responsible for colonization in the skin that results in increased sebum production, increased concentration of inflammatory markers, and finally the appearance of acne lesions. Acne is characterized by the growth of comedones, nodules, pustules, papules, and cysts scars on the skin, particularly on the face (Soleymani et al., 2020).

Antibiotics, both oral and topical, tretinoins and hormones are conventional treatment modalities for acne. The antibiotic resistance of acne nodules, on the other hand, poses a challenge to dermatologists who have been treating this problem (Habeshian and Cohen 2020) Recently, polyphenols have shown promising efficiency in treating acne. Chrysin is present in honey, propolis, and bee venom (Kurek-Górecka et al., 2020). Honey treats several skin infections owing to its antimicrobial properties. It has shown antibacterial effect against *Propionibacterium acnes,* a common cause for acne (McLoone et al., 2016).

In another study carried out in 40 patients with facial acne, topical application of propolis alcoholic extract showed bactericidal effect against gram-positive anaerobic bacteria (*Propionibacterium acnes*) and gram-positive aerobic (*Staphylococcus epidermidis*). The antimicrobial and anti-inflammatory effects of chrysin can make it a good candidate for treating acne (Mani and Natesan 2018).

3.2. Wound healing

Chronic wounds may eventually lead to cancer, so it is necessary to accelerate the process of wound healing. Venous ulcers, gastric ulcers, diabetic foot ulcers, or pressure ulcers are typically chronic wounds that take a long time to heal completely. Until the wound is completely healed, it goes through a series of events (Deldar et al., 2018). Wound healing is a complex biological process that necessitates the proliferation, differentiation, and migration of endothelial cells, keratinocytes, immune cells, and fibroblasts. The matrix metalloproteinases (MMPs), gene P 53, nitric oxide synthase (iNOS), interleukin-6 (IL-6), inducible, and play a vital role in the wound healing process (Mohammad Ali et al., 2015). To promote rapid wound closure, the essential measures in treating wounds include lowering inflammation and eliminating free radicals.

Several research studies have demonstrated that chrysin has a good antioxidant and anti-inflammatory potential (Cho et al., 2004, Deldar et al., 2018). The biological effect of chrysin-loaded nanofibers on wound healing and associated genes in rats was investigated in another investigation. The results showed a considerable reduction in p53 and iNOS expression, which resulted in wound healing (Mohammadi et al., 2019).

Another study looked into the influence of chrysin–curcumin-loaded nanofibers on the wound-healing process in male rats. The results of this study show accelerated wound healing using the chrysin-curcumin nanofibers (Mohammadi et al., 2019).

The therapeutic efficacy of a sodium alginate-chitosan scaffold loaded with chrysin in wound management was investigated. The wound healing was studied in vitro on cell lines and in vivo in rats. Both investigations revealed a faster wound healing time and a shorter period of re-epithelization. The researchers concluded that the chrysin-loaded scaffolds could be used for tissue regeneration and healing of wounds (Kaparekar et al., 2021).

3.3. Psoriasis

Psoriasis is a persistent inflammatory skin condition that has no known etiology. It is thought to be an immune-related skin condition characterized by scaling and lesions on the skin. According to the previous clinical research, it is known that IL-22, IL-17A, and TNF-α are involved in the pathogenesis of psoriasis (Di Cesare et al., 2009, Raychaudhuri 2013). The condition affects the skin, joints, and even the nails (Sobolewski et al., 2017). The inflammatory chemicals act on the keratinocytes and produce the symptoms of this condition. Dermatologists face a difficult task because of the condition's high prevalence, chronic nature, incapacity, and disfigurement of bodily parts. Treatment success is contingent on a thorough understanding of the interplay between the innate and adaptive immune systems of the individual (Boehncke and Schön 2015).

Severe side effects and frequent recurrence has forced researchers to search for safer alternatives to treat this condition. Chrysin is a potent antioxidant and has a good free radical scavenging activity. It is also a good anti-inflammatory agent. Besides, it is inexpensive and can be easily extracted from natural sources.

In an in-vitro study, they tested the efficacy of chrysin in an animal model in which psoriasis-like inflammation was induced. Inflammatory symptoms improved, and the area and severity index of psoriasis were reduced, according to histological studies of the chrysin-treated skin. On application to the skin, chrysin significantly reduced the loss of moisture and redness of the skin. It also improved skin suppleness. The cell line studies helped study

the mechanism of chrysin's antipsoriatic activity. Chrysin pretreatment on the epidermis keratinocytes attenuated activation of the NF-κB pathway.

Furthermore, chrysin inhibited the release of antimicrobial peptides from epidermal keratinocytes generated by CCL20, IL-22, TNF, and IL-17A. Chrysin has the potential to be an effective treatment drug for chronic inflammatory disorders like psoriasis (Li et al., 2020).

Another study found that chrysin can enhance human keratinocyte differentiation by boosting vitamin D receptor transcriptional activity (Choo and Lee 2013). Vitamin D is important for maintaining cutaneous barrier homeostasis in psoriasis, and there has been a link discovered between vitamin D receptor polymorphisms and psoriasis susceptibility (Barrea et al., 2017).

3.4. Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin condition. Redness, itching, and scratching are common symptoms. Genetic and environmental factors, skin architectural faults, and cell-mediated immune dysfunction may all play a role in the development of the illness. The multifunctional mast cells play an essential role in producing inflammatory mediators, growth factors, interleukins (IL)-1β, tumor necrosis factor-alpha (TNFα), lipid mediators, IL-4, cytokines, and IL-6 that are responsible for the symptoms of AD (Kawakami et al., 2009, Sirufo et al., 2020).

Several investigations have been conducted to assess the activity of chrysin in Alzheimer's disease, and scientists have sought to discover a mechanism of chrysin action in AD. In one such study, chrysin was orally administered to mice induced with atopic dermatitis. Histopathological investigation showed reduced AD symptoms. Chrysin inhibited Th1, Th2, and Th17 cell inflammatory responses in the lymph nodes and ears of mice. Tumor necrosis factor downregulation of p38 MAPK, NF-B, and STAT1 reduced the production of Th2 chemokines, cytokines, and C–C motif chemokine ligand (TNF) interferon-negative/interferon-positive / interferon-negative/ interferon-positive/ interferon-negative/ interferon-negative/interferon-negative/interferon-negative/inter (IFN) Keratinocytes from humans that have been triggered. Chrysin also inhibited TNF-α/IFN-γ-stimulated IL-33 expression in human and mouse keratinocytes. The interesting findings suggest the use of chrysin in the treatment of AD (Choi et al., 2017).

Another study found that a derivative of chrysin reduced the symptoms of Alzheimer's disease. The compounds demonstrated lower cytotoxicity while still having anti-inflammatory properties. They demonstrated that upregulation of tumor necrosis factor, interleukin (IL)-6, and nitric oxide can be inhibited to decrease inflammation in Alzheimer's disease (Song et al., 2019).

Another study was carried out in vivo in animals and in-vitro on cell lines to study the mechanism of action of chrysin in AD. The cell line studies indicated that chrysin inhibited the gene expression of all cytokines. The researchers also found that the inhibitory effect of chrysin on the pro-inflammatory cytokine was NF-κB and caspase-1 dependent. Chrysin's anti-inflammatory properties in vitro and in vivo make it a promising candidate for the treatment of allergic inflammatory illnesses like asthma and Alzheimer's disease (Bae et al., 2011).

In AD-like settings, the molecular mechanism underlying the chrysin-induced suppression of 5 (CCL5) gene expression was studied. According to their findings, chrysin inhibited CCL5 expression by targeting IKK and reducing mast cell infiltration, lowering inflammation (Yeo et al., 2020).

3.5. Photoaging and skin aging

Skin aging is an unavoidable intrinsic process**.** Several external factors are also responsible to trigger or fasten this process, most importantly the ultraviolet (UV) radiations. The formation of oxidative reactive species and changes in skin collagen are vital events that occur during skin aging (Kohl et al., 2011). Deep penetration of the UVA into the dermis causes sunburn, tanning, photoaging and eventually may also result in skin cancer. Photoaged skin is rough and fragile, with wrinkles, purpura, pigmentation, and a decreased ability to repair wounds (Tobin 2017).

Photoprotection and photosensitizers are needed to control the process of photoaging of the skin. In-vitro studies have shown the effectiveness of chrysin on photoaging of the skin. The ability of chrysin to protect keratinocytes from UV damage was investigated. The findings revealed that chrysin can reduce UVB and UVA-induced apoptosis, reactive oxygen species generation, and cyclooxygenase 2 expression. It also corrected UVB-induced downregulation of aquaporin 3 (AQP-3) as well as JNK activation. It also showed mild inhibition of p38 activation triggered by UVA and UVB. The researchers also studied the topical application of chrysin in animals was non-irritant and showed efficient dermal penetration. The study showed that chrysin has good photoprotective ability on the skin and can be included in preparations for skin aging (Wu et al., 2011).

Another group of researchers attempted to evaluate the effects and mechanisms of chrysin on photoaging and melanogenesis. The in-vitro studies showed that chrysin increased the synthesis of collagen I, reduced its degradation, and decreased the synthesis of melanin by suppressing the melanogenic proteins. The results of the study show that chrysin may be included in the cosmetic formulation for its use as anti-photoaging and its anti-melanogenesis use (Zhu et al., 2016).

One more study evaluated the photostability and low phototoxicity of chrysin and other related naturally occurring compounds. However, chrysin showed a lesser photoprotective effect than the other polyphenols under investigation (Kostyuk et al., 2018).

3.6. Skin cancer

Skin cancer is a common type of cancer across the globe. It is typically either melanoma or non-melanoma type of skin malignancy. Most types of skin cancers are non-melanomatous. They arise from keratinized epithelial cells and include basal cell carcinoma and squamous cell carcinoma. Melanoma accounts only for 2% of skin cancer cases but causes most of the skin cancer deaths (Linares et al., 2015, Patil and More 2020). Non-melanoma skin cancers can be treated by surgical excision, topical chemotherapy, or other treatments such as electrodesiccation. Melanoma requires surgical treatment and chemotherapy to treat cancer that has spread to deeper tissues.

Several researchers have looked into the anticancer properties of chysin and chysin derivatives. Chrysin derivatives suppressed human epidermoid carcinoma cells and reduced tumor growth in an in vitro investigation on cancer cell lines. The mechanism of action is the loss of phosphorylation sites on the retinoblastoma. Chrysin also reduced the kinase activity by direct binding to cyclin-dependent kinases 2 and 4 (Liu et al., 2013).

Another in vitro study carried out on a derivative of chrysin inhibits tumorigenesis by directly acting on the mitogen- and stress-activated kinase enzyme. The chrysin derivative has the potential to be exploited as a chemoprotective agent in the treatment of skin cancer, according to the researchers (Liu et al., 2014).

The effect of chrysin on migration and metastasis in human melanoma is investigated in one study. Chrysin prevents cells from migrating and infiltrating by reducing MMP-2 activity. It also affects the key metastasis-related proteins and the translocation of NF-κBp65. As a result, chrysin inhibits cell migration, invasion, and mobility in A375.S2 cells in vitro. It also halts the spread of cancer (Chen et al., 2019).

The effects of nano encapsulated chrysin and curcumin on the mouse B16F10 melanoma tumor model were investigated in a similar study. MMP-2, 9, TIMP-1, 2, and TERT expression levels were assessed as significant genes in tumor growth and metastasis. The results revealed that the nano encapsulated chrysin and curcumin arrested the tumor growth and inhibited the expression of the genes (Tavakoli et al., 2018).

In a recent study, we looked at the effectiveness of a topical chrysin nanoemulgel in the treatment of skin cancer. We carried the cytotoxicity studies on the cancer cell lines using the topical nanoemulgel loaded with chrysin. The results showed a significant effect on the cancer cell lines A375 and SK-MEL-2 (Nagaraja et al., 2021).

Chrysin is also present in a medicinal plant *Indigofera tinctoria* used widely in the Indian and Chinese medical systems. After the isolation of this bioactive compound, its effect was studied in vitro on the epidermoid carcinoma cells. The results of the study reveal that chrysin arrested the cell cycle at the Sub G1 phase. Furthermore, it also enhanced the expression of cytochrome *C*, caspase 9, caspase 3. It caused remarkable cell death by promoting apoptosis (Boothapandi and Ravichandran 2018).

Another study involved studying the chemoprotective potential of chrysin in skin cancer. The probable mechanisms proposed after the histopathological and biochemical examination reveal antilipid peroxidative effect, antioxidant effect, and ability to modulate carcinogen detoxification (Prabhakar et al., 2012).

3.7. Cutaneous leishmaniasis

Cutaneous leishmaniasis is a less severe form of the disease, Leishmaniasis, caused by a protozoan parasite, and characterized by ulcerative skin lesions. The condition is common in tropical and temperate regions of the world and affects the immune system of the body. The Leishmanial Mitogen-Activated Protein kinases

Table 1
Various commercially available skin care products containing chrysin.

Sr. No	Brand /Manufacturer	Type of skin-care product	Benefits claimed
1.	Correct eye cream	Anti-aging eye cream	Improves skin moisture, reduces fine lines, wrinkles and puffiness. Reduces the visible signs of dark circles for the entire eye area.
2.	AQ Eye Serum	Eye Rejuvenating System	Reduces the appearance of wrinkles, and fine lines around the eyes. Brightens dark circles under eyes. Moisturizes and conditions the delicate eye area.
3.	Arcona Peptide eye serum	Eye serum	Reduce puffiness and hydrate the delicate eye area. Protects from environmental damage. Helps to improve the elasticity of thinning, stressed skin.
4.	Osmotics Under Eye Rejuvenator	Eye Cream For Dark Circles	Hydrates and firms the sensitive under-eye skin. Brightens and tightens skin
5.	O HUI Chrysin Perfect Sun Powder SPF50	sunblock powder with high SPF	Helps to keep skin blot-free and fresh-looking. Absorbs excess sebum. Enhances complexion to achieve a luminous healthy look.
6.	Timeless Skin Care Dark Circle Eye Cream	Cream for dark circles	Regenerates the delicate skin under the eye. Nourishes and soothes the skin. Reduces wrinkles. Has antioxidant properties.
7.	Irem	Under Eye Cream	Reduces under-eye dark circles, eyes, wrinkles, and fine lines
8.	Faireye Advanced Dark circle cream	Cream for dark circle	Soothes the skin under the eye. Brightens the skin to reduce dark circles.
9.	Grit and Grace Liquid Facelift	Liquid drops for face	Lightweight Oil-free moisturizing drops. Goes deeper into wrinkles, gives an improved texture and appearance.
10.	Bee Safe Organic Mineral Sunscreen	Sunscreen to be massaged on the skin	Broad-spectrum UVA and UVB protection. Emollient and moisturizing effect.
11.	Brickell Men's Products Protein Peptides Booster for men	Boost of raw protein for wrinkled skin	Anti-aging and moisturizing effect.
12.	Dr. Reddy's Avarta Lightening Eye Cream	Under-eye cream	Lightens the under-eye area and rejuvenates the skin under the eyes
13.	Elisabeth Arden Visible	Eye cream with multiple Benefits	Prevents moisture loss and maintains skin hydration
14.	Loreal Youth Ferment De Essence	Facial essence	Smoothens and softens the skin. Increases skin's absorbing power and improves texture. Regain youthfulness and radiance.
15.	Sesderma Glicare Eye and Lip contour gel	Contouring lip gel	It reduces bags, dark circles, and puffiness. Also, thanks to its versatility, it can be applied to your lips.
16.	Air Repair Super hydrating eye cream	Eye hydrating cream	De puffs the areas around the eyes and reduces the appearance of dark circles.
17.	Biologique Recherche Paris Patchs Defatignas	Eye sheet masks	Treats fatigue and aging in the eye contour area. Anti-puff, anti-bag, and anti-wrinkle effect. Adheres comfortably to the eye contour. Lightens dark circles.
18.	Bye Bye Under Eye Concealer	Waterproof safe proof concealer	Reduce the appearance of wrinkles Conceals skin imperfections Makes the skin appear younger
19.	Allies of Skin 1A Retinal Peptides Overnight Mask	Overnight mask with timed-release ingredients	Alleviates fine lines and pores. Improves skin elasticity Rehydrates the skin Brightens the skin
20.	No. 7 Men Energising Eye Roll-On	Roll on for under eyes	Best for tired eyes. Removes dark circles. Gives a fresh look
21.	Cardon Dark circle eye rescue	Liquid formulation	Reduces the appearance of dark circles, puffiness, and wrinkles around the eyes. Soothes and moisturizes the skin.
22.	Allies of Skin Molecular saviour Mist	Mist for skin	Gives a glowing complexion. Has a moisturizing and exfoliating effect with rose fragrance.
23.	Botanics Refreshing Eye Roll-on	Alcohol-free, oil-free roll on	Moisturizes the skin and depuffs your eyes
24.	Maelove Eye Enhancer	Amber-colored gel	Improves texture, tone, and radiance around the eyes. Gives a fresh look.
25.	Dr. Belter Ocula Biomimetic Eye Cream	Eye cream	Keep the skin around the eyes moisturized with ingredients similar to your skin composition.

Table 2
List of patents showing the application of chrysin for various skin health-related benefits.

Sr. No	Patent no	Title of invention	Claim
1.	KR20190021306A	Composition for skin moisturizing and alleviating skin inflammation comprising chrysin	Promote differentiation of dead skin cells, enhance skin moisturization, reinforce the skin barrier, and/or alleviate skin inflammation.
2.	US8530426B2 EP1776161B1	At least one UDP glucuronosyltransferase (UGT) enzyme inducer in a cosmetic or dermopharmaceutical component	Protect and/or improve the state of the skin, as well as prevent and/or treat skin imperfections.
3.	US8790724B2	Formulation of dual cyclooxygenase (COX) and lipoxygenase (LOX) inhibitors for mammal skincare	A novel composition comprised of flavonoids and flavones for use in the prevention and treatment of diseases and conditions associated with the skin mediated by COX and LOX.
4.	EP2838547B1	Compounds used to treat and/or care for the skin and/or mucous membranes, as well as their use in cosmetic and pharmaceutical formulations	Inhibition of cytokine release, matrix metalloproteinase activity, and/or melanogenesis inhibition is used to treat skin and mucous membrane illnesses that improve or are prevented.
5.	CN103648536B9	For regenerative medicine and tissue support, biocompatible and biodegradable gradient layer technology has been developed.	A biomaterial for regenerative medicine to be used as a wound dressing or for tissue support.
6.	US9585821B2	Methods for making compositions for improving skin conditions	Fluid compositions comprising a matrix polymer and stabilizing component, for treating skin conditions.
7.	US8980344B2	Skincare products containing multiple enhancers	A skincare product containing skin conditioner
8.	US 2009/0234382 A1	Wrinkle-reducing skin patch, manufacturing process, and relevant articles	Tighten the skin and reduce fine wrinkles
9.	US 2012/ 00454.05 A1	Under-eye cream	Treats swelling under the eye, bags, wrinkles, and dark circles area underneath the eye.
10.	MX2012010769A	Perfluorocarbon eye cream formulations.	A topical formulation that helps deliver oxygen to the periocular skin
11.	WO 2008/043900 A2	Use of a cosmetic composition for the care of fatty skin	Prophylaxis and treatment of fatty skin
12.	JP5808080B2 JP2009530911A	Use of cosmetic compositions to care for oily skin	Acts on sebaceous glands and modulates production of sebum in oily skin
13.	US 9119974 B2 EP 2 680 865 B1	Skin Cream	Reduces under-eye puffiness and restores firmness
14.	EP2556043B1	New polyterpene-type chemicals, as well as formulations including them and topical applications, are being developed.	Prevents aging, treats acne, prevents hair loss and skin roughness
15.	US 10493020 B2	Method for enhancing the appearance of periorbital dyschromia	Treats dyschromia of periorbital cream

play an important role in the survival and infection-causing capacity of the parasite (Raj et al., 2019).

The current treatment of the condition is based on chemotherapy which has limited effects and several side effects. Hence, the recent focus is on the natural phytochemicals for treating cutaneous leishmaniasis.

MAPK3 is involved in the regulation of flagellar length in *Leishmania donovani*. It also plays a crucial role in the spread of disease. As a result, this enzyme could be used as a new therapeutic target. This enzyme has been demonstrated to be inhibited by chrysin (Raj et al., 2019).

Chrysin is an important ingredient in propolis and some research papers have studied the effect of propolis on cutaneous leishmaniasis. In one such study, the researchers have studied the effect of Brazilian green propolis hydroalcoholic extract in-vitro and in-vivo. The in-vitro studies have shown that the high concentration of this extract had an anti-leishmanial effect. The in-vivo studies were carried out in lesions induced by *Leishmania amazonensis* on the paw of mice. Results revealed that oral administration of the extract in animal models decreased the parasites and induced macrophage infiltration in the lesion (Cunha et al., 2020).

Another study carried out research on the Brazilian and Bulgarian propolis on different species of *Leishmania*. The results indicated that the extracts had leishmanicidal activities on the different species in the invitro assays (Machado et al., 2007).

A recently published review article also emphasizes that the Leishmania MPK1 and MPK2 enzymes are the targets for the treatment of cutaneous leishmaniasis and natural compounds such as chrysin may act on the macrophage or parasitic enzymes (Efstathiou and Smirlis, 2021).

4. Current status of chrysin in skin-care products

Although chrysin has several benefits for skin diseases, it is not yet clinically used. However, chrysin has been an important ingredient in several cosmetic formulations. It is commonly used in formulations related to skin aging, wrinkles, dark circles, and puffiness of the eyes. Sederma, the personal care products division of Croda Chemicals has developed a composition called Haloxyl™. Haloxyl contains chrysin along with matrikines and the product is specially used for reducing under-eye dark circles.

The following table is a short compilation of a few marketed formulations across the globe.

Additionally, there are several patents of chrysin being used in skincare regimens. Table 2 shows various patented formulations containing chrysin or derivatives of chrysin as one of the important ingredients.

5. Future opportunities for chrysin in skin disorders

Polyphenol chrysin has a high antioxidant potential owing to the free hydroxyl group in its chemical structure. The same functional group is a highly reactive site for functionalizing this compound. In this review, we have discussed several research papers that have used chrysin in the treatment of various skin disorders. The studies, however, are in-vitro or in-vivo performed in animal models. Human studies have not yet been carried out to test the efficacy of chrysin in the treatment of skin disorders. Chrysin is practically insoluble in water. Due to substantial metabolism and efflux of metabolites back into the intestine for hydrolysis and fecal excretion, in vitro cell line experiments have revealed that chrysin

has low bioavailability (Walle et al., 2001),Human pharmacokinetic studies have shown that plasma levels of chrysin metabolite namely chrysin sulfate are 30 times higher than that of parent molecule. Experiments in rat have shown higher levels of chrysin conjugates in bile (Walle et al., 2001).

The limited water solubility of chrysin makes it difficult to boost its biological activity and bioavailability in any dosing form. Several attempts have been made to improve the solubility of chrysin facilitating ease of formulation of chrysin. These are cyclodextrin complexation (Fenyvesi et al., 2020), use of hydroalcoholic mixtures (Zhou et al., 2014), solid dispersions (Lee et al., 2019) and nano-emulsification (Nagaraja et al., 2021).

Chrysin has the potential to be employed both orally and topically in the treatment of skin problems. Several skincare cosmetics have utilized its antiaging activity, and its ability to remove dark spots and dark circles owing to its anti-pigmentation effect (Tables 1 and 2) The future opportunities are in finding solutions to challenges such as developing stable chrysin-containing dosage forms that have enhanced bioavailability, enhanced permeation of chrysin, and improved pharmacological activity (Stompor-Gorący et al., 2021), Although chrysin has several potential benefits for the skin, its effect on hair growth is not yet studied. There is one report on the derivative that Chrysin 7-O-crotonate when applied topically to black mice (C57BL/6), promoted hair growth (Shin et al., 1999), However, the mechanism of action has not been explored in this study. Also, another study showed the effect of chrysin as an adjuvant therapy during docetaxel therapy in cancer helped prevent hair loss, a most commonly observed side effect of chemotherapy (Lim et al., 2017).

6. Conclusion

Polyphenol chrysin is a common ingredient of citrus fruits, honey, propolis and mushrooms, and passion fruit. Anticancer, antioxidant, hepatoprotective, antiviral, and anti-anxiety are only a few of its pharmacological properties. It can also be used to treat skin cancer, acne, psoriasis, and atopic dermatitis. It helps in wound healing and in treating cutaneous leishmaniasis. It has a promising ability to be used as an adjunct in various treatment regimens.

New formulations containing chrysin are being researched to increase its water solubility and biological activity. Recently, the skincare industry is flooded with products containing chrysin to be used in skin aging, eye puffiness, and hyperpigmentation of the skin. The current status of chrysin is excellent in terms of the prospectus available for the use of this polyphenol in treating skin disorders. However, chrysin is not yet reviewed by the Cosmetics Ingredients Review (CIR) Expert panel. Looking at the widespread use of chrysin in dermatological products, we express the need to evaluate the dermato-kinetic and topical toxicological profile of chrysin. Future scope lies in the research of stable and more bioavailable formulations of polyphenol chrysin.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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