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LITERATURE REVIEW: THE ROLE OF SAFFRON (*CROCUS SATIVUS L*) IN COSMETIC DERMATOLOGY

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ABSTRACT

Background : *Crocus sativus L* known as saffron is widely discussed in Indonesia. Although saffron has been used since ancient times for medicinal and cosmetic purposes, scientific research on the mechanism of saffron in its role in promoting skin health is lacking. **Objectives :** This literature review is to determine the role of saffron in cosmetic dermatology. **Methods :** This article is a narrative research. The library sources that used was carried out through the database Google Scholar, PubMed, and Cochrane. The article search does not limit study design or study level. All articles were searched from 2012 to June 2023. The study inclusion criteria included: data available in English and Indonesian. Exclusion criteria were articles on the benefits of using saffron in the other field of dermatology and the use of saffron in combination with other topical active ingredients. **Results :** There were 16 articles which meet the criterias. It was found that saffron play role in the cosmetic dermatology such as in skin aging, melasma, as a photoprotection agents, skin moisturizer, prevention and treatment of skin cancer, as well as preparation of cosmetic products. Saffron has antioxidant, antiinflammatory, antipigmentation, antiwrinkle, anticarcinogenic and photoprotective activities. **Conclusion :** *Crocus sativus L* is a natural ingredient that has the potential to be further developed into medicinal forms, both oral and topical preparations because it is proven to have various pharmacological effects that play role in the cosmetic dermatology.
Keywords: *Active Ingredients, Cosmetics, Cosmetic Dermatology, Role, Saffron*

INTRODUCTION

Crocus sativus L or known as saffron is currently widely discussed in Indonesia.[1] Saffron become the most expensive spice in the world and known as *"red gold"* due to little amount on each flowers, short planting process, and harvesting process that requires accuracy.[1,2] In ancient times saffron was used as a food ingredients, traditional medicines, and also known to be useful in cosmetic dermatology.[2] Benefits of saffron on the skin include as a form of skin rejuvenation therapy where saffron can be applied directly or, mixed with fat or donkey milk for topical use on the skin.[3,4] Although saffron has been known and used since ancient times for medicinal and cosmetic purposes, scientific research on the active mechanism of this ingredient in its role in promoting skin health is lacking.[5]

Cosmetics have now become one of the needs and trends in society. The large number of cosmetic product findings without distribution permits and or using ingredients that are prohibited in cosmetic products by the Food and Drug Monitoring Agency (FDA) in Indonesia makes consumers worry and afraid in choosing and using cosmetic products on the market. Consumers are starting to switch choosing cosmetic products which made from natural or herbal ingredients that are considered safer, easier to use, and healthier. The herbal cosmetic industry is starting to increase and become popular in the community.[6,7] One of the natural ingredients that have been used in cosmetic products is saffron (*Crocus sativus L*).[6] The purpose of compiling this literature review is to determine the role of saffron in cosmetic dermatology.

METHODS

The method used when writing this article is narrative research. The library sources that used for this literature review article was carried out through the database Google Scholar, PubMed, and Cochrane. The literature search terminology used was "*Crocus sativus L*" OR "Saffron" AND "Dermatology" OR "Skin" AND "Cosmetic". The article search does not limit study design or study level (International, national or regional). All articles were searched from 2012 to June 2023. The study inclusion criteria included: data available in English and Indonesian. Exclusion criteria were articles on the benefits of using saffron in the field of dermatology other than cosmetics and the use of saffron in combination with other topical active ingredients.

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RESULTS

Based on the search results, there were 2,011 articles consisting of 2,010 articles from Google Scholar, 1 article from PubMed, and 0 articles from Cochrane. The initial search results were then filtered again for titles and abstracts that were not relevant to the research topic and 100 articles were obtained from Google Scholar. Based on checking of the 100 articles, it was found that 84 articles did not meet the inclusion and exclusion criteria, so that the final results obtained were 16 articles which would be reviewed in this literature review. (Figure 1)

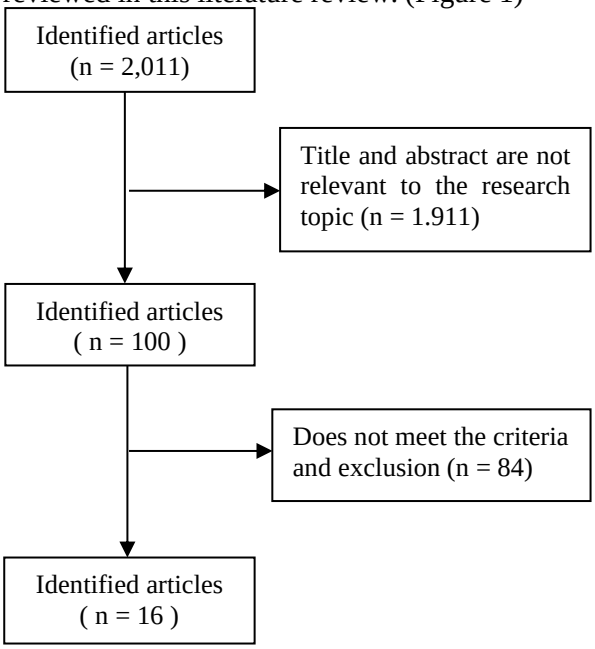

Figure 1. Paper Selection Algorithm

DISCUSSION

Saffron has various biological activities related to its phytochemicals. The main ingredients of saffron are crocin and crocetin which are carotenoids derived from zeaxanthin which give saffron its yellow color, picrocrocin which gives saffron its taste, and safranal which gives saffron its distinctive aroma.[1,3,5,8–10] The contents of these compounds are known to have pharmacological effects that can play a role in various disorders in the field of cosmetic dermatology including the following:

Skin Aging

Skin aging is a natural process that occurs in the skin. Intrinsic skin aging generally occurs with age and can be influenced by genetic, racial and hormonal factors. Process of intrinsic aging show production of collagen fibers as well as various types of proteins that make up the extracellular matrix will decrease, so that wrinkles begin to form, skin becomes looser, and the process of degeneration of elastic fibers will also increase, so that skin elasticity will decrease. Meanwhile, skin that is experiencing extrinsic aging or photoaging, there will be an increase in degradation of the extracellular matrix and a decrease in collagen synthesis. which will eventually lead to loss of collagen fibers and deposition of abnormal degenerative elastotic material in the dermis (actinic elastosis) over time. This photoaging process can cause changes in various skin compartments, including the epidermis, the pigment-forming system, the dermis connective tissue, blood vessels, and subcutaneous fat tissue.[11–13]

Key role in causing photoaging such as chronic and repetitive exposure to ultraviolet (UV), visible light, and infrared rays, as well as a number of other external factors such as consumption of alcoholic beverages, pollutants and cigarette smoke.[14] Parts of the skin that are affected by these external factors can experience premature skin aging (photoaging) due to damage to various skin structures (photodamage).[11–13] The predominant clinical features of photoaging are the formation of fine lines and wrinkles, which may be accompanied by dull and rough skin, telangiectasia, and patches of pigmentation on the skin.[11,14]

As the oxidative stress theory explains, cellular oxidative damage plays an important role in the aging process. Skin aging occurs as a result of reduced endogenous antioxidant systems and increased production of ROS which cause DNA damage. Reactive oxygen species (ROS) cause irreversible damage to the skin, including cross-linking proteins, DNA damage, cell death, and the formation of aging pigments.[2] The accumulation of ROS will activate intracellular signaling pathways, increase the activity of p38 mitogen-activated protein kinase (MPAK), which will produce proinflammatory cytokines such as IL-1, cyclooxygenase 2 (COX-2), and TNF-α expression in keratinocytes.[15]

Saffron can play role in the management of skin aging through several mechanisms below:

1. **Antioxidant Activity**

Saffron has high antioxidant activity which can

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fight free radicals from UV radiation on the skin.[2,8,16] The antioxidant activity of saffron mainly comes from crocin, crocetin, safranal, and quercetin. Other antioxidant potential comes from other carotenoids β-carotene, lycopene, lutein, zeaxanthin, monoterpenoids, kaempherol, and other phenolic components in *Crocus sativus L*.[2]

The high antioxidant activity of saffron comes from crocin and crocetin which are carotenoids, which are strong antioxidants in neutralizing superoxide anions.[1,5,8] Crocin showed high radical scavenging activity (50% in 500 ppm methanol solution and 65% and 1000 ppm methanol solution) followed by safranal which was 34% in 500 ppm methanol solution.[2,6] Fagot *et al* who conducted regarding the evaluation of antioxidant activity in saffron, found that crocin has very strong antioxidant activity compared to vitamin E and vitamin C.[8,17,18] Deng *et al* research on in vitro human fibroblasts used crocin to assess crocin activity in preventing photoaging where crocin was shown to reduce intracellular ROS levels by neutralizing ROS formed through its dose-dependent inhibitory activity, increasing cell cycle repair, and cell proliferation, increased extracellular matrix activity, and preventing apoptosis.[8] Crocin can inhibit UVA-induced cell membrane peroxidation and inhibit the expression of various proinflammatory mediators including IL-8, PGE-2, IL-6, TNF-α, IL-1 α, and Leukotriene B4 (LTB 4).[8,18]

Crocin and crocetin are natural carotenoids in saffron which prevent the formation of free radicals, reduce lipid peroxidation, and increase levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[14] Crocetin can decrease ROS production UV-light-induced and protect cells from cell death in human fibroblasts. Crocetin was also noted to be able to suppress oxidative stress on the skin of mice.[5]

Safranal has the ability to donate a hydrogen atom to the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The limitations of the research conducted are that there have been no studies proving the efficacy of safranal ex vivo or in vivo, where its antioxidant activity on safranal recently performed in *in vitro* studies.[2]

The antioxidant activity of saffron also comes from quercetin which is a flavonoid with the highest antioxidant activity. Topical preparations containing quercetin succeeded in inhibiting UV-B-induced skin damage in mice. [1]

2. Anti-inflammatory Activity

Saffron's antiinflammatory activity comes from its crocetin and crocin content.[5,6] Both of these components demonstrate their antioxidant capabilities by inhibiting the production of proinflammatory cytokines such as IL-1 production by inhibiting NF-B activity through inhibition of phosphorylation I kappa B kinase-a (IKK-a) and preventing nuclear translocation of the NF-B subunit p65. Giving crocin at a dose of 20 mg/kgBB can inhibit various proinflammatory cytokine activities including IL-1β, IL-6, and TNF-α), and a number of inflammatory mediators prostaglandin-2 (PGE-2), cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).[1,3,6] Crocin and safranal are also known to reduce the number of neutrophils and pain response in inflammation performed on rats.[6]

3. Anti-pigmentation Activity

Hyperpigmentation of the skin is influenced by various factors including UV radiation, free radicals, inflammatory mediators, and hormones. The color of the skin is influenced by the type of melanin and the amount of melanin in the skin, which is a natural pigment in the skin produced from the process of melanogenesis facilitated by the enzyme tyrosinase. [11] Saffron extract has tyrosinase inhibitor activity dose-dependent at a concentration of 0.05 – 1 mg/ml. The ability of this tyrosinase inhibitor is said better than α-arbutin, and slightly lower than β-arbutin.[5] Saffron has several capture points that are thought to play a role in inhibiting pigmentation of the skin including the following:

a. Saffron can directly inhibit tyrosinase activity in the process of melanogenesis through its crocin component which can inhibit the activity of the tyrosinase enzyme by destroying the hydrogen bonds in the tyrosinase enzyme thereby reducing the amount of melanin in the skin.[6]
b. Saffron contains crocetin which can inhibit the process of melanogenesis by suppressing and inhibiting the activity of the tyrosinase enzyme and reducing the quality of the melanin that is formed.[8,14]
c. Saffron contains kaempherol which is a flavonoid that has strong tyrosinase inhibitory activity.[4,5,17]

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Research by Akhtar N *et al* in 2013 has proven the use of a 3% *Crocus sativus* extract cream formulation on human skin could show skin depigmentation effects and antierythematous effects on human skin due to decreased levels of melanin and erythema in the skin.[17] Saffron is used as a mixture in cosmetic preparations which are intended as a brightening agent for hyperpigmentation disorders of the skin.[6,14–17]

4. Anti-wrinkle Activity

Collagen and elastin are protein components found in skin tissue, where collagen is found in connective tissue, and elastin is found in the superficial dermis. Chronic UV exposure in photoaging conditions cause a decrease in collagen and elastin production, which results in significant changes in the appearance of the skin including irregular epidermal thickening, wrinkles, skin atrophy and rough skin.[2,14] Antiwrinkle activity possessed by saffron comes from its antioxidant potential including kaempherol, crocin, crocetin, and safranal.[6] In a study, safranal showed significant inhibitory activity against enzymes involved in the aging process including elastase, collagenase, and hyaluronidase.[2,14] Safranal can also inhibit the activity of matrix metalloproteinases (MMPs) which play a role in skin aging and wrinkle formation.[5]

Photoprotection Agent

Saffron known to have a photoprotective effect that may protect the skin from harmful effects of exposure to ultraviolet light. Photoprotective ability and sunscreen potential of saffron comes from the antioxidant and antiinflammatory abilities of crocin, safranal, and crocetin, as well as saffron's ability as a natural ultraviolet absorbent or natural sunscreen.[1,5,6,10,16]

Carotenoids in saffron reduce the harmful effects of chronic sun exposure on the skin through an antioxidant mechanism. Crocin provides protection against cell damage due to UVB exposure in dermal fibroblast cultures, reduce intracellular ROS levels, improve cell cycle and cell proliferation.[14,19] Crocetin's photoprotective activity was demonstrated in studies using human skin-derived fibroblasts *in vitro* and in mice skin subjected to UVA-induced oxidative stress in vivo. Crocetin reduce cell apoptosis, suppress caspase-3 activity, reduce ROS production and lipid peroxidase levels in the skin.[14]

Research shows that use of saffron lotion have better effectiveness as a sunscreen than homosalate (an organic component used in sunscreen preparations) so that saffron can be used as a natural UV absorber.[2,3,5,14] Golmohammadzadeh *et al* measured Sun Protection Factor (SPF) *in vitro* to prove that saffron has the capacity as a UV absorber.[2,5,20] Zarkogianni *et al* proved that saffron has the ability as a natural UV absorbent material and can be used as a sunscreen ingredient in cosmetics, where the SPF level increases as the level of saffron emulsion used increases.[10]

1. Melasma

Melasma is one of the most common acquired chronic hyperpigmentation disorders in women. The clinical presentation of melasma is in the form of light brown to dark brown macules with irregular edges, symmetrical and affects areas frequently exposed to sunlight, especially the face and neck. Areas on the face that are often exposed are the cheeks, chin, forehead, nose, upper lip, and temples.[21,22] Although various treatments and combinations have been carried out, a distinct challenge for clinicians in treating melasma is due to the chronic and recurrent course of the disease. So that new strategies for the treatment of melasma are still needed.[23]

Early theories that *Crocus sativus L* could play a role in the treatment of melasma already revealed in research using molecular docking in 2022.[23] The role of *Crocus sativus L* in melasma is analyzed for its role in melanogenesis, and there are 8 targets that play a role, namely: Kit ligand (KITLG), Cyclic AMP-responsive element-binding protein 1 (CREB1), L-dopachrome tautomerase (DCT), Endothelin receptor type B (EDNRB), Microphtalmia-associated transcription factor (MITF), PKACA, 5,6-dihydroxyindole-2-carboxylic acid oxidase (TYRP1), and tyrosinase (TYR).[23] In this study, possible mechanism of action of *Crocus sativus L* in the pathophysiology of melasma include:

a. The key target role of *Crocus sativus L* in melanogenesis directly is through tyrosinase (TYR), 5,6-dihydroxyindole-2-carboxylic acid oxidase (TYRP1), and L-dopachrome tautomerase (DCT). Yin MS *et al* explained that crocetin is the strongest active ingredient contained in *Crocus sativus L* compared to other

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components such as quercetin, isorhamnetin, and kaempherol. In line with this research, Hashemi et al have also proven that crocetin can inhibit tyrosinase activity and reduce the amount of melanin that is formed.[23]

b. *Crocus sativus L* affect melanogenesis indirectly through Microphtalmia-associated transcription factor (MITF) which regulates the synthesis of TYR, TYRP1, and DCT through 3 pathways, including the cyclic adenosine monophospathe-dependent signaling pathway (cAMP signaling pathway), Wnt/β-catenin-signaling pathway, and mitogen activated protein kinase signaling pathway (MAPK-signaling pathway).
c. *Crocus sativus L* play a role in PKACA which will upregulate the expression of CREB1 which is associated with the CRE domain on the promoter of the MITF gene to initiate MITF expression.
d. *Crocus sativus L* play a role in stem cell growth factor (SCF) which binds through receptors and activates KIT, then through the MAPK-signaling pathway will catalyze MITF synthesis.
e. *Crocus sativus L* plays a role in regulating melanogenesis through EDNRB.[23] Increased vascularity in melasma lesions raises the suspicion that there is a relationship between skin pigmentation and vascularization. In a study using epilumination dermoscopy, confocal laser microscopy, and histological examination, was found that there is a picture of benign vascular lesions in hyperpigmented skin areas compared to the surrounding skin. Upon further investigation, it was discovered that endothelin 1 released by microvascular endothelial cells induces an increase in melanogenic signaling. Endothelin acts through endothelin receptor type B in inducing melanogenesis. [23]

The results of this study can be used as reference material to conduct further experimental research regarding the mechanism of *Crocus sativus L* in the treatment of melasma.[23]

2. Skin Moisturizer

Skin dryness in the epidermis occurs because there are changes both chemically and morphologically due to internal and external factors. The human skin loses approximately 0.5 L of fluid per day through the transepidermal route. When the water content reaches less than 10%, the skin is indicated as dry. Saffron has shown activity as an emollient and antipruritic in 0.025% dosage form.[14] In the study of Akhtar et al, it was found that the moisturizing effect of saffron on the skin was obtained from the phenolic components quercetin and kaempherol which have been shown to be potent moisturizers and antisolar agents.[24] Saffron in cream form (oil in water based) can reduce trans epidermal water loss (TEWL) and increase hydration levels in the skin.[24]

3. Prevention and Treatment of Skin Cancer

The role of saffron in preventing skin cancer comes from its antioxidant and photoprotective components. In several in vitro and in vivo studies, crocin and crocetin components showed anticarcinogenic activity.[3,14] Research on mice that were given a treatment in the form of applying topical saffron extract 100 mg/KgBB could prevent skin cancer induced by dimethylbenz (α) anthracene (DMBA). Crocetin can suppress the formation of skin tumors by preventing the synthesis of intracellular nucleic acids, proteins in malignant cells and preventing protein kinase C (PKC). Crocetin can also inhibit tumor formation in skin papillomas. The picrocrocin component can suppress human SK-MEL-2 malignant melanoma cells by inhibiting cell growth, inducing apoptosis and stopping the cell cycle.[14,25]

Crocin components from saffron in the treatment of cancer can inhibit cell proliferation, induce cell apoptosis, and stop the cancer cell cycle in the G0 or G1 phase.[25] Research proves that saffron can inhibit skin carcinoma in mice that are given early treatment.[25]

4. Use in Cosmetic Product

Cosmetics is ingredients or preparations intended for use on the outside of the human body (epidermis, hair, nails, lips and external genital organs) or teeth and oral mucosa, especially for cleaning, perfuming, change the appearance and or improve body odor or protect or maintain the body in good condition. Use of saffron as a cosmetic product mixture is still limited due to high raw material costs. Cosmetic products that use saffron include the following:[1,3,4,6,16]

a. Natural coloring agent: Saffron has long been used as a natural coloring agent in the cosmetic industry. The color produced by saffron is called reddish gold, which is orange and red-orange. This natural color comes from the crocetin and crocin components contained in saffron which have a

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carotenoid glycoside structure.[1,6] Some cosmetic preparations that use saffron as a natural dye are bindi. Indian women use saffron to make bindi or sindoor, which is a yellow circular dot in the middle of the forehead and can be accompanied by an image of a line on the part of a woman's hair (referred to as a mang in Indian).[3,26] Saffron is also used as a natural coloring agent developed in herbal lipsticks.[27]

b. Perfume or fragrance: Since ancient Greece, saffron has been used as the perfume of the nobility because of its fragrant fragrance and the Greeks' liking. Saffron contains more than 150 volatile and aroma-producing compounds so that saffron is used as a perfume component. Safranal is the main component of saffron essential oil which is formed from the hydrolysis of picrocrocin when it is dried and stored.[1,3,6]
c. Face toner preparations: Saffron is used in facial toner because it contains vitamin C, zinc, and flavonoids. Vitamin C works as an antioxidant, zinc can control oil production, heal acne vulgaris faster, and treat acne scars. In addition, zinc is also needed in the formation of cell membranes and proteins, as an anti-inflammatory, and protection from ultraviolet rays. Flavonoids contained in saffron also have the ability to brighten the face through inhibition of melanogenesis process.[1,4]
d. Skin Lightening Cosmetics: Saffron which already known as antiaging and antipigmentation agent has been use as a complexion promoter in skin care. Several formulations are available in the market such as cream based, lotion based, and face powder. These cosmetics are mainly intended for reducing the hyperpigmentation of the skin. [28]

CONCLUSION

Saffron *(Crocus sativus L)* is a natural ingredient that has the potential to be further developed into medicinal forms, both oral and topical preparations because it is proven to have various pharmacological effects that play role in the field of cosmetic dermatology, including skin aging, photoprotection agents, melasma, skin moisturizer, prevention and treatment of skin cancer, as well as preparation of cosmetic products. Saffron has the potential to become an active ingredient in various cosmetic dermatology disorders and cosmetic dosage forms due to its antioxidant, antiinflammatory, antipigmentation, antiwrinkle, anticarcinogenic and photoprotective activities. The compounds that play the most roles in saffron activity are crocin, crocetin, safranal, quercetin, and flavonoids.

ETHICAL APPROVAL

There is no ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

The author contributions to this review are as follows: conceptualization, collecting literature and writing draft: Galih Sari Damayanti; supervision, review and editing: Puguh Riyanto.

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