Carotenoids in red fruit (*Pandanus conoideus* Lam.) have a potential role as an anti-pigmentation agent (Review)

SRI TRISNAWATY[1], JULIA WINDI GUNADI[2,3], HANA RATNAWATI[4] and RONNY LESMANA[5]

[1]Master Program of Skin Ageing and Aesthetic Medicine; [2]Department of Physiology; [3]Maranatha Biomedical Research Laboratory; [4]Department of Histology, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, West Java 40164; [5]Physiology Division, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, West Java 45363, Indonesia

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Abstract. Melasma is a persistent condition characterized by excessive melanin production in the skin. The management of melasma necessitates a protracted treatment duration, which is associated with diminished levels of patient satisfaction. One effective strategy for mitigating occurrence of melasma is consumption of nutricosmetics with depigmentation properties. The present review aimed to investigate the potential of red fruit as a depigmentation agent. Carotenoids serve a crucial role in human nutrition as a precursor to vitamin A. Carotenoids serve as scavengers of reactive oxygen species generated by ultraviolet radiation. Carotenoids promote skin health. Red fruit, a fruit originating from Papua (Indonesia) has anti-pigmentation properties associated with its ability to block melanogenesis through various protein pathways such as PKA, ERK, and AKT signaling pathways. The consumption of food rich in carotenoids, such as red fruit, has advantageous properties to reduce hyperpigmentation and skin brightening.

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Correspondence to: Dr Julia Windi Gunadi, Department of Physiology, Faculty of Medicine, Universitas Kristen Maranatha, Surya Sumantri 65, Bandung, West Java 40164, Indonesia
E-mail: julia.windi@maranatha.ac.id

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1. Introduction

Melasma is a persistent condition characterized by excessive melanin production in the skin (1). Multiple investigations utilizing the melasma quality of life scale (MelasQoL) score have observed a decline in the overall quality of life attributed to melasma (2-4). However, severity of melasma measured by the melasma area severity index score (MASI) does not yield any statistically significant impact on quality of life (5,6). Melasma is observed across diverse ethnicities and geographical regions, with higher prevalence among populations with darker skin tones residing in regions characterized by high levels of solar radiation compared with individuals with lighter skin tones (4,7). Individuals with light brown skin tones, particularly those of Latino and Asian descent, tend to exhibit hyperpigmentation more frequently. The prevalence of pigmented phenotypes is higher among the populations of Southeast Asians, Middle East Asians, Mediterranean Africans, Hispanic Americans and Brazilians (7). The incidence of this condition in dermatological clinic patients in Southeast Asia ranges from 0.25 to 4.0%, but previous studies have shown higher prevalence of up to 40% in the general population (2,4,6).

Melasma is associated with cellular malfunction in melanocytes, which are responsible for pigment production (2). Melasma can be induced by various factors, including ultraviolet (UV) light exposure, hormonal fluctuations, genetic predisposition, racial background and the use of cosmetic products (3,5). UV radiation has the potential to induce generation of free radicals, initiating the production of reactive oxygen species (ROS) and resulting in DNA damage (8). Melanocytes serve a pivotal part in the process of melanogenesis by serving as the primary site for synthesis of melanin (9). During a typical melanogenesis process, melanin is conveyed to the outer layer of keratinocytes to protect against DNA harm caused by UV radiation (10). Excessive stimulation of melanogenesis can lead to the development of pigmentation problems (11). The process of melanin formation is initiated by generation of ROS, specifically hydrogen peroxide and quinone intermediates (12). UV light directly induce melanogenesis in melanocytes and activates signaling pathways on numerous cell types, such as keratinocytes, mast cells and fibroblasts (8).

Moreover, UV radiation has the potential to induce cutaneous inflammation, resulting in erythema of the skin (13). This arises because of augmentation of blood circulation in the skin, which triggers the activation of NF-κB transcription in immune cells, specifically keratinocytes and dermal fibroblasts. The activation of NF-κB leads to the production and release of cytokines, including IL-6 and TNF-α. This triggers manufacture and secretion of proteases, specifically matrix metalloproteinases (MMPs), which have the potential to cause damage to collagen in the skin (14).

The extent of skin damage caused by UV radiation is contingent upon the specific wavelength of light (10). UVA radiation induces melanin production primarily in the basal layer of skin cells, whereas UVB radiation promotes melanin dispersion across the epidermis. UVC, which is the most potent oncogenic kind of UV light, has a minimal impact on pigmentation (15,16). However, UV radiation can stimulate all components of the corticosteroid hormone axis, including glucosteroidogenesis (17). The stimulation is influenced by the wavelength of light, with the UVC spectrum, which has the shortest wavelength, having the greatest impact (15). UVB has less effect, whereas UVA has either no effect or only moderate impacts, limited to increases in corticotropin-releasing hormone (CRH) and endorphin peptides (15). UVB radiation increases the amounts of ß-endorphin in the skin. It is hypothesized that these responses may have evolved to protect against harmful UV radiation and pigmentary actions, which are dependent on ß-endorphin and regulated by p53 (18). UVB radiation increases expression and activity of the α-melanocyte stimulating hormone (α-MSH) and melanocortin 1 receptor (MC1R), as well as the expression of pro-opiomelanocortin (POMC) and the generation of POMC peptides, such as α-MSH, ß-endorphin and adrenocorticotropic hormone (ACTH) (18,19). This is hypothesized to regulate the pigmentation of mammalian skin, protect it from UV-induced damage and affect immunological responses in the skin (16). UVB radiation additionally triggers production of corticotropin hormone and urocortin while altering the expression of type 1 CRH receptor (15).

In addition to UV exposure, pigmentary abnormality can arise because of chronic inflammation, mechanical trauma to the skin and irregular production of α-MSH (8,20). This is facilitated by a sequence of biological mechanisms wherein melanocytes generate skin pigments, known as melanin, across numerous levels of the dermis (21). The regulation of melanin production in melanocytes involves the microphthalmia-associated transcription factor (MITF), as well as enzymes specific to melanocytes, namely, tyrosinase, tyrosinase-related protein 1 (TRP-1) and 2 (22). The primary objective in preventing skin problems, such as hyperpigmentation, is to target inhibition of melanogenic enzymes and MITF (23).

Nevertheless, management of hyperpigmentation conditions, such as melasma, typically necessitates a protracted duration for effective treatment (2). The extended length of treatment is associated with diminished patient satisfaction (20). Various treatment modalities necessitate both topical and oral interventions (11). The utilization of bleaching compounds, such as corticosteroids, hydroquinone, monobenzyl hydroquinone, tretinoin and mercury, has been prohibited in numerous regions (21). One example is hydroquinone 2%, a depigmenting agent employed for an extensive period due to its ability to impede activity of tyrosinase, the primary enzyme involved in melanogenesis (20). However, use of hydroquinone 2% is controversial as it induces irritation and is linked to the development of skin malignancies (24). In the context of oral therapy, certain antioxidants, such as vitamin C and glutathione, have been demonstrated to be effective in treatment of melasma (25).

Because melasma is a chronic and recurrent hyperpigmentation disease, protecting the skin from triggers is the best course of action (1). The prevention of hyperpigmentation can be achieved by strategies such as applying sunscreen, utilizing antioxidants and taking vitamins and nutrients (26). The role of nutrition in promoting skin health has been widely recognized as it offers numerous advantages such as preventing premature aging and reducing the risk of skin disease (24,27,28). 'Nutricosmetic' refers to food that contains specific components, such as vitamins, peptides, polysaccharides, polyphenols, coenzyme Q10, polyunsaturated fatty acid (PUFA) and carotenoids, which are intended to enhance cosmetic outcomes (24). Carotenoids can be acquired from a diverse range of dietary sources, including natural food sources and supplementary forms (29). Carotenoids play a notable role in human nutrition as they serve as precursors to vitamin A (28). Carotenoids have preventive attributes that safeguard the skin against oxidative free radical harm, as well as from high-energy sources, such as UV radiation (24). Carotenoids are present in both topical and oral formulations, with the most prevalent variants being β- and α-carotene, lycopene, lutein, zeaxanthin and α- and β-cryptoxanthin (30).

The mechanism by which carotenoids exert their antioxidant activity is hypothesized to involve prevention of lipid peroxidation and the scavenging of singlet oxygen (31). These potent antioxidants may inhibit deposition of pigments by inhibiting the enzyme tyrosinase, decreasing inflammation and interfering with the generation of free radicals (32). The administration of carotenoids in oral formulations facilitates dissemination of their systemic effects to the dermis and epidermis, resulting in a decrease in migration of pigments from the epidermis to the dermis (33). Carotenoids possess high efficacy as natural antioxidants (28,29). O_2 quenching has been demonstrated to be highly effective as a scavenging agent, particularly for carotenoids with 11 conjugated double bonds (29). Carotenoids also function as chemical quenchers of singlet oxygen, undergoing changes such as oxidation or oxygenation (28,29). Carotenoids are involved in three widely recognized primary mechanisms for scavenging free radicals: Transfer of electrons between carotenoids and free radicals; direct addition of free radicals to carotenoids and hydrogen atom transfer to carotenoids (24,34,35). Carotenoid radical products have potential to undergo additional changes, resulting in secondary carotenoid derivatives with varying levels of reactivity (29). This is key because the newly produced carotenoid species may cease to function as effective antioxidants and may become potentially damaging, pro-oxidant agents (24,31).

Carotenoids can be derived from fruit extracts, such as those obtained from red fruit (*Pandanus Conoideus* Lam.). The consumption of red fruit, which exerts anti-diabetic, anti-tumor, anti-inflammatory, and anti-atherosclerosis, is prevalent

in the Papua region of Indonesia (36-41). Several studies have indicated that red fruit has a significant concentration of carotenoids and tocopherols (36,37,39,42-44). To the best of our knowledge, however, the amount of research studying the impact of carotenoids found in red fruit on skin health remains limited. The lack of studies may be attributed to the fact that red fruit is exclusively found in Indonesia. The primary objective of the present literature review was to assess the potential role of red fruit as an anti-pigmentation agent in the prevention of melasma.

2. Melanogenesis and melasma treatment

The skin can respond to numerous stimulatory signals through a cutaneous neuroendocrine system (45). The skin contains parts of the hypothalamic-pituitary-adrenocortical (HPA) axis, affected by environmental stresses and associated with skin functions, including melanogenesis (45,46). Exposure to stressful events triggers activation of the central HPA axis (47,48). Under stress, the body produces and releases CRH, which, in turn, enhances the expression of POMC (49,50). POMC undergoes enzymatic conversion to produce ACTH and other melanocortin peptides, including α-MSH (48,50). CRH has been detected in the human skin and promotes ACTH synthesis and release (49,51). ACTH attaches to MC2R in the adrenal cortex, which triggers production and release of glucocorticoids into the bloodstream (50,51). This leads to a range of physiological effects such as regulating metabolism, reducing inflammation, and suppressing the immune response (49-51). Hence, it is key to determine the skin's ability to control processing of POMC-derived peptides and to examine variations in this process between keratinocytes and melanocytes (19,50).

Multiple signaling molecules/ligands are necessary throughout melanocyte formation (17,52). The involvement of specific G-protein-coupled receptors (GPCRs) in transformation of melanocytes may be because of their crucial role in the development and maintenance of melanocytes (51-53). GPCRs play significant roles in the physiology of melanocyte lineage, influencing all stages of development and functions of mature melanocytes (52,53). GPCR ligands are found in the skin and control melanocyte homeostasis, which includes pigmentation regulation (52). Endothelins (ETs) and endothelin receptor type B (EDNRB) are involved in melanocyte transformation and the advancement of melanoma (53). The ET system comprises three closely related short peptides (ET-1, 2 and 3), two GPCRs (EDNRA and EDNRB) and two proteinases endothelin-converting enzyme 1 and 2 (52,53).

Melanocytes have a receptor called MC1R, which regulates melanogenesis. MC1R is a member of a minor group of GPCRs that are divided into five distinct subtypes that play a key role in essential physiological functions (19,49,51). MC1R is the sole melanocortin receptor that is present in melanocytes (50,53). MC1R is a receptor belonging to class A and is linked to Gs protein (46). MC1R interacts with α-MSH, which is produced from pro-opiomelanocortin (18,19). A number of enzymes act as prohormone convertases on POMC leading to the generation of numerous hormones, such as ACTH, α-MSH, β-MSH, γ-MSH, β-endorphin (β-END) and β-lipotropic hormone (47,53). Various POMC-derived peptides are generated dependent of tissue origin and these peptides exert effects on distinct melanocortin receptors (16,54,55). POMC is locally expressed in the skin (18,19,50). The processing of POMC in human skin is similar to that in the hypothalamus as ACTH, α-MSH and β-END have been detected in melanocytes and keratinocytes and skin biopsies of rats (49,51,53).

Melanogenesis refers to the biological process of synthesizing melanin pigments, predominantly by specialized cells known as melanocytes (56). The principal role of melanocytes is synthesis of melanin pigments (57). Melanin pigments are regulated by positive and negative regulators (16). The positive regulators are MC1R ligands with melanocortins and ACTH (16). The negative regulator is locally produced agouti signaling protein, which acts as an antagonist to melanocortins by binding to the same or separate sites on MC1R, causing a switch from eumelanogenesis to pheomelanogenesis and inhibiting melanogenesis (16).

Melanocytes within the epidermis are enveloped by keratinocytes, with an estimated ratio of 1 melanocyte to 36 keratinocytes (9). These melanocytes effectively transfer melanin pigment to the surrounding keratinocytes (58). Melanocytes have melanosomes, which are organelles resembling lysosomes at the subcellular level (59). These melanosomes are responsible for synthesis and storage of melanin pigments, which are distributed to the neighboring keratinocytes (56). The regulation of melanogenesis involves coordination of several signaling networks, including the Wnt/β-catenin, PI3K/Akt, cAMP/protein kinase (PK) A, and stem cell factor (SCF)/c-kit-mediated signaling pathways (60).

Wnt signaling serves a critical role in melanocyte development (61,62). Research has demonstrated that canonical Wnt signaling, specifically Wnt1 and Wnt3a, has crucial roles in the development of melanocytes (62,63). A typical canonical Wnt pathway molecule, promoted melanogenesis of melanocytes via the up-regulation of the expression of MITF, tyrosinase and TRP (56,62,63). The initiation of Wnt receptor complexes induces substitution of the versatile glycogen synthase kinase-3β, resulting in buildup of β-catenin (61). The stable form of β-catenin is translocated to the nucleus, where it upregulates production of MITF, thereby promoting melanogenesis (63). The upregulation of Wnt expression either via the canonical or non-canonical signaling pathway happens in a gradual manner inside the hyperpigmented skin regions of individuals with melasma (56).

An increased intracellular concentration of cAMP facilitates the activation of PKA, which, in turn, phosphorylates CREB and CREB binding protein (64). This phosphorylation results in the upregulation of MITF expression (65). The activation of melanogenic gene promoters by MITF leads to upregulation of melanogenesis (56). A study investigating the dominant negative mutant of MITF, which lacks the transactivation domain, demonstrated the essential role of MITF in cAMP-induced stimulation of tyrosinase production (66).

During melanogenesis, tyrosine and levodopa serve as substrates for tyrosinase (12,56). In addition, they serve as bioregulatory agents for other cellular activities (11,67). These processes encompass development of dendrites and the promotion of cell migration, achieved by reducing activity of PKC (68). Although PKC serves a regulatory role in melanogenesis, cAMP is the most important biochemical

regulator (12,26,58). Furthermore, control of melanogenesis is associated with the p38 MAPK and PI3K/AKT signaling pathways (22). The process of phosphorylating p38 MAPK leads to upregulation of MITF and tyrosinase, hence inducing the activation of melanin production (69). In addition, activation of the PI3K/AKT pathway leads to a decrease in melanin synthesis by downregulating MITF, tyrosinase and TRPs) (56). Conversely, inhibiting the PI3K/AKT pathway enhances melanin formation by activating MITF and inducing expression of tyrosinase (70).

The involvement of this signaling system in physiological adaptations of the skin to environmental variables, such as exposure to UV radiation, is widely acknowledged (12,56,71,72). The most important function of the skin is as a physical barrier, which is determined by its location between internal and external environments (45). The epidermal pigmentary system protects skin from the damaging effect of solar radiation (45). Research has demonstrated that UV radiation stimulates the activation of the MC1R (46), which may be why the skin darkening effects of α-MSH and ACTH are particularly noticeable in sun-exposed parts of the skin (68). UV radiation can also induce the release of POMC peptides in the skin (48,53). Studies have demonstrated that cultured keratinocytes generate α-MSH and ACTH when exposed to UV radiation (46,58,73). POMC peptides may serve as both paracrine and autocrine mediators in the tanning response, as evidenced by similar reactions in melanocytes (46). Moreover, these peptides are not limited to melanogenesis; they may serve a role in other processes related to the pigmentary response, such as enhancing the branching of melanocytes and promoting interactions with keratinocytes and extracellular matrix (49,50). As aforementioned, POMC peptides may have a key function in coordinating the events that take place during a pigmentary response (46). The expression of POMC varies in many situations such as normal hair development, production of immune cytokines, presence of skin disease or exposure to UV radiation (46). The activation of the MC1R by α-MSH or ACTH leads to an elevation in cAMP synthesis (74). This indirectly triggers a shift from the creation of pheomelanin to the synthesis of eumelanin (67). In addition to the α-MSH-MC1R signaling route, the SCF/receptor tyrosine kinase Kit (SCF/c-Kit) pathway serves a role in melanocyte pigmentation and development by activating the MITF transcription factor, specifically the M-MITF isoform that is exclusive to the melanocyte lineage (56). The induction of pigmentation by UV and visible light is facilitated by release of SCF (75). SCF acts as a ligand for the tyrosine kinase receptor c-KIT, thereby initiating downstream actions that result in proliferation of melanocytes (10). The secretion of 19 SCF, often referred to as mast cell growth factor, is observed in human keratinocytes and fibroblasts (64). The dermal manifestation of melasma is characterized by upregulation of SCF due to prolonged exposure to UV radiation, leading to skin inflammation and activation of fibroblasts (11). This upregulation of SCF serves a key role in the stimulation of melanogenesis, resulting in an increase in melanin production (69).

The management of melasma poses a challenge and necessitates the implementation of long-term therapy strategies involving topical medicines (1). The outcomes frequently yield dissatisfaction, and the utilization of topical medications may lead to notable adverse responses such as skin irritation, redness, and dryness (4). The proposed first-line topical treatment for this pigmentary condition is a triple combination of hydroquinone, retinoic acid and corticosteroids (1). Numerous compounds such as kojic acid, arbutin, cysteamine, that impede the process of melanogenesis have been created (1,25,76). The assessment of melasma involves numerous evaluation tools, including the MASI and modified MASI score, MelasQoL, colorimetry and mexametry (4,67). Melasma mostly affects parts of the skin that are exposed to sunlight, particularly in female subjects in their reproductive years due to hormonal imbalance (2). There is currently no known cure for this condition, which has a substantial negative impact on overall quality of life (2,4,6). This impact includes a decrease in self-esteem, leading to social challenges, heightened anxiety and symptoms of depression (6).

The absence of a universally effective medicine results in a preference for combination treatment (67). Various therapeutic modalities are available for treatment of pigmentation disorders (11). These include topical hypopigmenting agents, utilization of laser technology, microneedling techniques, administration of chemical peels, utilization of radiofrequency devices, and the use of oral drugs (77). Moreover, it is imperative for patients to refrain from activities or circumstances that may worsen their condition (12).

Promising strategies encompass the reduction of both local and systemic oxidative stress, stabilization of mast cells in the upper dermis, reduction of melanogenesis without causing damage to melanocytes, removal of epidermal melanin without inducing inflammatory responses, reversal of senescence and induction of autophagy (64). Owing to the incomplete understanding of the etiology of melasma, there are potential opportunities for the advancement of novel therapeutic approaches that target mechanisms responsible for persistent pigmentation, as opposed to only reducing melanin production and eliminating melanin from the outer layer of the skin (11). Treatment of this condition should involve a comprehensive approach that integrates photoprotective agents, antioxidant therapies, skin-lightening agents, exfoliants and resurfacing procedures in instances of severe manifestation (26,77). Numerous novel oral, topical and combination medications have been developed and require clinical trials to validate their effectiveness and safety (25).

Endogenous photoprotection through the consumption of dietary elements, such as carotenoids, has been the topic of study (30). The greatest proportion of dietary carotenoids is derived from fruits and vegetables, which serve a crucial role in nutritional intake (28). Humans rely on regular availability of carotenoids as they serve as precursors for vitamin A (29). This vitamin is needed for various bodily functions, including eyesight and cell signaling (24). Carotenoid pigments serve as a protective mechanism for the photosynthetic system in plants by effectively dissipating surplus energy (31). Moreover, multiple lines of evidence substantiate the hypothesis that carotenoids play a crucial role in safeguarding human skin against diseases generated by UV radiation (24,29,30). Enhancing the carotenoid concentration in plants may enhance the nutritional value of food derived from them as essential cellular signaling systems and defensive mechanisms are typically preserved across organisms in natural environments (28).

Table I. Carotenoid effects on skin health.

First author, year	Methods	Results	(Refs.)
Juturu *et al*, 2016	In a randomized, double-blind, placebo-controlled clinical trial for 12 weeks with 50 participants using lutein supplements, zeaxanthin was measured with a chromameter.	Carotenoid content in lutein and zeaxanthin isomers protects the skin from sunlight	(81)
Hashemi-Shahri *et al*, 2018	Spectrophotometric evaluation was conducted to assess impact of crocetin on activity of intracellular and mushroom tyrosinase, as well as melanin concentration. Protein levels of tyrosinase and MITF were assessed in control and crocetin-treated cells. Anti-oxidative activity was also assessed	Crocetin, a naturally occurring carotenoid, inhibits the action of tyrosinase and MITF	(79)
Lee *et al*, 2018	Anti-pigmentation effects mediated by CE were assessed by three-dimensional rebuilt pigmented epidermis model, Fontana-Masson staining and melanin content assays.	Extract derived from CE inhibits mRNA and protein levels of microphthalmia-associated transcription factor, tyrosinase, tyrosinase-related protein-1, and tyrosinase-related protein-2 and suppresses the phosphorylation of protein kinase A and extracellular signal-related kinase, both of which serve key roles as upstream regulators in melanogenesis. Efficacy of extracts from *Chlamydomonas reinhardtii* plant to mitigate pigmentation was validated	(78)
Phacharapiyangkul *et al*, 2021	Analysis of molecular process within B16F10 murine melanoma cells.	Significant inhibitory effect of MPE on melanogenesis in B16F10 cells stimulated with α-MSH. The concentration-dependent effect of MPE on suppression of MITF and tyrosinase expression was observed The inhibitory effect of *Musa sapientum*, which contains β-carotene, on melanogenesis in α-MSH-induced B16F10 cells was demonstrated.	(70)

MITF, microphthalmia-associated transcription factor; CE, *Chlamydomonas reinhardtii*; MPE, *Musa sapientum* Linn. peel ethanol extract; MSH, melanocyte stimulating hormone.

3. Carotenoid effects on skin health

The effect of carotenoids from various plants on skin health has been widely studied (28,70,78-81). β-carotene can absorb UVB rays and serve as a ROS scavenger to reduce the production of inflammatory cytokines (31). β-carotene is a potent antioxidant due to its ability to neutralize singlet oxygen, which decreases skin aging due to sun exposure. In tissue, β-carotene is a source of vitamin A (82). Research regarding the effect of carotenoids on skin health is shown in Table I.

Clinical research by Juturu *et al* (81)on lutein and zeaxanthin (L/Zi) isomers showed skin color brightening and improved skin structure: The study was a clinical trial conducted over a 12-week supplementation period, employing a randomized, double-blind and placebo-controlled design. A total of 50 individuals who were in good health were selected to participate, with 46 of them successfully completing the research. The participants consisted of both males and females, ranging in age from 18 to 45 years. All individuals had mild to moderate dry skin. The skin type was categorized according to the Fitzpatrick skin type II-IV scale (2,3). The participants were given either a daily oral dietary supplement consisting of 10 mg L and 2 mg Zi isomers [3R,3'R-Zi and 3R,3'S (meso)-Zi] or a placebo. The measurement of the least erythemal dose and skin lightening (L*) was conducted using Chromameter®. The individual typological angle (ITA˚) was computed, based on

L* value and sallowness (b* value) of the skin. Furthermore, subjective evaluations were documented (81).

The skin-lightening action of L/Zi may be attributed to its ability to block high-energy blue light rays found in both sunshine and indoor lighting (83). In addition, as a UV absorber/filter, it may promote inhibition of tyrosinase and boost antioxidant capacity (80). The pigmentation of the skin is determined by the presence and distribution of different forms of melanin, namely, pheomelanin and eumelanin (16). L/Zi decreases inflammation and inhibits the activity of free radicals, hence decreasing the production of both forms of melanin (81). A decrease in eumelanin results in an increase in the L* value, whereas a decrease in pheomelanin leads to a decrease in b* value (81). Consequently, this will result in an augmentation of the ITA°, causing a brightening effect on the entire complexion (81). When the L/Zi is ingested, it enters the dermis and then the epidermis, causing a decrease in the depth of pigmentation in the skin (81). Numerous ongoing investigations are examining the precise method by which it affects skin whitening and pigmentation (80,81,83). L and Zi possess carotenoid properties that inhibit melanin pathways, decrease cytokine levels and enhance antioxidant activity inside the skin (81).

Hashemi-Shahri *et al* (79) discovered crocetin (a carotenoid) in saffron plants has antioxidant and anti-melanogenesis effects in melanoma culture cells (79). The aforementioned study was undertaken to investigate the anti-tyrosinase effects of crocetin, given its well-documented antioxidant activity in several studies and the significant role it plays as an antioxidant (32,79,84).

At the protein level, crocetin decreases expression of tyrosinase and MITF (79). Therefore, crocetin may be proposed as a promising dermatological depigmenting agent in the formulation of skin care products (85). The presence of antioxidants derived from natural sources that possess anti-tyrosinase activity serves a significant role in reducing skin damage caused by melanogenesis (33). Phytochemicals serve as precursors to produce molecules that exhibit decreased toxicity in comparison with synthetic substances (86). Crocetin is a naturally occurring carotenoid and a constituent of saffron (*Crocus sativus* L.) (87). Crocetin is a diterpene dicarboxylic acid possessing symmetrical characteristics, featuring seven double bonds and four methyl groups. The glycosylated form of crocetin, known as crocin, accounts for ~94% of the total crocetin content in saffron and the remaining 6% exists in the free form (79). The aforementioned study showed that crocetin effectively suppresses expression of tyrosinase and MITF proteins in comparison with control cells when administered at concentrations of 1, 2, 4, 8 and 16 μM (79). Tyrosinase is a key enzyme involved in melanogenesis in the skin, where it plays a role in controlling formation of melanin (58). The decrease in melanin synthesis in cultivated B16 melanoma cells is hypothesized to be associated with inhibition of tyrosinase activity (79). Alternatively, degradation of MITF indicates suppression of TRPs and production of tyrosinase (79). The levels of tyrosinase protein directly influence the degree of melanin synthesis in cells (26).

The participation of dioxygen at the dinuclear copper ions located at the active site of tyrosinase may influence production of ROS during the melanin synthesis process (69). Hence, substances that impede the generation of both free radicals and the activity of tyrosinase might augment protection of the skin from oxidative stress and hyperpigmentation (79). The reduction in tyrosinase and MITF protein levels caused by crocetin, together with its antioxidant properties, indicates its potential as an agent for inhibiting melanogenesis (79).

The anti-melanogenic effects of plant extracts derived from *Chlamydomonas reinhardtii* (CE) were examined by Lee *et al* (78). The study evaluated the probable mechanisms underlying the inhibitory impact of CE on B16F10 melanoma cells and normal human epidermal melanocyte cells and human skin-equivalent models (78). CE is a microalgae species containing antioxidants, phenolic components and pigments such as carotenoids (78). Multiple studies have demonstrated that carotenoids effectively scavenge ROS and can provide protection against the generation of ROS by UV radiation, as well as hyperpigmentation in melanocytes (24,28,31,32,44,88). The aforementioned study revealed a dose-dependent decrease in cellular melanin content as a result of treatment with CE extract (78). Nevertheless, this did not arise from a direct inhibition of tyrosinase activity, suggesting that CE extract may operate via alternative inhibition pathways not reliant on the enzyme catalytic activities (32,57,78). The expression of additional genes necessary for the production of melanin, such as TRP-1 and TRP-2, was similarly decreased (78). One potential explanation could be that the extract has a suppressive impact on the protein function, as tyrosinase, Trp-1 and Trp-2 all have MITF as a shared transcription factor (28,32,57,78). CREB phosphorylation enhances its ability to attach to the MITF promoter (78). The aforementioned study clearly demonstrated that the treatment with the extract effectively prevented phosphorylation of PKA and CREB in α-MSH-stimulated B16F10 cells (78). This indicates that downregulation of MITF by the CE extract was achieved by inhibiting the PKA/CREB pathway triggered by α-MSH (78). Subsequent investigations will elucidate the precise processes and molecular target of CE extract-induced suppression of the PKA/CREB pathway in melanocytes. UV irradiation induces melanogenesis by phosphorylating and activating ERK in human melanocytes, but JNK and p38 remain unaffected (14,71,78).

Another source of carotenoids that are well known for their antioxidant properties is banana (*Musa sapientum*; MS) (70,89). Phacharapiyangkul *et al* (70) demonstrated a significant inhibitory effect of MS extract (MPE) on melanogenesis in B16F10 cells stimulated with α-MSH. The concentration-dependent inhibition of MITF and tyrosinase expression is observed upon treatment with MPE (70). Furthermore, MPE results in a substantial concentration-dependent reduction in the levels of melanosome transfer protein indicators such as Rab27a and Pmel17) (70). The aforementioned study observed a reduction in the heightened phosphorylation of AKT in B16F10 cells following treatment with MPE. In addition, MPE treatment resulted in alterations in microtubule-associated protein 1 light chain 3-II and p62, which are recognized as indicators of autophagy (70,73). The aforementioned study suggested that MPE has the potential to serve as a viable treatment for inhibiting melanogenesis. This inhibitory impact may be achieved by the modulation of the AKT pathway, leading to a decrease in MITF expression and suppression of tyrosinase enzyme family production (70). The aforementioned study suggested

Table II. Carotenoid contents in red fruits and its potential role as an anti-pigmentation agent.

First author, year	Methods	Results	(Refs.)
Roreng *et al*, 2014	Carotenoid depletion and repletion to evaluate the carotenoid bioavailability of red fruit extract and determine retinol accumulation factor in rat liver.	Carotenoids in red fruit extract are absorbed, metabolized and stored. The retinol accumulation factor was 49.2 and relative bioavailability with pure β-carotene was 86.52%.	(92)
Dumaria *et al*, 2018	Experimental study using post-test-only group design. *Cavia porcellus* was exposed to UVB, basic cream, 4% hydroquinone or 10% red fruit extract cream. The amount of melanin was compared using the percentage of the pixel area	10% red fruit extract cream prevents increase in amount of melanin in guinea pig skin exposed to UVB light as effectively as 4% hydroquinone cream	(93)
Sugianto *et al*, 2019	A total of 30 male Wistar rats were examined for MMP-1 expression and MDA levels. RFO was identified with β-carotene and tocopherol content phytochemical screening assay. Identification of β-carotene and tocopherol by TLC, UVB irradiation, RT-PCR and TBARS assay	RFO contains tocopherol and β-carotene, which can reduce MMP-1 gene expression but has no significant effect on MDA levels	(44)
Wulansari *et al*, 2020	HLPC analysis was performed using an HLPC system.	Concentration of β-carotene varied between 193.9 and 1,003.8 μg/ml, whereas the concentration of β-cryptoxanthin ranged from 3.3 to 48.9 μg/ml	(91)

MDA, malondialdehyde; RFO, red fruit oil; TLC, thin layer chromatography; RT, reverse transcription; TBARS, thiobarbituric acid reactive substances; HLPC, high performance liquid chromatography.

that MPE has potential as a depigmenting agent in cosmeceuticals (24,31,32,70). MPE containing β-carotene has benefits as a suppressor of melanogenesis in α-MSH-induced B16F10 cells associated with the AKT signaling pathway (34,70). MPE inhibits melanogenesis by inhibiting melanosome transport and autophagy (70). There also studies that show that MPE effectively inhibits melanin production in B16F10 mouse and G361 human melanoma cells (89,90).

4. Carotenoid content in red fruit and its potential role as an anti-pigmentation agent

Red fruit (*Pandanus conoideus* Lam.) is a traditional fruit from Papua that is high in antioxidant content. Table II summarizes the potential anti-pigmentation role of carotenoids in red fruit. Red fruit oil (RFO) has high carotenoid and tocopherol contents (42,91,92). Roreng *et al* (92) showed that carotenoids (pro-vitamin A) in red fruit extracts have high bioavailability. Red fruit contains high levels of bioactive compounds, including flavonoids 238.63 mg/100 g quercetin equivalent, tannins 600.71 mg/100 g tannic acid equivalent; vitamin C (958.18 mg/100 g), β-carotene (287,416.99 μg/100 g) and antioxidants 372.15 mg/l Garlic acid equivalent antioxidant capacity (GAEAC) (93). The variation in RFO antioxidant content depends on where red fruit is grown.

Current research regarding the potential advantages of red fruit for promoting skin health remains limited. To the best of our knowledge, over the last decade, only two articles that specifically examined the advantages of red fruit in relation to skin health have been published (44,93). The aforementioned study on red fruits explores the advantages of consuming red fruit in relation to its anti-inflammatory, anticancer and antioxidative stress capabilities. However, the aforementioned investigations have shown encouraging findings, indicating that red fruit may enhance skin health. Sugianto *et al* (44) conducted *in vivo* research on rat skin exposed to UVB light and it was proven that RFO contained β-carotene and tocopherol, which decreased expression of the MMP-1 gene. The aforementioned study used 30 male Wistar rats grouped as follows: P0, no treatment, whereas; P1, UVB light; P2, UVB light and 0.5 ml/200 g body weight (BW) RFO; P3, UVB light and 1 ml/200 g BW RFO and P4, UVB light and 2 ml/200 g BW RFO. The expression of MMP-1 and the levels of malondialdehyde were assessed. RFO can be characterized by its β-carotene and tocopherol levels. The aforementioned experiment used a phytochemical screening assay to identify presence of flavonoids, phenolics, triterpenoids, saponins,

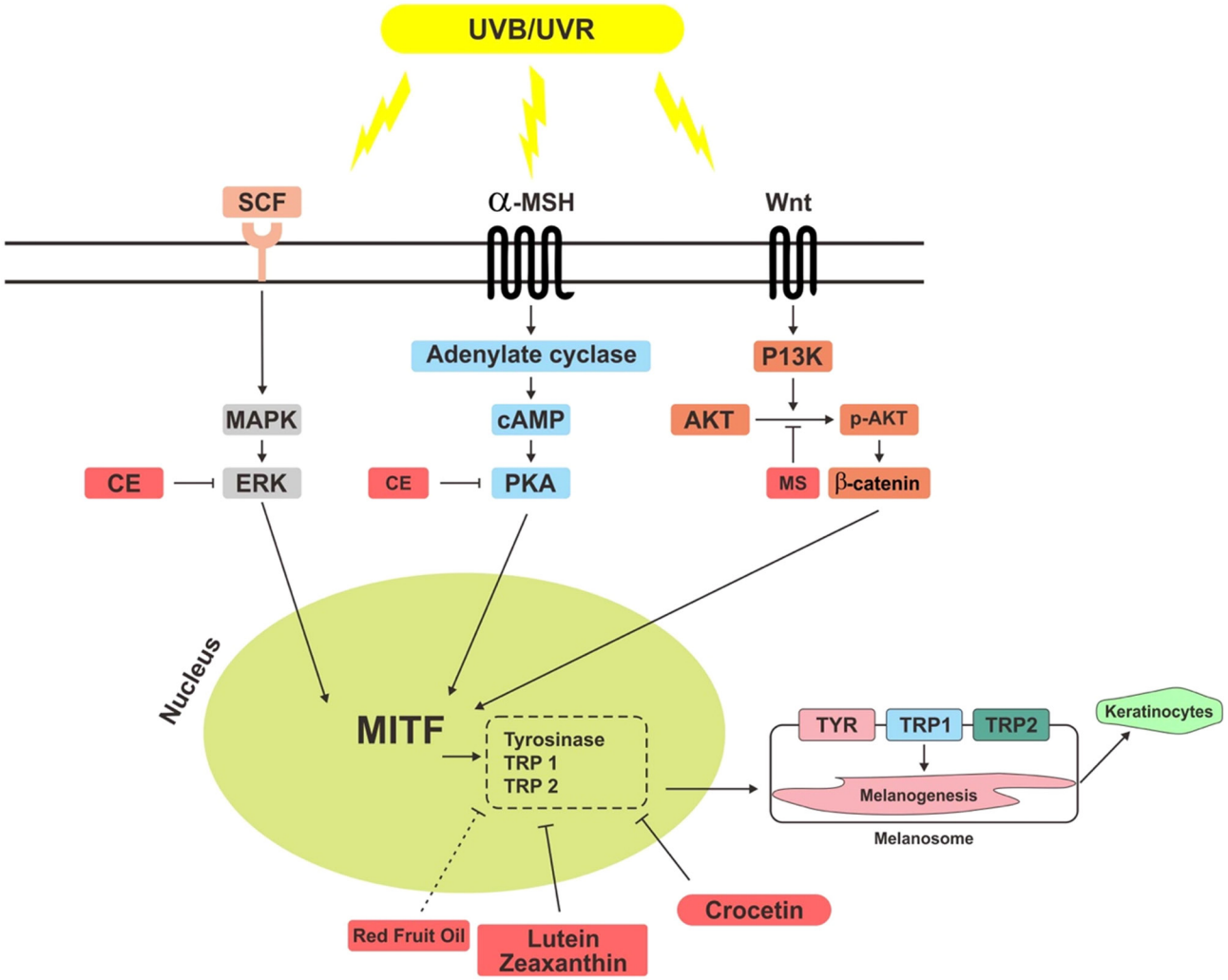

Figure 1. Potential mechanisms of carotenoids in red fruit as an anti-pigmentation agent. RFO contains carotenoids inhibit MITF by suppressing tyrosinase. Lutein, zeaxanthin, crocetin, CE, and MS have carotenoid contents that inhibit ERK, PKA, and PI3K/AKT pathways, thereby inhibiting activation of MITF. MITF, microphthalmia-associated transcription factor; CE, *Chlamydomonas reinhardtii*; MS, *musa sapientum*; PKA, protein kinase A; UVR, Ultraviolet Radiation; SCF, stem cell factor; MSH, melanocyte stimulating hormone; p-, phosporylated; TRP, tyrosinase related protein; TYR, tyrosinase.

tannins, steroids and alkaloids in RFO; identification of β-carotene and tocopherol was performed using thin layer chromatography, malondialdehyde levels were tested with thiobarbituric acid reactive substances assay and reverse transcription-quantitative PCR was used to see MMP-1 mRNA expression (44).

Research on anti-melanocyte effects conducted on *Cavia porcellus* skin exposed to UVB light by Dumaria *et al* (93) revealed that 10% red fruit extract cream could prevent an increase in amount of melanin in guinea pig skin exposed to UVB rays as effectively as 4% hydroquinone. The aforementioned experimental study employed post-test-only control group design. The subjects were divided into three groups of 10 guinea pigs as follows: Group 1 (control group), UVB radiation and standard cream; group 2, UVB radiation and topical cream containing 4% hydroquinone and group 3, UVB radiation and cream containing 10% red fruit extract. The cumulative UVB dosage administered over 2 weeks was 390 mJ/cm^2. The quantification of melanin content was performed by determining the proportion of the pixel area occupied by melanin and compared with all epidermal tissues. The aforementioned study revealed that group 1 exhibited the highest proportion of melanin area, with a mean value of 19.78±3.79%. The melanin area percentage in group 3 was found to be 1.25±0.76%, whereas in group 2, it was 0.85±0.37%. There were statistically significant variations in the proportion of melanin observed between group 1 and groups 2 and 3. There was no statistically significant difference in the proportion of melanin between group 2 and group 3 (93).

Antioxidants inhibit generation of ROS, which can initiate the melanogenesis process (94), thus inhibiting UVB-induced melanogenesis (12,26,58). The red fruit extract in a previous study contained 372.15 mg/l GAEAC (93). Red fruits contain flavonoids that directly inhibit the enzyme tyrosinase, making them potential anti-pigmentation agents when exposed to UV rays. Tannins have antioxidant properties and anti-tyrosinase activity (93). UVB radiation does not lead to an increase in melanin formation due to suppression of the melanin synthesis process (93). Topical treatment such as cream has a high antioxidant content (84) which is effective in mitigating the impact of ROS on the skin (94). Furthermore, incorporation

of antioxidants in cream can enhance skin hydration and decrease water loss through the skin. The findings of the aforementioned study indicate that the red fruit extract in ointment as topical treatment effectively inhibits the melanin production in marmot skin exposed to UVB radiation (93).

Wulansari *et al* (91) showed that the bioactivity of red fruit is influenced by its natural antioxidant content, including carotenoids, α-tocopherol and unsaturated fatty acids. The aforementioned study involved the collection of five distinct cultivars of red fruit, specifically Maler, Bergum, Wesi, Uaghelu and Kenen, originating from various places in Papua. High performance liquid chromatography analysis was employed to assess the carotenoid content, specifically β-carotene and β-cryptoxanthin, in red fruit oil of the five clones. The concentration of β-carotene varied between 193.9 and 1003.8 μg/ml, whereas the concentration of β-cryptoxanthin ranged from 3.3 to 48.9 μg/ml. Red fruit exhibits a notable concentration of carotenoids, with β-carotene being recognized for its antioxidant properties (42,44). In addition, β-cryptoxanthin exerts preventive effects against lung cancer, emphysema and osteoporosis (91).

The aforementioned studies demonstrate the potential role of carotenoids in red fruit as an anti-pigmentation agent via several pathways such as PKA, ERK, AKT, MMP1 and MITF. These pathways lead to pigmentation process through collagen degradation and tyrosinase, which regulates synthesis of melanin. Carotenoids in red fruit have a potential role in inhibiting the aforementioned pathways (Fig. 1).

5. Conclusion

Skin protection is the primary prevention method for melasma. Consuming carotenoids has benefits for the skin as melanogenesis inhibition occurs via PKA, ERK, and AKT signaling pathway, which can reduce tyrosinase activity as well as MITF gene expression. Red fruit (*Pandanus conoideus* Lam.) contains high amounts of carotenoids. This fruit also has benefits as an antioxidant and anti-inflammatory agent and it has the possibility of being an anti-pigmentation agent that can inhibit melanogenesis, similar to other plants that contain carotenoids. Further *in vitro* and *in vivo* research needs to be conducted on the potential of red fruit against melanogenesis.

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Authors' contributions

ST and JWG conceived the study and performed the literature review. HR and RL performed the literature review. All authors wrote the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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