IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Advantages Of Hesperidin For Skin Health"

[1]Nabishek Kanwar, [2]Pryanka, [3]Manpreet Kaur Walia

[1]Masters of Pharmaceutics,[2]Guide 1,[3]Guide 2

University school of pharmaceutical sciences,

Rayat Bahra University, Mohali, India

Abstract

Hesperidin is a type of bioflavonoid that is found in large amounts in citrus fruits. Besides its famous advantages for heart health, type II diabetes management, and reducing inflammation, recent research has shown that hesperidin offers various benefits for skin health. These include helping with wound healing, protecting against UV damage, fighting inflammation, acting against harmful microbes, reducing the risk of skin cancer, and lightening the skin. Additionally, hesperidin improves the balance of the skin's protective barrier in both young and older skin. Hesperidin helps skin functions in several ways. It acts as an antioxidant, blocks certain signaling pathways, and promotes the growth, development, and production of lipids in the outer skin layer. Due to its affordability, easy accessibility, and excellent safety profile, hesperidin may be beneficial for treating various skin conditions.

1. Introduction

No other organ in the human body has garnered as much interest as the skin, due to its importance in both beauty and health. On average, American women spend about $8.00 a day on facial care for cosmetic reasons (1). In 2017, the value of skin care product sales in China surpassed $26 billion each year. Recent research has found that using specific skin care products on the skin can provide several advantages for both long-term skin issues and skin damaged by the sun, as well as offering antimicrobial and anti-inflammatory effect (2). As the popularity of skin care products grows, a lot of effort has been put into finding ingredients that offer various benefits for the skin when creating these products [3-7]. Since skin can experience as many diseases as any other organ in the body, it is crucial to manage skin conditions effectively. Throughout our lives, everyone will likely experience skin issues at some point. This is because our skin constantly interacts with the environment, which makes it more susceptible to outside physical, chemical, and microbial challenges. Besides affecting the mental and social well-being of patients and their families, some chronic skin conditions can also lead to the onset of other health issues in the body. For instance, both psoriasis and eczematous dermatitis raise the levels of proinflammatory cytokines in the blood [8-10], which seem to contribute to the development of cardiovascular diseases, obesity, type II diabetes, and Alzheimer's disease [11-14]. Due to its large area, even minor inflammation in the skin can significantly raise the levels of cytokines in the blood. This increase may be related to some disorders that come with age [12-15]. Because of the intricate nature of skin functions and the chance of developing various skin issues, it's highly preferred to use ingredients that offer multiple benefits for the skin. When looking for these ingredients, hesperidin seems to be a promising option. Research has shown that using hesperidin on the skin or

taking it systemically can improve different skin functions in both healthy and affected skin. In this review, we provide a thorough overview of the advantages of hesperidin for skin functions.

2. Origins and Chemical Characteristics of Hesperidin

Hesperidin was initially extracted from the inner part of orange peels in 1828. Hesperidin, along with other related bioflavonoids, used to be known as "vitamin P" (as discussed in [16]). Hesperidin is found in large quantities in citrus fruits such as lemons, oranges, limes, and grapefruits. The amount of hesperidin found in citrus fruits differs significantly depending on the species, the specific part of the fruit, where it is grown, and how it is processed (Table 1) [17–22]. For instance, fresh Satsuma pulp contains 73 mg of hesperidin per kilogram, while the fresh peel has 157 mg per kilogram [20]. Typically, the amount of hesperidin is greater in citrus peels compared to other parts of citrus fruits. However, lemon seeds have a higher amount of hesperidin compared to the peel when extracted using methanol. Freshly squeezed orange juice from Florida has between 335 and 351 mg of hesperidin per liter, while Ortanique citrus juice from Israel contains 273 to 287 mg per liter [24]. Juice from colorful citrus fruits has a higher amount of hesperidin compared to juice from citrus fruits that lack pigment [25]. Immature citrus fruits probably have higher levels of hesperidin compared to ripe citrus fruits [26]. Heating citrus juice through pasteurization did not reduce the hesperidin levels, even when the juice was stored at 4°C for as long as 12 days. Instead, the amount of hesperidin rises when citrus juice is pasteurized at 90°C for 20 seconds [27]. The amount of hesperidin varies in citrus juice, with single-strength juice containing between 555 and 761 mg per liter, while concentrated juice has between 470 and 614 mg per liter [28]. This indicates that the method used for processing the juice influences its hesperidin levels. Besides citrus fruits, peppermint (Mentha x piperita L.) also has hesperidin, and its levels rise when exposed to UVB light [29]. The methanol extract from Porphyra dentata, a type of red edible seaweed, has 5% hesperidin [30].

Table 1. "The amount of hesperidin found in citrus fruits."

Variety	Location of horticulture	Extraction solvent	Peel (mg/g dried)	Ref
C. reticulate “Erythrosa”	Shimen County, Hunan, China	Mehanol	74.236 ± 0.845	[17]
C. reticulate “Chachi”	Meijiang, Jiangmen, Guangdong, China	50% Method	42	[18]
C. Sinensis (linn.) Osbeck	North of Iran	Petrolatum ether first, followed by methanol	5.2-6.2	[19]
C. reticulate Blanco	Neretva Valley, Croatia	1.2M HCI in 80% methanol/water	0.47	[20]
Pulp removing	Adana, Turkey		*81.5 ± 12.7mg/litter	[21]

3. Safety

Hesperidin is usually considered safe for use on the skin and when taken into the body. Applying 2% hesperidin on the skin of mice for 9 days did not lead to any harmful skin reactions [32]. In a similar study, rats that were given Daflon-500 mg, which has 10% hesperidin, at a daily dose of 100 mg did not exhibit any signs or symptoms of side effects [75]. Similarly, feeding diets that included either methyl hesperidin or hesperidin to mice and rats did not result in any noticeable side effects or symptoms [76,77]. Additionally, researchers did not notice any negative effects in mice that received daily intraperitoneal injections of phosphorylated hesperidin at a dose of 20 mg/kg body weight for more than 4 weeks [78]. While one study indicated that taking Daflon-500 mg orally twice a day for 60 days led to slight, temporary side effects like headaches and dizziness [79], other research has confirmed that oral Daflon-500 mg is safe for people [80, 81].

4. Advantages of Hesperidin for Skin Health

Hesperidin, which is also referred to as lemon peel extract or orange peel extract, is a naturally occurring flavonoid found in citrus fruits, particularly in the peels of lemons and oranges. In skin care, hesperidin can be found as a white or clear crystalline form. Research indicates that it can offer antioxidant and calming benefits, which together help enhance and brighten the skin's appearance. Hesperidin’s antioxidant properties work to neutralize free radicals found in the environment. This reduces the amount of reactive oxygen species in the skin, which can help enhance the skin's brightness. When applied to the skin, hesperidin has a calming effect and strengthens the skin's barrier to keep it protected. Consequently, skincare items like creams and ointments frequently include hesperidin in their formulas to help soothe dry skin.

Today, people recognize the health benefits of bioflavonoids, such as hesperidin. Many studies have shown that taking hesperidin systemically can help with various diseases, such as heart disease, diabetes, Alzheimer's disease, and cancer [82-88]. Similarly, the advantages of hesperidin for different skin conditions have been clearly demonstrated (see Table 2).

Table 2. Advantages of Hespiridin on cutaneous functions.

Animal	Therapy	Advantages	Procedure	Ref.
Young mice	Apply a 2% hesperidin solution to the skin two times a day for six days.	Rapid recovery from obstacles	"Increased growth; enhanced expression of filaggrin; and greater secretion of lamellar bodies."	[31]
Old mice	Apply a 2% hesperidin solution to the skin two times a day for nine days.	Rapid recovery from obstacles	"Increased growth; enhanced expression of filaggrin; and greater secretion of lamellar bodies."	[32]
Mice with glucocorticoid treatment	One hour after applying 0.05% clobetasol propionate, 2% hesperidin was used. The treatments were administered two times a day for a total of 9 days.	Rapid barrier recovery Decreased surface ph	"Increased growth; enhanced expression of filaggrin; and greater secretion of lamellar bodies."	[33]

4.1 Function of the Epidermal Permeability Barrier

The epidermal permeability barrier, located in the outer layer of the skin called the stratum corneum, stops substances and water from passing through this layer. Recent research shows that the epidermal permeability barrier is vital in the development of skin diseases and may also impact systemic disorders [89-91]. Consequently, skincare product manufacturers have been working hard to create items that can effectively enhance the skin's barrier function. Due to the frequent occurrence of negative skin reactions to skincare products, it's becoming crucial to find safe and effective ingredients [92-93]. Our team showed that applying 2% hesperidin to the skin of young mice two times a day for 6 days helped speed up the recovery of the skin's barrier after it was disrupted. However, the basic levels of water loss through the skin, moisture in the outer layer, and

the acidity of the skin's surface did not change [31]. Older skin shows a slower recovery of the permeability barrier and has a higher skin surface pH [94,95], which may both play a role in causing some disorders linked to aging. There are few treatments available that can enhance the skin's barrier function, especially at the genetic level. One study found that applying a 2% hesperidin solution to the skin twice a day for 9 days significantly sped up the recovery of the skin's barrier and notably lowered the skin's surface pH in older mice [32]. Besides healthy skin, applying topical hesperidin can also stop issues with the skin's barrier that are caused by using topical glucocorticoids in mice. For instance, using glucocorticoids on the skin multiple times slowed down the healing of the skin barrier. When hesperidin was applied to the skin of mice after each glucocorticoid treatment, it helped to fix problems with how well the skin could recover and balanced the skin's surface pH [33]. There were no negative reactions noticed after applying hesperidin on the skin. Overall, these studies show that applying hesperidin on the skin helps to improve the barrier function of the outer layer of skin in both healthy skin and skin affected by glucocorticoids.

4.1 Damage to the Skin Caused by UV Rays

Since the skin is the body's outer layer, it is more exposed to ultraviolet (UV) rays, which can cause photoaging and other skin problems like actinic keratosis and skin cancer [96,97]. So, protecting yourself from UV rays can help stop or reduce skin damage caused by the sun. A study found that treating keratinocytes with 50 μM hesperidin can reduce the rate of cell death caused by UVB exposure by more than 70% when compared to keratinocytes that were not treated with any medication. Besides UVB, hesperidin can also shield keratinocytes from harm caused by UVA [34]. Sure! Please provide the text you'd like me to paraphrase. According to a report, treating keratinocytes with hesperidin for 24 hours led to a dosedependent rise in the survival of UVA-irradiated keratinocytes [35]. Treating keratinocytes with hesperidin at a dose of 220 μg/ml greatly lowered the oxidative stress caused by UVA and decreased the levels of proinflammatory cytokines. These findings show that hesperidin helps shield keratinocytes from damage caused by both UVA and UVB rays. UVA has a wavelength of 320-400 nm, and it can go deep into the dermis. This repeated exposure can cause the skin to age early, a process known as photoaging. It seems that hesperidin can also reduce the damage caused to fibroblasts by UVA rays [36]. Hesperidin breaks down into hesperetin thanks to the gut microbiota, and [38] the large intestine absorbs it through passive transport [39]. Hesperidin helps shield cells from damage caused by UV light in lab tests, and it also guards the skin from UV damage in real-life situations. Applying topical hesperidin to mouse skin before exposure to UVB rays might stop the rise in skin cytokine levels and reduce lipid peroxidation. It also boosts the production of antioxidant enzymes like glutathione peroxidase-1, glutathione reductase, and heme oxygenase-1 in mouse skin after one or more UVB exposures. Moreover, applying hesperidin on the skin significantly stopped UVB rays from causing redness, swelling, and growth of the outer skin layer [39,40]. Additionally, giving hesperidin methyl chalcone directly into the abdomen can stop the decrease in antioxidant levels and the increase in skin cytokine levels and myeloperoxidase activity caused by UVB rays [41]. A study from [42] showed that drinking water with hesperidin every day helped reduce several skin problems caused by repeated UVB exposure. These problems included a weakened skin barrier, more wrinkles, higher levels of cytokines, and increased expression and activity of matrix metalloproteinase-9. Additionally, applying hesperidin on the skin of mice before exposure could help improve the repair of DNA damage caused by UVB rays [43]. In the end, applying topical hesperetin reduced trans epidermal water loss by about 50% in guinea pigs that received repeated UVB exposure [44]. Both topical and oral forms of hesperidin can work together to shield the skin from harm caused by UVA and UVB rays.

4.3 Melanin production

Skin whitening is a very popular beauty trend, especially in Asia. Hesperidin has been used for a long time as a skin whitening ingredient, but there is some disagreement about how it affects the process of melanogenesis. Research found that treating murine B16-F10 melanoma cells with 20 μg/mL of citrus extract (which had 362.3 ± 16.7 μg/mL of hesperetin) led to a onefold rise in melanin levels. Additionally, using hesperidin by itself boosted melanin content by more than 20% [45]. In the same way, a concentration of 50μM hesperetin raised the

melanin levels by more than 80% in B16-F10 melanoma cells from mice. In contrast, other research showed that hesperidin had no impact on melanin production in B16F10 murine melanoma cells [47–49]. Most other research found that both citrus extract and hesperidin slowed down the production of melanin in mouse B16-F10 melanoma cells and human melanocytes [36-54,50-53]. For instance, when treated with 50μM hesperidin for 48 to 72 hours, there was a 60% decrease in melanin levels in mouse B16-F10 melanoma cells and about a 30% decrease in human melanocytes [50]. Applying a 0.2% hesperidin solution to rebuilt human skin for 14 days lowered the pigment by about 25%. Also, using hesperetin on the skin, which comes from hesperidin, helped reduce skin darkening caused by UVB exposure. Topical use of hesperidin and its metabolite can lessen skin pigmentation in both healthy skin and skin that has been exposed to UVB rays.

4.2 Skin gash healing

Skin wounds are quite common, but treating them can be difficult, especially in cases like diabetic and venous wounds. Several studies have shown that hesperidin speeds up the healing of wounds both in lab settings and in living organisms. [54] A study found that when a culture medium with 0.05% hesperidin was added for 24 hours, it sped up wound healing by 39% compared to the control group in lab scratch tests. In diabetic rats, wounds nearly healed completely (97%) after being given 100 mg/kg of hesperidin by mouth for 21 days. In contrast, the wounds in the control group that received no treatment did not close at all [55]. In diabetic rats, taking hesperidin by mouth helped with wound healing and improved other markers, like blood sugar and glycated hemoglobin, just as well as insulin treatments did [56]. In addition to treating diabetic wounds, healing wounds in people with venous insufficiency can also be challenging. The healing times for wounds were about the same for patients who took oral diosmin/hesperidin (450/50 mg) and those who received pycnogenol [57]. However, after two months of treatment, a higher percentage of patients in the diosmin/hesperidin group were completely healed compared to those who received a placebo, with 32% healed in the first group and only 13% in the second [58]. In addition, using hesperidin either on the skin or by mouth helped wounds heal about 3 days faster in mice that were exposed to gamma rays [59,60]. These findings show that applying hesperidin on the skin or taking it by mouth can speed up the healing of skin in different situations.

4.3 Irritation and Infections

Research has shown that flavonoids can help reduce both overall and specific types of inflammation [98,99]. Since nitric oxide acts as an inflammatory mediator, people frequently use it as a marker to assess the body's inflammatory response. An in vitro study showed that when mouse RAW 264.7 cells were treated with lipopolysaccharide (LPS) for 24 hours, the nitrite levels increased by more than nine times. Adding hesperidin (250 μg/ml) to the culture medium reduced nitrite levels by about 75% in cells treated with LPS [30].[61] conducted a similar study that focused on hesperetin and its breakdown products." The findings indicated that when RAW 264.7 cells were stimulated with LPS, there was a considerable rise in both nitric oxide and the mRNA levels of inducible nitric oxide synthase. However, when RAW 264.7 cells were incubated together with LPS and 10 μM of the hesperetin metabolite, both levels significantly dropped. Interestingly, hesperetin at a low dose of 1μM reduced the levels of nitric oxide and the mRNA for inducible nitric oxide synthase. However, when hesperetin was given at a dose of 10μM, it did not have any effect. The skin acts as the body's first defense against outside things. Keratinocytes can create and release proinflammatory cytokines when they are stimulated [90]. Hesperidin can reduce the production of cytokines in cultures of keratinocytes. For example, before exposing cells to H2O2 (100 μM), treating keratinocytes with hesperidin (20 μg/ml) for 2 hours could reduce the production of IL-8 and TNFα by 96% and 78%, respectively [62]. The levels of cyclooxygenase-2 (COX-2) protein and mRNA in keratinocytes dropped significantly when they were treated with hesperidin along with H2O2, compared to those treated with H2O2 alone. Research shows that hesperidin can also stop the production of cytokines caused by bacterial pathogens. When keratinocytes were treated with both Propionibacterium acnes and 55 μg/mL of hesperidin for 24 hours, they showed a 49% decrease in IL-8 production and a 71% decrease in TNFα production [63]. These reductions were similar to those seen with dexamethasone treatment. Additionally, treating hesperidin methyl chalcone (0.2 mg/ml) before the experiment significantly reduced the

number of dilated blood vessels by 48%, lowered the total area of the vessels by 72%, and decreased the production of IL-8 by 79% in human skin samples after being stimulated with substance P [64]. Thirty minutes before the subcutaneous injection of 1% carrageenan, injecting hesperidin at doses of 50 and 100 mg/kg decreased the swelling in the paw by 47% and 63%, respectively, within 5 hours [65]. Hesperidin, given at a dose of 100 mg/kg, reduced dextran-induced swelling by 33%. The effectiveness of hesperidin on swelling was similar to the results achieved with oral indomethacin at a dose of 10 mg/kg. However, hesperidin did not stop the swelling in the paw caused by histamine. "Pelzer and others." A study found that giving hesperidin through an injection into the abdominal cavity could reduce swelling in the paw caused by carrageenan by 36 to 40% within 7 hours. One hour before causing swelling in the paw with carrageenan, giving hesperidin (40 mg/kg of body weight) by mouth reduced the swelling by 50%, 51%, 63%, and 77% at 1, 2, 3, and 4 hours, respectively. In comparison, indomethacin (10 mg/kg) cut down the swelling by 65%, 71%, 72%, and 74% at the same time points [67]. These findings show that hesperidin can stop and help treat skin inflammation caused by different factors.

4.4 Skin cancer

Besides its prevention and treatment advantages for other types of cancer[100,101], research indicates that hesperidin and its breakdown products also help skin cancers. Sure! Please provide the text you'd like me to paraphrase. A study found that when A431 cells were treated with hesperetin at a low concentration of 10 μM, it caused DNA fragmentation [68]. This treatment also led to a significant rise in the expression of Bax, which is a protein linked to cell death, while decreasing the levels of cyclin B1, D1, D3, and E1 proteins by more than double. A related study showed that when A431 cells were treated with 10 μM hesperidin, there was more than a 10-fold increase in cell death and DNA damage [69]. A study conducted in living organisms showed that hesperidin can stop skin tumors from forming. For instance, giving a daily subcutaneous injection of 125 μl of 1% hesperidin one week before starting skin tumor treatment with topical 12-O-Tetradecanoylphorbol-13-acetate (TPA) led to a 50% decrease in tumor occurrence and a 48% drop in the number of papilloma per mouse after 20 weeks of TPA use [70]. So, hesperidin might be a good option for preventing and treating skin cancers.

4.5 Other skin functions

Research also shows that hesperidin has advantages for other skin functions. Taking hesperidin by mouth 30 minutes before exposure to γ rays increased the levels of mRNA for vascular endothelial growth factor by more than 25 times [102]. Hesperidin showed it can fight germs, including common ones that cause skin infections like Staphylococcus aureus, Candida albicans, Candida tropicalis, and Streptococcus pyogenes. The lowest amount needed to stop both Candida albicans and Staphylococcus aureus was 8.25% [103– 106]. A study on people found that taking 500 mg of hesperidin by mouth every day for 28 days significantly improved facial smoothness. It also showed a 33% decrease in beta-galactosidase, which is a marker of aging, over a period of 6 months[107].

5. Mechanisms

While there is evidence that hesperidin helps with various skin functions, the exact ways it works are not yet fully understood. Hesperidin and its metabolite seem to work through different methods, depending on the specific role that hesperidin is influencing.

5.1 Enhancements in the Function of the Epidermal Permeability Barrier

The creation of the epidermal permeability barrier is carefully controlled by several functions of keratinocytes. These include their growth, development, production of lipids, acid levels, and the expression of antimicrobial peptides. In young mice, applying hesperidin on the skin mainly increased the levels of filaggrin and encouraged keratinocyte growth [108]. In contrast, in older mice, using topical hesperidin raised the levels of various mRNA linked to the skin's barrier function. This included sodium/hydrogen exchanger (NHE1), secretory phospholipase A2 (sPLA2), proteins related to skin cell development (filaggrin, involucrin, and loricrin), enzymes that help

make lipids (fatty acid synthase and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), and a lipid transport protein (ATP-binding cassette subfamily A member 12)[32].

In mice with skin treated with glucocorticoids, applying hesperidin significantly boosted the levels of filaggrin protein and the mRNA for glutathione reductase. It also enhanced the activity of β-glucocerebrosidase and increased skin cell growth[33]. Therefore, the way that topical hesperidin helps to enhance the skin's barrier function might be due to its ability to boost these processes, which can vary based on the condition of the skin.

5.2 Shielding from UV rays

UV rays harm the skin in three main ways: they create oxidative stress, break down DNA, and trigger inflammation. Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a key role in controlling the antioxidant system within cells [109,110]. A lack of Nrf2 speeds up photoaging and inflammation [111,112] caused by UV radiation. On the other hand, turning on Nrf2 can help protect against cell death and inflammation triggered by UV exposure[113,114]. Besides increasing the Nrf2 expression in old rat hearts, methyl hesperidin, which is a modified version of hesperidin, helped move Nrf2 from the cytoplasm into the nucleus[115]. This action led to an increase in the expression of genes related to antioxidants and a decrease in reactive oxygen species. As a result, it protected skin cells from damage caused by UVB rays in lab cultures[116]. The decrease in DNA damage and cytokine levels caused by hesperidin seems to result from lower oxidative stress in keratinocytes exposed to UV light [34,35]. Additionally, hesperidin reduced the rise in phosphorylation levels of mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinases (ERK) caused by UVB exposure in mice [42]. Therefore, the UV protection of hesperidin likely comes from increasing antioxidants and decreasing the activity of the MAPK/ERK signaling pathway.

5.3 Melanin production

Skin color comes from two main processes: the creation of melanin and the movement of melanosomes. Proteins that play a role in melanogenesis are tyrosinase, tyrosinase-related proteins (TRP), and the microphthalmiaassociated transcription factor (MITF). Increasing the expression levels of tyrosinase, TRPs, and MITF can boost melanin production [117,118]. Several studies showed that hesperidin reduced the expression and activity of tyrosinase, TRPs, and MITF in B16 mouse melanoma cells as well as in human melanocytes [36,50-52]. Additionally, hesperidin may trigger the α adrenergic receptor, causing the melanophores in B to clump together. Melanostictus indicates that the skin lightening caused by hesperidin happens through the adrenergic receptor [119]. Another way that hesperidin can lighten skin might be due to its ability to block the transport of melanosomes in melanocytes, rather than stopping the production of melanin[49]. Hesperidin brightens the skin by stopping the production of melanin and the movement of melanosomes.

5.4 Skin wound healing

Wound healing includes the processes of cells multiplying, moving, and forming new blood vessels. The activation of tumor growth factor beta (TGF-
β) signaling and the expression of vascular endothelial growth factor (VEGF) are important for healing wounds and restoring the skin's protective barrier[120-123]. Research demonstrated that giving hesperidin orally at a dose of 50 mg per kg of body weight raised the levels of TGF-β and VEGF-c mRNA expression by more than two times in a diabetic model using Sprague Dawley rats[55]. Moreover, the levels of mRNA for VEGF receptors went up after taking hesperidin orally at a dose of 50 mg for every kilogram of body weight [56]. Oxidative stress can slow down the healing of wounds in both people with diabetes and those without it. On the other hand, antioxidants can help wounds heal better[124-126]. In diabetic rats, taking hesperidin by mouth greatly boosted the levels of SOD and GSH in the skin while lowering the MDA levels. This also sped up the healing of skin wounds, showing that hesperidin’s antioxidant qualities help speed up skin healing[55,56]. The body needs an inflammatory response to heal wounds in the early stages. Using cytokines like recombinant human granulocyte-macrophage colonystimulating factor on the skin can speed up the healing of wounds [127-129]. Too much

inflammation can slow down the healing process of wounds and may lead to the formation of scars [130]. As a result, reducing inflammation might speed up the healing of skin wounds [131,132]. Hesperidin reduced the levels of cytokines like TNFα, IL-6, and IL-8 in both rat skin and cultures of human skin cells. In summary, the way hesperidin speeds up the healing of skin wounds is due to its ability to increase the levels of VEGF, boost antioxidant enzymes, and reduce inflammation.

5.5 Reduction of Inflammation

Inflammation develops through a complicated process that includes the interactions of several molecules in different signaling pathways, such as the p38 mitogen-activated protein kinase (MAPK) pathway [133]. Blocking the p38 MAPK signaling pathway can significantly reduce the levels of IL-1β, IL6, IL-8, IL-18, and TNFα in cultures of macrophages and in mice [134,135]. A study found that treating keratinocytes with hesperidin for 2 hours before H2O2 stimulation led to more than a 50% decrease in NF-κB and phosphorylated p38 MAPK levels compared to those that did not receive hesperidin treatment. In a similar way, treating mouse RAW 264.7 cells with the hesperetin metabolite almost fully brought down the rise in NF-κB expression caused by lipopolysaccharide. It also decreased the levels of phosphorylated p38 MAPK and c-Jun N-terminal kinase 1/2 [61]. So, the way hesperidin blocks the p38 MAPK signaling pathway might help reduce inflammation.

5.6 Managing Skin Cancers

Research has shown that hesperidin and its metabolite have anticancer effects both in lab tests and in living organisms [68-70]. However, the exact ways these effects happen are still unclear. [69] A study found that treating A431 human skin cancer cells with hesperidin (25 μM) for 72 hours caused more than a 1-fold increase in reactive oxygen species. It also led to a 40% decrease in the ATP levels inside the cells and an 80% drop in the amount of SOD. Research using different cell lines has shown that hesperidin can trigger stress in the endoplasmic reticulum and activate the activities of caspase-9, caspase-8, and caspase-3 [136-138]. Additionally, the TGFβ-Smad signaling pathway, especially Smad3, is important in the growth of some types of cancer [139-140]. A previous study showed that giving hesperidin (100 mg/kg of body weight) by mouth for 18 weeks stopped the TGFβ-Smad3 signaling and helped prevent the growth of liver cancer [141]. Additionally, multiple studies have shown that lowering the creation of micronuclei might help explain the cancer-fighting benefits of hesperidin, especially in certain models of cancers caused by chemicals. The protection from DNA damage caused by gamma rays that Hesperidin provides might also be because it lowers the creation of micronuclei. Hesperidin can also boost the death of cancer cells by increasing the expression of peroxisome proliferatoractivated receptor γ. The signaling pathways that play a role in how hesperidin fights cancer include: (a) blocking the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which, when active, can boost the growth, spread, and invasion of cancer cells; (b) preventing the activation of the phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) pathways, both of which are important for the growth, survival, invasion, and spread of cancer cells when they are turned on; and (c) triggering the Notch pathway, where activating Notch receptors causes Notch to move into the nucleus and attach to specific genes, leading to increased cell death (apoptosis) [142]. Certainly! Other signaling pathways, including MAPK-ERK, Wingless, INT-1, NF-κB, and cyclooxygenase-2, have also been suggested to play a role in how hesperidin helps prevent and block cancers [142]. So, the cancer-fighting effects of hesperidin probably happen through several ways. These include blocking the TGFβ-Smad3, PI3K/Akt, and JAK/STAT signaling pathways, activating the Notch pathway, lowering ATP levels, and triggering cell death.

5.7 Antioxidation

Oxidative stress is connected to the onset of many different disorders [143,144]. As stated earlier, Nrf2 plays an important role in controlling the antioxidant system [109,110]. Under normal conditions, Nrf2 exists as a complex with Keap1 in the cytoplasm and gets broken down in the proteasome. When oxidative stress occurs, Nrf2 detaches from Keap1 and moves into the nucleus. In the nucleus, Nrf2 attaches to the antioxidant response

element (ARE) in the gene promoter area. This process activates gene transcription, which includes enzymes that help scavenge reactive oxygen, such as superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and heme oxygenase 1 [109,145]. These enzymes are essential for protecting cells from oxidative stress. Earlier research has demonstrated that hesperidin and its byproduct, hesperitin, can boost Nrf2 levels while promoting the breakdown of Keap1. This leads to more Nrf2 moving into the nucleus, which helps produce antioxidant enzymes and decreases oxidation [109,146-148]. Therefore, the antioxidant qualities of hesperidin play a big role in its advantages for the skin. In conclusion, using hesperidin on the skin or taking it in other forms seems to help various skin functions through different ways. Consuming citrus juice or products that contain hesperidin might help improve skin functions. "To confirm the advantages of hesperidin for skin issues, we need to conduct proper clinical trials."

Abbreviations

VEGF: Vascular endothelial growth factor

SOD: Superoxide dismutase

GSH: Reduced glutathione

MDA: Malondialdehyde

TGF-β: Transforming growth factor beta

MAPK: Mitogen-activated protein kinases.

References

- 1 Johnson S., *How much is your face worth? American women average at $8 per day*, 2018, https://www.huffingtonpost.com/entry/how-much-is-your-face-worth-americanwomen-average_us_58befa65e4b06660f479e594.

Google Scholar

- 2 Market status of skin care products in China, http://china-trade-research.hktdc.com/business-news/article/中国消费市场/中国化妆品市场概况/ccm/sc/1/1X000000/1X002L09.htm, (obtained on December 9th, 2018).

Google Scholar

- 3 Milani M. and Sparavigna A., Antiaging efficacy of melatonin-based day and night creams: A randomized, split-face, assessor-blinded proof-of-concept trial, *Clinical, Cosmetic and Investigational Dermatology*. (2018) **11**, 51–57, 2-s2.0-85041417020, https://doi.org/10.2147/CCID.S153905.

CASPubMedWeb of Science®Google Scholar

- 4 Choi S. J., Lee S., Kim K., Joo D. H., Shin S., Lee J., Lee H. K., Kim J., Kwon S. B., Kim M. J., Ahn K. J., An I., An S., and Cha H. J., Biological effects of rutin on skin aging, *International Journal of Molecular Medicine*. (2016) **38**, no. 1, 357–363, https://doi.org/10.3892/ijmm.2016.2604.

CASPubMedWeb of Science®Google Scholar

5 Sethi A., Kaur T., Malhotra S. K., and Gambhir M. L., Moisturizers: The slippery road, *Indian Journal of Dermatology*. (2016) **61**, no. 3, 279–287, 2-s2.0-84971320860, https://doi.org/10.4103/00195154.182427.

PubMedWeb of Science®Google Scholar

6 Liu M., Li X., Chen X.-Y., Xue F., and Zheng J., Topical application of a linoleic acid-ceramide containing moisturizer exhibit therapeutic and preventive benefits for psoriasis vulgaris: a randomized controlled trial, *Dermatologic Therapy*. (2015) **28**, no. 6, 373–382, 2-s2.084955188431, https://doi.org/10.1111/dth.12259.

PubMedWeb of Science®Google Scholar

7 Zasada M., Debowska R., Pasikowska M., and Budzisz E., The assessment of the effect of a cosmetic product brightening the skin of people with discolorations of different etiology, *Journal of Cosmetic Dermatology*. (2016) **15**, no. 4, 493–502, 2-s2.0-84977635574, https://doi.org/10.1111/jocd.12249, 27349716.

PubMedWeb of Science®Google Scholar

8 Solberg S. M., Sandvik L. F., Eidsheim M., Jonsson R., Bryceson Y. T., and Appel S., Serum cytokine measurements and biological therapy of psoriasis - Prospects for personalized treatment?, *Scandinavian Journal of Immunology*. (2018) **88**, e12725.

PubMedWeb of Science®Google Scholar

9 Brunner P. M., Suárez-Fariñas M., He H., Malik K., Wen H.-C., Gonzalez J., Chan T. C.-C., Estrada Y., Zheng X., Khattri S., Dattola N., Krueger J. G., and Guttman-Yassky E., The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins, *Scientific Reports*. (2017) **7**, no. 1, 8707, 2-s2.0-85027877982.

PubMedWeb of Science®Google Scholar

10 Vakirlis E., Lazaridou E., Tzellos T. G., Gerou S., Chatzidimitriou D., and Ioannides D., Investigation of cytokine levels and their association with SCORAD index in adults with acute atopic dermatitis, *Journal of the European Academy of Dermatology and Venereology*. (2011) **25**, no. 4, 409–416, 2-s2.0-79952386115, https://doi.org/10.1111/j.1468-3083.2010.03800.x, 21371129.

CASPubMedWeb of Science®Google Scholar

11 Souza C. S., de Castro C. C., Carneiro F. R., Pinto J. M., Fabricio L. H., Azulay-Abulafia L., Romiti R., Cestari T. F., Suzuki C. E., Biegun P. M., Guedes L. S., and Oyafuso L. K., Metabolic syndrome and psoriatic arthritis among patients with psoriasis vulgaris: Quality of life and prevalence, *The Journal of Dermatology*. (2019) **46**, no. 1, 3–10, https://doi.org/10.1111/1346-8138.14706.

PubMedWeb of Science®Google Scholar

12 Franceschi C. and Campisi J., Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases, *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. (2014) **69**, no. supplement 1, s4–s9, https://doi.org/10.1093/gerona/glu057.

PubMedWeb of Science®Google Scholar

13 Mishra A. and Brinton R. D., Inflammation: bridging age, menopause and APOEε4 genotype to alzheimer's disease, *Frontiers in Aging Neuroscience*. (2018) **10**, https://doi.org/10.3389/fnagi.2018.00312.

PubMedWeb of Science®Google Scholar

14 Ellulu M. S., Patimah I., Khaza'ai H., Rahmat A., and Abed Y., Obesity and inflammation: the linking mechanism and the complications, *Archives of Medical Science*. (2017) **4**, 851– 863, https://doi.org/10.5114/aoms.2016.58928.

Web of Science®Google Scholar

15 Atienza M., Ziontz J., and Cantero J. L., Low-grade inflammation in the relationship between sleep disruption, dysfunctional adiposity, and cognitive decline in aging, *Sleep Medicine Reviews*. (2018) **42**, 171–183, 2-s2.0-85053723509, https://doi.org/10.1016/j.smrv.2018.08.002.

PubMedWeb of Science®Google Scholar

16 Garg A., Garg S., Zaneveld L. J. D., and Singla A. K., Chemistry and pharmacology of the Citrus bioflavonoid hesperidin, *Phytotherapy Research*. (2001) **15**, no. 8, 655–669, 2-s2.00035667114, https://doi.org/10.1002/ptr.1074.

CASPubMedWeb of Science®Google Scholar

17 Liu E.-H., Zhao P., Duan L., Zheng G.-D., Guo L., Yang H., and Li P., Simultaneous determination of six bioactive flavonoids in Citri Reticulatae Pericarpium by rapid resolution liquid chromatography coupled with triple quadrupole electrospray tandem mass spectrometry, *Food Chemistry*. (2013) **141**, no. 4, 3977–3983, https://doi.org/10.1016/j.foodchem.2013.06.077, 2-s2.084884629702.

CASPubMedWeb of Science®Google Scholar

18 Ye X., Song F., Fan G., and Wu F., Simultaneous determination of 11 constituents in Citrus reticulate 'Chachi' by high performance liquid chromatography, *Chinese Journal of Chromatography*. (2015) **33**, no. 4, 423–427, 2-s2.0-84928891671, https://doi.org/10.3724/SP.J.1123.2014.12015.

CASGoogle Scholar

19 Omidbaigi R. and Faghih N. M., Quantitative distribution of hesperidin in Citrus species, during fruit maturation and optimal harvest time, *Natural Product Radiance*. (2004) **4**, 12–15.

Google Scholar

20 Levaj B., Verica D.-U., Kovačević D. B., and Krasnići N., Determination of flavonoids in pulp and peel of mandarin fruits, *Agriculturae Conspectus Scientificus*. (2009) **74**, no. 3, 221–225, 2-s2.076649143735.

Google Scholar

21 Ağçam E., Akyıldız A., and Evrendilek G. A., Comparison of phenolic compounds of orange juice processed by pulsed electric fields (PEF) and conventional thermal pasteurisation, *Food Chemistry*. (2014) **143**, 354–361, https://doi.org/10.1016/j.foodchem.2013.07.115, 2-s2.0-84882403671.

CASPubMedWeb of Science®Google Scholar

22 Abad-García B., Berrueta L. A., Garmón-Lobato S., Urkaregi A., Gallo B., and Vicente F., Chemometric characterization of fruit juices from spanish cultivars according to their phenolic compound contents: I. Citrus fruits, *Journal of Agricultural and Food Chemistry*. (2012) **60**, no. 14, 3635–3644, 2-s2.0-84859581674, https://doi.org/10.1021/jf300022u, 22423971.

CASPubMedWeb of Science®Google Scholar

23 Bocco A., Cuvelier M.-E., Richard H., and Berset C., Antioxidant activity and phenolic composition of citrus peel and seed extracts, *Journal of Agricultural and Food Chemistry*. (1998) **46**, no. 6, 2123– 2129, https://doi.org/10.1021/jf9709562, 2-s2.0-0000087917.

CASWeb of Science®Google Scholar

24 Mouly P., Gaydou E. M., and Auffray A., Simultaneous separation of flavanone glycosides and polymethoxylated flavones in citrus juices using liquid chromatography, *Journal of Chromatography A*. (1998) **800**, no. 2, 171–179, 2-s2.0-0032571496, https://doi.org/10.1016/S0021-9673(97)01131X, 9561761.

CASPubMedWeb of Science®Google Scholar

25 Proteggente A. R., Saija A., De Pasquale A., and Rice-Evans C. A., The compositional characterisation and antioxidant activity of fresh juices from sicilian sweet orange (Citrus sinensis L. Osbeck) varieties, *Free Radical Research*. (2003) **37**, no. 6, 681–687, 2-s2.0-0037613653, https://doi.org/10.1080/1071576031000083198, 12868495.

CASPubMedWeb of Science®Google Scholar

26 Barreca D., Bellocco E., Caristi C., Leuzzi U. G. O., and Gattuso G., Flavonoid composition and antioxidant activity of juices from chinotto (Citrus x myrtifolia Raf.) fruits at different ripening stages, *Journal of Agricultural and Food Chemistry*. (2010) **58**, no. 5, 3031–3036, 2-s2.077949401977, https://doi.org/10.1021/jf9044809, 20155909.

CASPubMedWeb of Science®Google Scholar

27 Uçan F., Ağçam E., and Akyildiz A., Bioactive compounds and quality parameters of natural cloudy lemon juices, *Journal of Food Science and Technology*. (2016) **53**, no. 3, 1465–1474, 2-s2.084953278008, https://doi.org/10.1007/s13197-015-2155-y.

CASPubMedWeb of Science®Google Scholar

28 Leuzzi U., Caristi C., Panzera V., and Licandro G., Flavonoids in pigmented orange juice and second-pressure extracts, *Journal of Agricultural and Food Chemistry*. (2000) **48**, no. 11, 5501–5506, 2-s2.0-0033673117, https://doi.org/10.1021/jf000538o, 11087509.

CASPubMedWeb of Science®Google Scholar

29 Dolzhenko Y., Bertea C. M., Occhipinti A., Bossi S., and Maffei M. E., UV-B modulates the interplay between terpenoids and flavonoids in peppermint (Mentha×piperita L.), *Journal of Photochemistry and Photobiology B: Biology*. (2010) **100**, no. 2, 67–75, 2-s2.0-77954383662, https://doi.org/10.1016/j.jphotobiol.2010.05.003, 20627615.

CASPubMedWeb of Science®Google Scholar

30 Kazłowska K., Hsu T., Hou C.-C., Yang W.-C., and Tsai G.-J., Anti-inflammatory properties of phenolic compounds and crude extract from *Porphyra dentata*, *Journal of Ethnopharmacology*. (2010) **128**, no. 1, 123–130, https://doi.org/10.1016/j.jep.2009.12.037, 2-s2.0-76749145986.

CASPubMedWeb of Science®Google Scholar

31 Hou M., Man M., Man W., Zhu W., Hupe M., Park K., Crumrine D., Elias P. M., and Man M.Q., Topical hesperidin improves epidermal permeability barrier function and epidermal differentiation in normal murine skin, *Experimental Dermatology*. (2012) **21**, no. 5, 337–340, 2-s2.084859922507, https://doi.org/10.1111/j.1600-0625.2012.01455.x.

CASPubMedWeb of Science®Google Scholar

32 Man G., Mauro T. M., Zhai Y., Kim P. L., Cheung C., Hupe M., Crumrine D., Elias P. M., and Man M.-Q., Topical hesperidin enhances epidermal function in an aged murine model, *Journal of Investigative Dermatology*. (2015) **135**, no. 4, 1184–1187, https://doi.org/10.1038/jid.2014.486, 2s2.0-84925446541.

CASPubMedWeb of Science®Google Scholar

33 Man G., Mauro T. M., Kim P. L., Hupe M., Zhai Y., Sun R., Crumrine D., Cheung C., Nuno-Gonzalez A., Elias P. M., and Man M.-Q., Topical hesperidin prevents glucocorticoid-induced abnormalities in epidermal barrier function in murine skin, *Experimental Dermatology*. (2014) **23**, no. 9, 645–651, 2s2.0-84921944210, https://doi.org/10.1111/exd.12480.

CASPubMedWeb of Science®Google Scholar

34 Hewage S. R., Piao M. J., Kang K. A., Ryu Y. S., Han X., Oh M. C., Jung U., Kim I. G., and Hyun J. W., Hesperidin attenuates ultraviolet b-induced apoptosis by mitigating oxidative stress in human keratinocytes, *Biomolecules & Therapeutics*. (2016) **24**, no. 3, 312– 319, https://doi.org/10.4062/biomolther.2015.139.

CASPubMedWeb of Science®Google Scholar

35 Li M., Lin X.-F., Lu J., Zhou B.-R., and Luo D., Hesperidin ameliorates UV radiation-induced skin damage by abrogation of oxidative stress and inflammatory in HaCaT cells, *Journal of Photochemistry and Photobiology B: Biology*. (2016) **165**, 240–245, 2-s2.084995676361, https://doi.org/10.1016/j.jphotobiol.2016.10.037.

CASPubMedWeb of Science®Google Scholar

36 Zhang R. Z., Zhu W. Y., Xie F., Ge X. S., and Jin H. L., Effect of hesperidin on B16 and HaCaT cell lines irradiated by narrowband-UVB light, *Journal of Clinical Dermatology*. (2008) **37**, 146–149.

CASGoogle Scholar

37 Bae J. T., Ko H. J., Kim G. B., Pyo H. B., and Lee G. S., Protective effects of fermented citrus unshiu peel extract against ultraviolet-a-induced photoageing in human dermal fibrobolasts, *Phytotherapy Research*. (2012) **26**, no. 12, 1851–1856, 2-s2.0-84871301162, https://doi.org/10.1002/ptr.4670, 22422675.

CASPubMedWeb of Science®Google Scholar

38 Proteggente A. R., Basu-Modak S., Kuhnle G., Gordon M. J., Youdim K., Tyrrel R., and Rice-Evans C. A., Hesperetin glucuronide, a photoprotective agent arising from flavonoid metabolism in human skin fibroblasts, *Photochemistry and Photobiology*. (2003) **78**, no. 3, 256–261, 2-s2.0-0141509858, https://doi.org/10.1562/0031-8655(2003)078<0256:HGAPAA>2.0.CO;2, 14556312.

CASPubMedWeb of Science®Google Scholar

39 Petrova A., Davids L. M., Rautenbach F., and Marnewick J. L., Photoprotection by honeybush extracts, hesperidin and mangiferin against UVB-induced skin damage in SKH-1 mice, *Journal of Photochemistry and Photobiology B: Biology*. (2011) **103**, no. 2, 126–139, 2-s2.079954578979, https://doi.org/10.1016/j.jphotobiol.2011.02.020, 21435898.

CASPubMedWeb of Science®Google Scholar

40 Martinez R. M., Pinho-Ribeiro F. A., Steffen V. S., Caviglione C. V., Pala D., Baracat M. M., Georgetti S. R., Verri W. A., and Casagrande R., Topical formulation containing hesperidin methyl chalcone inhibits skin oxidative stress and inflammation induced by ultraviolet B irradiation, *Photochemical & Photobiological Sciences*. (2016) **15**, no. 4, 554–563, 2-s2.084971645579, https://doi.org/10.1039/C5PP00467E.

CASPubMedWeb of Science®Google Scholar

41 Martinez R. M., Pinho-Ribeiro F. A., Steffen V. S., Caviglione C. V., Vignoli J. A., Baracat M. M., Georgetti S. R., Verri W. A., and Casagrande R., Hesperidin methyl chalcone inhibits oxidative stress and inflammation in a mouse model of ultraviolet B irradiation-induced skin damage, *Journal of Photochemistry and Photobiology B: Biology*. (2015) **148**, 145–153, 2-s2.0-84928492991, https://doi.org/10.1016/j.jphotobiol.2015.03.030, 25916506.

CASPubMedWeb of Science®Google Scholar

42 Lee H. J., Im A.-R., Kim S.-M., Kang H.-S., Lee J. D., and Chae S., The flavonoid hesperidin exerts anti-photoaging effect by downregulating matrix metalloproteinase (MMP)-9 expression via mitogen activated protein kinase (MAPK)-dependent signaling pathways, *BMC Complementary and Alternative Medicine*. (2018) **18**, no. 1, article no. 39, 2-s2.0-85041362695.

Web of Science®Google Scholar

43 Jin S., Zhou B., and Luo D., Hesperidin promotes cyclobutane pyrimidine dimer repair in UVBexposed mice epidermis, *Irish Journal of Medical Science*. (2011) **180**, no. 3, 709–714, 2-s2.079961126298, https://doi.org/10.1007/s11845-010-0503-5, 20535600.

CASPubMedWeb of Science®Google Scholar

44 Tsai Y.-H., Lee K.-F., Huang Y.-B., Huang C.-T., and Wu P.-C., In vitro permeation and in vivo whitening effect of topical hesperetin microemulsion delivery system, *International Journal of Pharmaceutics*. (2010) **388**, no. 1-2, 257–262, 2-s2.0-76549120706, https://doi.org/10.1016/j.ijpharm.2009.12.051, 20060453.

CASPubMedWeb of Science®Google Scholar

45 Huang Y.-C., Liu K.-C., and Chiou Y.-L., Melanogenesis of murine melanoma cells induced by hesperetin, a Citrus hydrolysate-derived flavonoid, *Food and Chemical Toxicology*. (2012) **50**, no. 34, 653–659, 2-s2.0-84863254774, https://doi.org/10.1016/j.fct.2012.01.012, 22266363.

CASPubMedWeb of Science®Google Scholar

46 Usach I., Taléns-Visconti R., Magraner-Pardo L., and Peris J.-E., Hesperetin induces melanin production in adult human epidermal melanocytes, *Food and Chemical Toxicology*. (2015) **80**, 80–84, 2-s2.0-84925010693, https://doi.org/10.1016/j.fct.2015.02.017, 25765751.

CASPubMedWeb of Science®Google Scholar

47 Zhang C., Lu Y., Tao L., Tao X., Su X., and Wei D., Tyrosinase inhibitory effects and inhibition mechanisms of nobiletin and hesperidin from citrus peel crude extracts, *Journal of Enzyme Inhibition and Medicinal Chemistry*. (2007) **22**, no. 1, 91–98, 2-s2.0-34247869692, https://doi.org/10.1080/14756360600988989.

PubMedWeb of Science®Google Scholar

48 Zhang C., Lu Y., Tao L., Tao X., Su X., and Wei D., Tyrosinase inhibitory effects and inhibition mechanisms of nobiletin and hesperidin from citrus peel crude extracts, *Journal of Enzyme Inhibition and Medicinal Chemistry*. (2007) **22**, no. 1, 83–90, 2-s2.0-33847728947, https://doi.org/10.1080/14756360600953876, 17373552.

CASPubMedWeb of Science®Google Scholar

49 Kim B., Lee J.-Y., Lee H.-Y., Nam K.-Y., Park J., Lee S. M., Kim J. E., Lee J. D., and Hwang J. S., Hesperidin suppresses melanosome transport by blocking the interaction of rab27amelanophilin,

Biomolecules & Therapeutics. (2013) **21**, no. 5, 343–348, 2-s2.084887325985, https://doi.org/10.4062/biomolther.2013.032.

CASPubMedWeb of Science®Google Scholar

50 Lee H. J., Lee W. J., Chang S. E., and Lee G.-Y., Hesperidin, a popular antioxidant inhibits melanogenesis via Erk1/2 mediated MITF degradation, *International Journal of Molecular Sciences*. (2015) **16**, no. 8, 18384–18395, 2-s2.0-84938846039, https://doi.org/10.3390/ijms160818384.

CASPubMedWeb of Science®Google Scholar

51 Kim S. S., Kim M.-J., Choi Y. H., Kim B. K., Kim K. S., Park K. J., Park S. M., Lee N. H., and Hyun C.G., Down-regulation of tyrosinase, TRP-1, TRP-2 and MITF expressions by citrus press-cakes in murine B16 F10 melanoma, *Asian Pacific Journal of Tropical Biomedicine*. (2013) **3**, no. 8, 617–622, 2-s2.0-84884314673, https://doi.org/10.1016/S2221-1691(13)60125-2.

CASPubMedGoogle Scholar

52 Kiefer S., Weibel M., Smits J., Juch M., Tiedke J., and Herbst N., Citrus flavonoids with skin lightening effects – safety and efficacy studies, *International Journal of Applied Sciences SOFW*. (2010) **136**, 46–54.

Google Scholar

53 Lou S.-N., Yu M.-W., and Ho C.-T., Tyrosinase inhibitory components of immature calamondin peel, *Food Chemistry*. (2012) **135**, no. 3, 1091–1096, 2-s2.0-84865732634, https://doi.org/10.1016/j.foodchem.2012.05.062, 22953829.

CASPubMedWeb of Science®Google Scholar

54 Wessels Q., Pretorius E., Smith C. M., and Nel H., The potential of a niacinamide dominated cosmeceutical formulation on fibroblast activity and wound healing in vitro, *International Wound Journal*. (2014) **11**, no. 2, 152–158, 2-s2.0-84897098607, https://doi.org/10.1111/j.1742481X.2012.01052.x, 22892041.

CASPubMedWeb of Science®Google Scholar

55 Li W., Kandhare A. D., Mukherjee A. A., and Bodhankar S. L., Hesperidin, a plant flavonoid accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats: Role of TGFB/SMADS and ANG-1/TIE-2 signaling pathways, *EXCLI Journal*. (2018) **17**, 399–419, 2-s2.085051512837.

CASPubMedWeb of Science®Google Scholar

56 Wang L., He T., Fu A., Mao Z., Yi L., Tang S., and Yang J., Hesperidin enhances angiogenesis via modulating expression of growth and inflammatory factor in diabetic foot ulcer in rats, *European Journal of Inflammation*. (2018) **16**, https://doi.org/10.1177/2058739218775255.

Web of Science®Google Scholar

57 Toledo R. R., Santos M. E. R. D. C., and Schnaider T. B., Effect of Pycnogenol on the Healing of Venous Ulcers, *Annals of Vascular Surgery*. (2017) **38**, 212–219, 2-s2.084995395244, https://doi.org/10.1016/j.avsg.2016.04.014.

PubMedWeb of Science®Google Scholar

58 Guilhou J. J., Dereure O., Marzin L., Ouvry P., Zuccarelli F., Debure C., Van Landuyt H., GilletTerver M.-N., Guillot B., Levesque H., Mignot J., Pillion G., Février B., and Dubeaux D., Efficacy of Daflon 500 mg

in venous leg ulcer healing: A double-blind, randomized, controlled versus placebo trial in 107 patients, *Angiology*. (1997) **48**, no. 1, 77–85, 2-s2.00031022415, https://doi.org/10.1177/000331979704800113.

CASPubMedWeb of Science®Google Scholar

59 Jagetia G. C. and Rao K. V. N. M., Hesperidin treatment abates radiation-induced delay in healing of deep cutaneous excision wound of mice hemi-body exposed to different doses of γradiation, *Clinical Dermatology Dermatitis*. (2018) **1**, https://doi.org/10.23880/CDOAJ-16000147.

Google Scholar

60 Jagetia G. C. and Rao K. V. N. M., Topical application of hesperidin, a citrus bioflavanone accelerates healing of full thickness dermal excision wounds in mice exposed to 6 Gy of whole body γ-radiation, *Transcriptomics*. (2015) **3**, no. 111, https://doi.org/10.15226/23781726/4/3/00162.

Google Scholar

61 Yang H.-L., Chen S.-C., Senthil Kumar K. J., Yu K.-N., Lee Chao P.-D., Tsai S.-Y., Hou Y.-C., and Hseu Y.-C., Antioxidant and anti-inflammatory potential of hesperetin metabolites obtained from hesperetin-administered rat serum: An ex vivo approach, *Journal of Agricultural and Food*

Chemistry. (2012) **60**, no. 1, 522–532, 2-s2.0-84862960597, https://doi.org/10.1021/jf2040675, 22098419.

CASPubMedWeb of Science®Google Scholar

62 Moon P.-D. and Kim H.-M., Antiinflammatory effects of traditional Korean medicine, JinPi-tang and its active ingredient, hesperidin in HaCaT cells, *Phytotherapy Research*. (2012) **26**, no. 5, 657– 662, 2-s2.0-84859926942, https://doi.org/10.1002/ptr.3627, 21984511.

CASPubMedWeb of Science®Google Scholar

63 Fu S., Sun C., Tao X., and Ren Y., Anti-inammatory effects of active constituents extracted from Chinese medicinal herbs against *Propionibacterium acnes*, *Natural Product Research (Formerly Natural Product Letters)*. (2012) **26**, no. 18, 1746–1749, https://doi.org/10.1080/14786419.2011.608675, 2-s2.0-84865178305.

CASPubMedWeb of Science®Google Scholar

64 Hernandez-Pigeon H., Garidou L., Galliano M., Delga H., Aries M., Duplan H., Bessou-Touya S., and Castex-Rizzi N., Effects of dextran sulfate, 4-t-butylcyclohexanol, pongamia oil and hesperidin methyl chalcone on inflammatory and vascular responses implicated in rosacea, *Clinical, Cosmetic and Investigational Dermatology*. (2018) **11**, 421–429, https://doi.org/10.2147/CCID.S168621.

CASPubMedWeb of Science®Google Scholar

65 Emim J. A., Oliveira A. B., and Lapa A. J., Pharmacological evaluation of the anti-inflammatory activity of a citrus bioflavonoid, hesperidin, and the isoflavonoids, duartin and claussequinone, in rats and mice, *Journal of Pharmacy and Pharmacology*. (1994) **46**, no. 2, 118–122, https://doi.org/10.1111/j.2042-7158.1994.tb03753.x, 2-s2.0-0028199826.

CASPubMedWeb of Science®Google Scholar

66 Pelzer L. E., Guardia T., Juarez A. O., and Guerreiro E., Acute and chronic antiinflammatory effects of plant flavonoids, *Farmaco*. (1998) **53**, no. 6, 421–424, https://doi.org/10.1016/s0014827x(98)00046-9, 2-s2.0-0032580939.

CASPubMedWeb of Science®Google Scholar

67 Kaidama W. M. and Gacche R. N., Anti-inflammatory properties of hesperidin in guinea pigs, *International Journal of Pharmacy and Pharmaceutical Research*. (2016) **6**, 206–217.

CASGoogle Scholar

68 Smina T. P., Mohan A., Ayyappa K. A., Sethuraman S., and Krishnan U. M., Hesperetin exerts apoptotic effect on A431 skin carcinoma cells by regulating mitogen activated protein kinases and cyclins, *Cellular and Molecular Biology*. (2015) **61**, no. 6, 92–99, 2-s2.0-84962141567, https://doi.org/10.14715/cmb/2015.61.6.12, 26518900.

CASPubMedWeb of Science®Google Scholar

69 Zhao W., Chen Y., and Zhang X., Hesperidin-triggered necrosis-like cell death in skin cancer cell line A431 might be prompted by ROS mediated alterations in mitochondrial membrane potential, *International Journal of Clinical and Experimental Medicine*. (2018) **11**, 1948–1954.

Web of Science®Google Scholar

70 Berkarda B., Koyuncu H., Soybir G., and Baykut F., Inhibitory effect of Hesperidin on tumour initiation and promotion in mouse skin, *Research in Experimental Medicine*. (1998) **198**, no. 2, 93– 99, 2-s2.0-0031666252, https://doi.org/10.1007/s004330050093, 9782529.

CASPubMedWeb of Science®Google Scholar

71 Anwer M. K., Al-Shdefat R., Jamil S., Alam P., Abdel-Kader M. S., and Shakeel F., Solubility of bioactive compound hesperidin in six pure solvents at (298.15 to 333.15) K, *Journal of Chemical & Engineering Data*. (2014) **59**, no. 6, 2065–2069, 2-s2.084902303880, https://doi.org/10.1021/je500206w.

CASWeb of Science®Google Scholar

72 Cao R., Zhao Y., Zhou Z., and Zhao X., Enhancement of the water solubility and antioxidant activity of hesperidin by chitooligosaccharide, *Journal of the Science of Food and Agriculture*. (2018) **98**, no. 6, 2422–2427, 2-s2.0-85034755903, https://doi.org/10.1002/jsfa.8734, 29023808.

CASPubMedWeb of Science®Google Scholar

73 Xu R., Cong Y., Zheng M., Chen G., Chen J., and Zhao H., Solubility and modeling of hesperidin in cosolvent mixtures of ethanol, isopropanol, propylene glycol, and n -propanol + water, *Journal of Chemical & Engineering Data*. (2018) **63**, no. 3, 764–770, https://doi.org/10.1021/acs.jced.7b00948, 2-s2.0-85043532108.

CASWeb of Science®Google Scholar

74 Yamada M., Tanabe F., Arai N., Mitsuzumi H., Miwa Y., Kubota M., Chaen H., and Kibata M., Bioavailability of glucosyl hesperidin in rats, *Bioscience, Biotechnology, and Biochemistry*. (2006) **70**, no. 6, 1386–1394, 2-s2.0-33745505358, https://doi.org/10.1271/bbb.50657.

CASPubMedWeb of Science®Google Scholar

75 Damon M., Flandre O., Michel F., Perdrix L., Labrid C., and Crastes de Paulet A., Effect of chronic treatment with a purified flavonoid fraction on inflammatory granuloma in the rat. Study of prostaglandin E_2 and $F_{2\alpha}$ and thromboxane B_2 release and histological changes, *Drug Research*. (1987) **37**, no. 10, 1149–1153, 2-s2.0-0023629450.

CASPubMedWeb of Science®Google Scholar

76 Mayumi K., Seiko T., Masa-Aki S., Masao H., Shoji F., and Nobuyuki I., Subchronic toxicity study of methyl hesperidin in mice, *Toxicology Letters*. (1993) **69**, no. 1, 37–44, 2-s2.00027172534, https://doi.org/10.1016/0378-4274(93)90143-L, 8356566.

PubMedWeb of Science®Google Scholar

77 Kawaguchi K., Mizuno T., Aida K., and Uchino K., Hesperidin as an inhibitor of lipases from porcine pancreas and pseudomonas, *Bioscience, Biotechnology, and Biochemistry*. (1997) **61**, no. 1, 102–104, 2-s2.0-0030945165, https://doi.org/10.1271/bbb.61.102, 9028038.

CASPubMedWeb of Science®Google Scholar

78 Sieve B. F., A new antifertility factor (a preliminary report), *Science*. (1952) **116**, no. 3015, 373– 385, 2-s2.0-0000346675, https://doi.org/10.1126/science.116.3015.373, 12984128.

CASPubMedWeb of Science®Google Scholar

79 Shoab S. S., Porter J. B., Scurr J. H., and Coleridge-Smith P. D., Effect of oral micronized purified flavonoid fraction treatment on leukocyte adhesion molecule expression in patients with chronic venous disease: A pilot study, *Journal of Vascular Surgery*. (2000) **31**, no. 3, 456–461, 2-s2.00034064656, https://doi.org/10.1067/mva.2000.102724.

CASPubMedWeb of Science®Google Scholar

80 Cospite M., Double-blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids, *Angiology*. (1994) **45**, no. 6, 566–573, 2-s2.00028206203, 8203789, https://doi.org/10.1177/000331979404500612.

CASPubMedWeb of Science®Google Scholar

81 Rabe E., Agus G. B., and Roztocil K., Analysis of the effects of micronized purified flavonoid fraction versus placebo on symptoms and quality of life in patients suffering from chronic venous disease: From a prospective randomized trial, *International Angiology*. (2015) **34**, no. 5, 428–436, 2s2.0-84946900108, 25972136.

CASPubMedWeb of Science®Google Scholar

82 Sugasawa N., Katagi A., Kurobe H., Nakayama T., Nishio C., Takumi H., Higashiguchi F., Aihara K.I., Shimabukuro M., Sata M., and Kitagawa T., Inhibition of atherosclerotic plaque development by oral administration of α-glucosyl hesperidin and water-dispersible hesperetin in apolipoprotein E knockout mice, *Journal of the American College of Nutrition*. (2018) 1–8, 2-s2.0-85055024782.

Web of Science®Google Scholar

83 Morand C., Dubray C., Milenkovic D., Lioger D., Martin J. F., Scalbert A., and Mazur A., Hesperidin contributes to the vascular protective effects of orange juice: a randomized crossover study in healthy volunteers, *American Journal of Clinical Nutrition*. (2011) **93**, no. 1, 73– 80, https://doi.org/10.3945/ajcn.110.004945, 2-s2.0-78651304738.

CASPubMedWeb of Science®Google Scholar

84 Xue M., Weickert M. O., Qureshi S., Kandala N.-B., Anwar A., Waldron M., Shafie A., Messenger D., Fowler M., Jenkins G., Rabbani N., and Thornalley P. J., Improved glycemic control and vascular function in overweight and obese subjects by glyoxalase 1 inducer formulation, *Diabetes*. (2016) **65**, no. 8, 2282–2294, 2-s2.0-84980371738, https://doi.org/10.2337/db16-0153.

CASPubMedWeb of Science®Google Scholar

85 Homayouni F., Haidari F., Hedayati M., Zakerkish M., and Ahmadi K., Hesperidin supplementation alleviates oxidative dna damage and lipid peroxidation in type 2 diabetes: a randomized doubleblind placebo-controlled clinical trial, *Phytotherapy Research*. (2017) **31**, no. 10, 1539– 1545, https://doi.org/10.1002/ptr.5881, 2-s2.0-85030315492.

CASPubMedWeb of Science®Google Scholar

86 Justin Thenmozhi A., William Raja T. R., Manivasagam T., Janakiraman U., and Essa M. M., Hesperidin ameliorates cognitive dysfunction, oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease, *Nutritional Neuroscience*. (2016) **20**, no. 6, 360– 368, 2-s2.0-84978524683, https://doi.org/10.1080/1028415X.2016.1144846.

PubMedWeb of Science®Google Scholar

87 Thenmozhi A. J., Raja T. R. W., Janakiraman U., and Manivasagam T., Neuroprotective effect of hesperidin on aluminium chloride induced alzheimer's disease in wistar rats, *Neurochemical Research*. (2015) **40**, no. 4, 767–776, https://doi.org/10.1007/s11064-015-1525-1, 2-s2.084937572354.

CASPubMedWeb of Science®Google Scholar

88 Ahmadi A. and Shadboorestan A., Oxidative stress and cancer; the role of hesperidin, a citrus natural bioflavonoid, as a cancer chemoprotective agent, *Nutrition and Cancer*. (2016) **68**, no. 1, 29– 39, 2-s2.0-84957937421, https://doi.org/10.1080/01635581.2015.1078822, 26381129.

CASPubMedWeb of Science®Google Scholar

89 Elias P. M., Primary role of barrier dysfunction in the pathogenesis of atopic dermatitis, *Experimental Dermatology*. (2018) **27**, no. 8, 847–851, 2-s2.085052498425, https://doi.org/10.1111/exd.13693.

CASPubMedWeb of Science®Google Scholar

90 Hu L., Mauro T. M., Dang E., Man G., Zhang J., Lee D., Wang G., Feingold K. R., Elias P. M., and Man M.-Q., Epidermal dysfunction leads to an age-associated increase in levels of serum inflammatory cytokines, *Journal of Investigative Dermatology*. (2017) **137**, no. 6, 1277– 1285, https://doi.org/10.1016/j.jid.2017.01.007, 2-s2.0-85019963923.

CASPubMedWeb of Science®Google Scholar

91 Man M., Ye L., Hu L., Jeong S., Elias P. M., and Lv C., Improvements in epidermal function prevent relapse of psoriasis: a self-controlled study, *Clinical and Experimental Dermatology*. (2019) https://doi.org/10.1111/ced.13888.

Web of Science®Google Scholar

92 Huang L., Zhong Y., Liu D., Wang X., Gong C., Wen S., Elias P. M., Yang B., and Man M., Adverse cutaneous reactions to skin care products on the face vary with age, but not with sex, *Contact Dermatitis*. (2018) **79**, no. 6, 365–369, https://doi.org/10.1111/cod.13102.

PubMedWeb of Science®Google Scholar

93 Kwa M., Welty L. J., and Xu S., Adverse events reported to the US food and drug administration for cosmetics and personal care products, *JAMA Internal Medicine*. (2017) **177**, no. 8, 1202–1204, 2s2.0-85027265766, https://doi.org/10.1001/jamainternmed.2017.2762.

PubMedWeb of Science®Google Scholar

94 Elias P. M. and Ghadially R., The aged epidermal permeability barrier: Basis for functional abnormalities, *Clinics in Geriatric Medicine*. (2002) **18**, no. 1, 103–120, 2-s2.00036141548, https://doi.org/10.1016/S0749-0690(03)00037-5.

PubMedWeb of Science®Google Scholar

95 Man M. Q., Xin S. J., Song S. P., Cho S. Y., Zhang X. J., Tu C. X., Feingold K. R., and Elias P. M., Variation of skin surface pH, sebum content and stratum corneum hydration with age and gender in a large chinese population, *Skin Pharmacology and Physiology*. (2009) **22**, no. 4, 190–199, 2-s2.0-67749116410, https://doi.org/10.1159/000231524, 19648780.

CASPubMedWeb of Science®Google Scholar

96 D′Orazio J., Jarrett S., Amaro-Ortiz A., and Scott T., UV radiation and the skin, *International Journal of Molecular Sciences*. (2013) **14**, no. 6, 12222–12248, https://doi.org/10.3390/ijms140612222, 2-s2.0-84879014065.

CASPubMedWeb of Science®Google Scholar

97 Amaro-Ortiz A., Yan B., and D′Orazio J. A., Ultraviolet radiation, aging and the skin: Prevention of damage by topical cAMP manipulation, *Molecules*. (2014) **19**, no. 5, 6202–6219, 2-s2.084901458883, https://doi.org/10.3390/molecules19056202.

PubMedWeb of Science®Google Scholar

98 Peluso I., Miglio C., Morabito G., Ioannone F., and Serafini M., Flavonoids and immune function in human: a systematic review, *Critical Reviews in Food Science and Nutrition*. (2015) **55**, no. 3, 383– 395, https://doi.org/10.1080/10408398.2012.656770.

CASPubMedWeb of Science®Google Scholar

99 Kawaguchi K., Maruyama H., Kometani T., and Kumazawa Y., Suppression of collagen-induced arthritis by oral administration of the Citrus flavonoid hesperidin, *Planta Medica*. (2006) **72**, no. 5, 477–479, 2-s2.0-33645993314, https://doi.org/10.1055/s-2005-916254, 16557465.

CASPubMedWeb of Science®Google Scholar

100 Tanaka T., Tanaka T., Tanaka M., and Kuno T., Cancer chemoprevention by citrus pulp and juices containing high amounts of β-cryptoxanthin and hesperidin, *Journal of Biomedicine and Biotechnology*. (2012) **2012**, 516981, 2-s2.0-84855521755.

CASPubMedWeb of Science®Google Scholar

101 Al-Ashaal H. A. and El-Sheltawy S. T., Antioxidant capacity of hesperidin from Citrus peel using electron spin resonance and cytotoxic activity against human carcinoma cell lines, *Pharmaceutical Biology*. (2011) **49**, no. 3, 276–282, 2-s2.0-79951758670, https://doi.org/10.3109/13880209.2010.509734.

CASPubMedWeb of Science®Google Scholar

102 Haddadi G., Abbaszadeh A., Mosleh-Shirazi M., Okhovat M., Salajeghe A., and Ghorbani Z., Evaluation of the effect of hesperidin on vascular endothelial growth factor gene expression in rat skin animal models following cobalt-60 gamma irradiation, *Journal of Cancer Research and Therapeutics*. (2018) **14**, no. 7, 1098–1104, https://doi.org/10.4103/0973-1482.202892.

Web of Science®Google Scholar

103 Karayıldırım Ç. K., Characterization and in vitro evolution of antibacterial efficacy of novel hesperidin microemulsion, *Celal Bayar Üniversitesi Fen Bilimleri Dergisi*. (2017) **13**, 943– 947, https://doi.org/10.18466/cbayarfbe.370370.

CASGoogle Scholar

104 Corciova A., Ciobanu C., Poiata A., Nicolescu A., Drobota M., Varganici C. D., Pinteala T., Fifere A., Marangoci N., and Mircea C., Inclusion complexes of hesperidin with hydroxypropyl-*β*cyclodextrin. Physico-chemical characterization and biological assessment, *Digest Journal of Nanomaterials and Biostructures*. (2014) **9**, no. 4, 1623–1637, 2-s2.0-84937552335.

Web of Science®Google Scholar

105 Cvetnić Z. and Vladimir-Knežević S., Antimicrobial activity of grapefruit seed and pulp ethanolic extract, *Acta Pharmaceutica*. (2004) **54**, no. 3, 243–250, 2-s2.0-6344291042, 15610620.

CASPubMedGoogle Scholar

106 Nagem S. A., Mohammud T. K., Zair S. K., and Abass E. H., Recovery of pure Hesperidin from Iraqi Sweet Oranges Peel and study the effect in some bacteria, *Baghdad Science Journal*. (2014) **11**, 455–460.

Google Scholar

107 Guéniche A., Philippe D., Buyukpamukcu E., Bastien P., Bourassa S., Bernard D., Delattre C., and Castiel-Higounenc I., The natural flavonoid, hesperidin improves skin aging surface parameters following oral intake, *Research Gate*. (2012) https://www.researchgate.net/publication/327832482_THE_NATURAL_FLAVONOID_HESPERIDIN_IMPROVES_SKIN_AGING_SURFACE_PARAMETERS_FOLLOWING_ORAL_INTAKE.

Google Scholar

108 Feingold K. R. and Elias P. M., Role of lipids in the formation and maintenance of the cutaneous permeability barrier, *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*. (2014) **1841**, no. 3, 280–294, https://doi.org/10.1016/j.bbalip.2013.11.007, 2-s2.0-84896723424.

CASPubMedWeb of Science®Google Scholar

109 Nguyen T., Nioi P., and Pickett C. B., The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress, *The Journal of Biological Chemistry*. (2009) **284**, no. 20, 13291– 13295, 2-s2.0-67649402187, https://doi.org/10.1074/jbc.R900010200.

CASPubMedWeb of Science®Google Scholar

110 Ikehata H. and Yamamoto M., Roles of the KEAP1-NRF2 system in mammalian skin exposed to UV radiation, *Toxicology and Applied Pharmacology*. (2018) **360**, 69–77, 2-s2.085054184095, https://doi.org/10.1016/j.taap.2018.09.038.

CASPubMedWeb of Science®Google Scholar

111 Hirota A., Kawachi Y., Yamamoto M., Koga T., Hamada K., and Otsuka F., Acceleration of UVBinduced photoageing in nrf2 gene-deficient mice, *Experimental Dermatology*. (2011) **20**, no. 8, 664– 668, https://doi.org/10.1111/j.1600-0625.2011.01292.x, 2-s2.0-79960311040.

CASPubMedWeb of Science®Google Scholar

112 Saw C. L. L., Yang A. Y., Huang M.-T., Liu Y., Lee J. H., Khor T. O., Su Z.-Y., Shu L., Lu Y., Conney A. H., and Kong A.-N. T., Nrf2 null enhances UVB-induced skin inflammation and extracellular matrix damages, *Cell & Bioscience*. (2014) **4**, no. 1, article 39, https://doi.org/10.1186/2045-3701-4-39, 2s2.0-84906928528.

PubMedWeb of Science®Google Scholar

113 Hirota A., Kawachi Y., Itoh K., Nakamura Y., Xu X., Banno T., Takahashi T., Yamamoto M., and Otsuka F., Ultraviolet A irradiation induces NF-E2-related factor 2 activation in dermal fibroblasts: protective role in UVA-induced apoptosis, *Journal of Investigative Dermatology*. (2005) **124**, no. 4, 825–832, https://doi.org/10.1111/j.0022-202x.2005.23670.x, 2-s2.016844375366.

CASPubMedWeb of Science®Google Scholar

114 Saw C. L., Huang M.-T., Liu Y., Khor T. O., Conney A. H., and Kong A.-N., Impact of Nrf2 on UVBinduced skin inflammation/photoprotection and photoprotective effect of sulforaphane, *Molecular Carcinogenesis*. (2011) **50**, no. 6, 479–486, https://doi.org/10.1002/mc.20725, 2-s2.079955710308.

CASPubMedWeb of Science®Google Scholar

115 Elavarasan J., Velusamy P., Ganesan T., Ramakrishnan S. K., Rajasekaran D., and Periandavan K., Hesperidin-mediated expression of Nrf2 and upregulation of antioxidant status in senescent rat heart, *Journal of Pharmacy and Pharmacology*. (2012) **64**, no. 10, 1472–1482, 2-s2.084865864438, https://doi.org/10.1111/j.2042-7158.2012.01512.x, 22943178.

CASPubMedWeb of Science®Google Scholar

116 Kuwano T., Watanabe M., Kagawa D., and Murase T., Hydrolyzed methylhesperidin induces antioxidant enzyme expression via the nrf2-are pathway in normal human epidermal keratinocytes, *Journal of Agricultural and Food Chemistry*. (2015) **63**, no. 36, 7937– 7944, https://doi.org/10.1021/acs.jafc.5b01992, 2-s2.0-84941749757.

CASPubMedWeb of Science®Google Scholar

117 Videira I. F. D. S., Lima Moura D. F., and Vasconcelos Magina S. B. L. M., Mechanisms regulating melanogenesis, *Anais Brasileiros de Dermatologia*. (2013) **88**, no. 1, 76–83, 2-s2.084875383441, https://doi.org/10.1590/S0365-05962013000100009.

PubMedWeb of Science®Google Scholar

118 Park H. Y., Kosmadaki M., Yaar M., and Gilchrest B. A., Cellular mechanisms regulating human melanogenesis, *Cellular and Molecular Life Sciences*. (2009) **66**, no. 9, 1493–1506, 2-s2.067649509828, https://doi.org/10.1007/s00018-009-8703-8.

CASPubMedWeb of Science®Google Scholar

119 Galgut J. M. and Ali S. A., Hesperidin induced melanophore aggregatory responses in tadpole of bufo melanostictus via a-adrenoceptors, *Pharmacologia*. (2012) **3**, no. 10, 519– 524, https://doi.org/10.5567/pharmacologia.2012.519.524.

CASGoogle Scholar

120 Finnson K. W., McLean S., Di Guglielmo G. M., and Philip A., Dynamics of transforming growth factor beta signaling in wound healing and scarring, *Advances in Wound Care*. (2013) **2**, no. 5, 195– 214, https://doi.org/10.1089/wound.2013.0429.

PubMedGoogle Scholar

121 Johnson K. E. and Wilgus T. A., Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair, *Advances in Wound Care*. (2014) **3**, no. 10, 647– 661, https://doi.org/10.1089/wound.2013.0517.

PubMedGoogle Scholar

122 Wilgus T. A., Matthies A. M., Radek K. A., Dovi J. V., Burns A. L., Shankar R., and DiPietro L. A., Novel function for vascular endothelial growth factor receptor-1 on epidermal keratinocytes, *The American Journal of Pathology*. (2005) **167**, no. 5, 1257–1266, 2-s2.027544485277, https://doi.org/10.1016/S0002-9440(10)61213-8.

CASPubMedWeb of Science®Google Scholar

123 Elias P. M., Arbiser J., Brown B. E., Rossiter H., Man M.-Q., Cerimele F., Crumrine D., Gunathilake R., Eung H. C., Uchida Y., Tschachler E., and Feingold K. R., Epidermal vascular endothelial growth factor production is required for permeability barrier homeostasis, dermal angiogenesis, and the development of epidermal hyperplasia: Implications for the pathogenesis of psoriasis, *The American Journal of Pathology*. (2008) **173**, no. 3, 689–699, 2-s2.0-51349107424, https://doi.org/10.2353/ajpath.2008.080088.

CASPubMedWeb of Science®Google Scholar

124 Kido D., Mizutani K., Takeda K., Mikami R., Matsuura T., Iwasaki K., and Izumi Y., Impact of diabetes on gingival wound healing via oxidative stress, *PLoS ONE*. (2017) **12**, e0189601, 2-s2.085038889150.

PubMedWeb of Science®Google Scholar

125 Schäfer M. and Werner S., Oxidative stress in normal and impaired wound repair, *Pharmacological Research*. (2008) **58**, no. 2, 165–171, 2-s2.053249117183, https://doi.org/10.1016/j.phrs.2008.06.004.

CASPubMedWeb of Science®Google Scholar

126 El-Ferjani R. M., Ahmad M., Dhiyaaldeen S. M., Harun F. W., Ibrahim M. Y., Adam H., Mohd Yamin B., Al-Obaidi M. M. J., and Al Batran R., In vivo assessment of antioxidant and wound healing improvement of a new schiff base derived Co (ii) complex in rats, *Scientific Reports*. (2016) **6**, 38748, 2-s2.0-85006042901.

CASPubMedWeb of Science®Google Scholar

127 Bianchi L., Ginebri A., Hagman J. H., Francesconi F., Carboni I., and Chimenti S., Local treatment of chronic cutaneous leg ulcers with recombinant human granulocyte-macrophage colonystimulating factor, *Journal of the European Academy of Dermatology and Venereology*. (2002) **16**, no. 6, 595–598, 2-s2.0-0036853689, https://doi.org/10.1046/j.1468-3083.2002.00526.x.

CASPubMedWeb of Science®Google Scholar

128 Remes K. and Rönnemaa T., Healing of chronic leg ulcers in diabetic necrobiosis lipoidica with local granulocyte-macrophage colony-stimulating factor treatment, *Journal of Diabetes and*

its Complications. (1999) **13**, no. 2, 115–118, 2-s2.0-0344654752, https://doi.org/10.1016/S10568727(98)00025-7, 10432176.

CASPubMedWeb of Science®Google Scholar

129 Jaschke E., Zabernigg A., and Gattringer C., Recombinant human granulocyte-macrophage colony-stimulating factor applied locally in low doses enhances healing and prevents recurrence of chronic venous ulcers, *International Journal of Dermatology*. (1999) **38**, no. 5, 380–386, 2-s2.00033037994, https://doi.org/10.1046/j.1365-4362.1999.00665.x, 10369552.

CASPubMedWeb of Science®Google Scholar

130 Rosique R. G., Rosique M. J., and Farina Junior J. A., Curbing inflammation in skin wound healing: a review, *International Journal of Inflammation*.
(2015) **2015**, 9, https://doi.org/10.1155/2015/316235, 316235, 2-s2.0-84940761948.

PubMedWeb of Science®Google Scholar

131 Streit M., Beleznay Z., and Braathen L. R., Topical application of the tumour necrosis factor*α* antibody infliximab improves healing of chronic wounds, *International Wound Journal*. (2006) **3**, no. 3, 171–191, 2-s2.0-33748885429, https://doi.org/10.1111/j.1742-481X.2006.00233.x.

CASPubMedGoogle Scholar

132 Nguyen V.-L., Truong C.-T., Nguyen B. C. Q., Van Vo T.-N., Dao T.-T., Nguyen V.-D., Thi Trinh D.-T., Huynh H. K., and Bui C.-B., Anti-inflammatory and wound healing activities of calophyllolide

isolated from Calophyllum inophyllum Linn, *PLoS ONE*. (2017) **12**, no. 10, e0185674, 2-s2.085031004599.

PubMedWeb of Science®Google Scholar

133 Zarubin T. and Han J., Activation and signaling of the p38 MAP kinase pathway, *Cell Research*. (2005) **15**, no. 1, 11–18, 2-s2.0-19644367000, https://doi.org/10.1038/sj.cr.7290257.

CASPubMedWeb of Science®Google Scholar

134 Westra J., Doornbos-van der Meer B., de Boer P., van Leeuwen M. A., van Rijswijk M. H., and Limburg P. C., Strong inhibition of TNF-alpha production and inhibition of IL-8 and COX-2 mRNA expression in monocyte-derived macrophages by RWJ 67657, a p38 mitogen-activated protein
kinase (MAPK) inhibitor, *Arthritis Research & Therapy*. (2004) **6**, no. 4, R384–
R392, https://doi.org/10.1186/ar1204, 2-s2.0-7244243748.

CASPubMedWeb of Science®Google Scholar

135 Song W., Wei L., Du Y., Wang Y., and Jiang S., Protective effect of ginsenoside metabolite compound K against diabetic nephropathy by inhibiting NLRP3 inflammasome activation and NF*κ*B/p38 signaling pathway in high-fat diet/streptozotocin-induced diabetic mice, *International Immunopharmacology*. (2018) **63**, 227–238, 2-s2.0-
85051271145, https://doi.org/10.1016/j.intimp.2018.07.027.

CASPubMedWeb of Science®Google Scholar

136 Wang Y., Yu H., Zhang J., Gao J., Ge X., and Lou G., Hesperidin inhibits HeLa cell proliferation through apoptosis mediated by endoplasmic reticulum stress pathways and cell cycle arrest, *BMC Cancer*. (2015) **15**, no. 1, article no. 682, 2-s2.0-84944065622.

Web of Science®Google Scholar

137 Zhao J., Li Y., Gao J., and De Y., Hesperidin inhibits ovarian cancer cell viability through endoplasmic reticulum stress signaling pathways, *Oncology Letters*. (2017) **14**, no. 5, 5569–5574, 2s2.0-85030150991.

PubMedWeb of Science®Google Scholar

138 Banjerdpongchai R., Wudtiwai B., Khaw-on P., Rachakhom W., Duangnil N., and Kongtawelert P., Hesperidin from Citrus seed induces human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways, *Tumor Biology*. (2016) **37**, no. 1, 227– 237, https://doi.org/10.1007/s13277-015-3774-7, 2-s2.0-84937622393.

CASPubMedWeb of Science®Google Scholar

139 Syed V., TGF-β signaling in cancer, *Journal of Cellular Biochemistry*. (2016) **117**, no. 6, 1279– 1287, https://doi.org/10.1002/jcb.25496.

CASPubMedWeb of Science®Google Scholar

140 Petersen M., Pardali E., Van Der Horst G., Cheung H., Van Den Hoogen C., Van Der Pluijm G., and Ten Dijke P., Smad2 and Smad3 have opposing roles in breast cancer bone metastasis by differentially affecting tumor angiogenesis, *Oncogene*. (2010) **29**, no. 9, 1351–1361, 2-s2.077949265948, https://doi.org/10.1038/onc.2009.426.

CASPubMedWeb of Science®Google Scholar

141 Mahmoud A. M., Mohammed H. M., Khadrawy S. M., and Galaly S. R., Hesperidin protects against chemically induced hepatocarcinogenesis via modulation of Nrf2/ARE/HO-1, PPARγ and TGFβ1/Smad3 signaling, and amelioration of oxidative stress and inflammation, *Chemico-Biological Interactions*. (2017) **277**, 146–158, 2-s2.0-85029717969, https://doi.org/10.1016/j.cbi.2017.09.015.

CASPubMedWeb of Science®Google Scholar

142 Liguori I., Russo G., Curcio F., Bulli G., Aran L., Della-Morte D., Gargiulo G., Testa G., Cacciatore F., Bonaduce D., and Abete P., Oxidative stress, aging, and diseases, *Clinical Interventions in Aging*. (2018) **13**, 757–772, 2-s2.0-85047073565, https://doi.org/10.2147/CIA.S158513.

CASPubMedWeb of Science®Google Scholar

143 Giustarini D., Dalle-Donne I., Tsikas D., and Rossi R., Oxidative stress and human diseases: origin, link, measurement, mechanisms, and biomarkers, *Critical Reviews in Clinical Laboratory Sciences*. (2009) **46**, no. 5-6, 241–281, https://doi.org/10.3109/10408360903142326, 2-s2.0-71849114694.

CASPubMedWeb of Science®Google Scholar

144 Ahmadinejad F., Møller S. G., Hashemzadeh-Chaleshtori M., Bidkhori G., and Jami M.S., Molecular mechanisms behind free radical scavengers function against oxidative stress, *Antioxidants*. (2017) **6**, no. 3, 2-s2.0-85026314820.

PubMedWeb of Science®Google Scholar

145 Zhu C., Dong Y., Liu H., Ren H., and Cui Z., Hesperetin protects against H2O2-triggered oxidative damage via upregulation of the Keap1-Nrf2/HO-1 signal pathway in ARPE-19 cells, *Biomedicine & Pharmacotherapy*. (2017) **88**, 124–133, 2-s2.0-85009373516, https://doi.org/10.1016/j.biopha.2016.11.089, 28103505.

CASPubMedWeb of Science®Google Scholar

146 Ren H., Hao J., Liu T., Zhang D., Lv H., Song E., and Zhu C., Hesperetin suppresses inflammatory responses in lipopolysaccharide-induced RAW 264.7 cells via the inhibition of NF-*κ*B and activation of Nrf2/HO-1 pathways, *Inflammation*. (2016) **39**, no. 3, 964–973, https://doi.org/10.1007/s10753016-0311-9, 2-s2.0-84961198478.

CASPubMedWeb of Science®Google Scholar

147 Hemanth Kumar B., Dinesh Kumar B., and Diwan P. V., Hesperidin, a citrus flavonoid, protects against l-methionine-induced hyperhomocysteinemia by abrogation of oxidative stress, endothelial dysfunction and neurotoxicity in wistar rats, *Pharmaceutical Biology*. (2017) **55**, no. 1, 146–155, 2s2.0-85027932691, https://doi.org/10.1080/13880209.2016.1231695.

CASPubMedWeb of Science®Google Scholar

148 Aly M. S., Galaly S. R., Moustafa N., Mohammed H. M., Khadrawy S. M., and Mahmoud A. M., Hesperidin protects against diethylnitrosamine/carbon tetrachloride-induced renal repercussions via up-regulation of Nrf2/HO-1 signaling and attenuation of oxidative stress, *Journal of Applied Pharmaceutical Science*. (2017) **7**, no. 11, 7–14, 2-s2.0-85037055398.

CASGoogle Scholar