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MINI-REVIEW ARTICLE

Potential of Hesperidin in the Medicinal Field

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Abstract: Hesperidin has gained major interest recently due to the outbreak of COVID-19. The traction has led to more research being conducted on the compound hesperidin. Recent studies have shown its anti-inflammatory and anti-viral attributes, which have beneficial effects on severe acute respiratory syndrome (SARS-CoV-2). Hesperidin has also shown unique effects on the protein of SARS-CoV-2, which lead to a good preventative measure for SARS-CoV-2. Hesperidin also causes a suppression of appetite, which helps to combat obesity through the release of cholecystokinin. Furthermore, hesperidin has shown cardioprotective properties, which cause an increase in plasma high-density lipoprotein levels and a decrease in plasma low-density lipoprotein levels. Hesperidin is also used in combination with the Japanese herb Rikkunshito, which has shown potential in a discovery of a new drug for gastrointestinal motility as hesperidin can depolarize pacemaker potential in interstitial cells of Cajal (ICC). The chemo-preventive effects of hesperidin are caused by its antioxidant effect, which may prevent tissue necrosis due to oxidative stress. The photo-protective effect of hesperidin can reduce the damage to the skin caused by UV rays. Hesperidin also possesses wound-healing properties.

Keywords: Anti-inflammatory, chemo-preventive effects, hesperidin, LDL levels, SARS-CoV-2, cardioprotective properties.

1. INTRODUCTION

Hesperidin was discovered by Lebreton, a French scientist, in 1828. It was found to be present in the mesocarp of citrus fruits. Hesperidin is a type of flavonoid that is present in citrus fruits as a glycoside. It is commonly used in conjunction with other bioflavonoids (*e.g.,* diosmin) for blood vessel conditions (*e.g.,* hemorrhoids, varicose veins, *etc*.). Moreover, it is also used for the treatment of lymphedema [1]. Although it is commonly used for these conditions, there is still insufficient evidence to provide concrete proof regarding its effectiveness. Nevertheless, hesperidin exhibits great potential pharmacologically in terms of antihyperlipidemic, cardioprotective, antidiabetic, and antihypertensive attributes, which come from its anti-inflammatory and antioxidant characteristics [2]. Some studies even demonstrated that hesperidin has ameliorative attributes against memory impairment and AB pathology, which leads to dementia and cognitive decline in old age [3]. Although flavonoids like hesperidin are widely used, they do not seem to have sufficient evidence that substantiates their expected potential in the work of Szent–Györgyi in 1935. Citrus fruits have long been integrated into the daily diet of many people. It has been reported that citrus flavonoids can decrease capillary fragility and radiation damage [4].

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Recently, hesperidin has gained enormous attention due to its effectiveness in COVID-19 prevention. As nutrition is always underestimated in terms of disease prevention, hesperidin sheds light on the impact of nutrition, especially citrus fruits, on health. Some recent studies have shown the beneficial aspects of hesperidin due to its antiviral actions and immune-modulating properties against infections [5]. Furthermore, hesperidin has been shown to counteract the damage caused by oxygen-free radicals triggered by inflammation and viral infection. Recently, increased emphasis on hesperidin is also due to its binding affinity towards the key protein of severe acute respiratory syndrome (SARS-CoV-2) [6]. The schematic illustration representing various pharmacological effects of hesperidin is depicted in Fig. (**1**). Considering the potential of hesperidin, the present review is conducted to outline recent breakthroughs in the pharmacological properties of hesperidin and its role in the prevention of COVID-19.

2. PHARMACOLOGICAL ACTIVITIES

2.1. COVID-19

Recently, the structure of hesperidin able to bind to the SARS-CoV-2 virus has been discovered, which attracts increased scientific interest [7] (Fig. **2**). A lot of researchers have started to study more about the chemical and physical structure of hesperidin in terms of its binding to the virus by

understanding the basic protein structure of the virus and the mode of binding.

A research study by Haggag *et al.* [8] stated that the SARS-CoV-2 virus usually forms a SARS-CoV-2 RBD-ACE-2 complex with ACE-2 receptor through the spike-receptor binding domain (RBD-S) present on the surface of the virus. In this research, the homology modeling method was used to screen 78 antiviral drugs, including hesperidin, against ACE-2 receptors in humans. The result showed that only hesperidin was capable of targeting the SARS-CoV-2 spike protein by binding to ACE-2 receptors. It was concluded that hesperidin inhibited the entry of SARS-CoV-2 into the lung cells by interfering with the reaction between the ACE-2 and RBD of SARS-CoV-2. Hence, it plays a role in prophylactic activity toward the SARS-CoV-2 virus [8]. The role of hesperidin in the SARS-CoV-2 virus is depicted in Fig. (**3**).

Furthermore, the results of a study by Bellavite *et al.* [9] supported the findings of a study conducted by Haggag *et al.* [8] and reported that hesperidin has a high binding affinity towards SARS-CoV-2 main protein receptors, such as the protease domain of SARS-CoV-2, RBD-S, and protease domain ACE-2 RBD. The researchers performed a molecular docking simulation to show the strong binding affinity of hesperidin with RBD-ACE-2. A group of researchers examined 78 antiviral drugs for their affinities to bind to the SARS-CoV-2 proteins. Hesperidin was reported to exhibit the best binding ability to the spike protein. An overlapping of hesperidin with the ACE-2 interface was found when ACE-2 RBD superimposed the hesperidin RBD complex. This is the main mechanism for the inhibitory effect of hesperidin against SARS-CoV-2. In a molecular docking study, 33 natural known antiviral agents are being tested. It was found that hesperidin is the third agent that showed low binding energy. This is explained by the binding ability of hesperidin hydrogen bonds with amino acids, such as THR24, THR25, SER46, *etc.* [10].

Hesperidin can activate the mitogen-activated protein kinase (MAPK) pathway, exerting antiviral activity against the influenza virus. MAPK plays a major role in preventing tissue damage by controlling the spread and replication of the virus [8]. Hesperidin was found to activate a defense cascade in the pathway. It has been observed that activation of the interferon-MAPK pathway defense mechanism is essential to cope with the SARS-CoV-2 virus as the antibodies that are produced during the pathway are important in the immune response [9]. COVID-19 infects patients and causes a serious inflammatory response where interferons, interleukins, chemokines, and also tumor necrosis factor- α (TNF-α) are produced uncontrollably and lead to a phenomenon known as a "cytokine storm" [11]. Hesperidin plays an important role in restraining the immune-active molecules from release by inhibiting the IL-1β-stimulated inflammatory responses. Therefore, it is used to suppress the inflammatory reaction in COVID-19-infected patients as adjuvant therapy [8]. However, prolonged administration and exposure to hesperidin have fewer side effects on the body as only a low concentration of cytotoxicity is produced, and it only stays in the body for a short period [12].

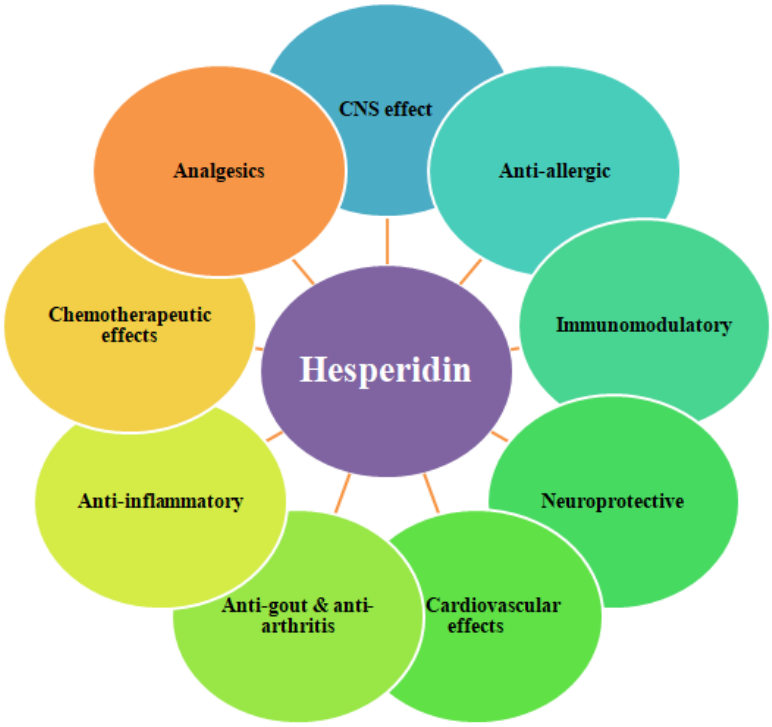
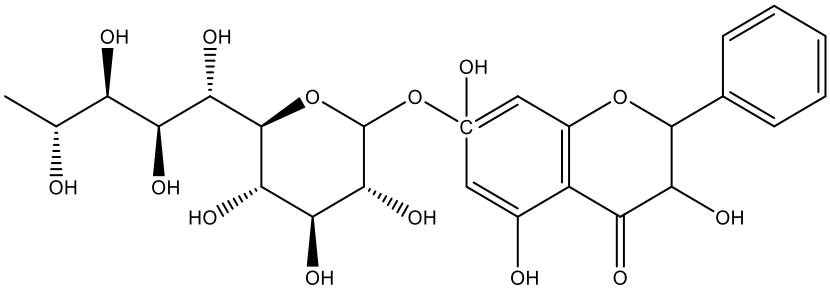


Fig. (1). Schematic diagram representing pharmacological activities of hesperidin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



3,5,7-trihydroxyflavanone-7-rhamnoglucoside

Fig. (2). Structure of Hesperidin.

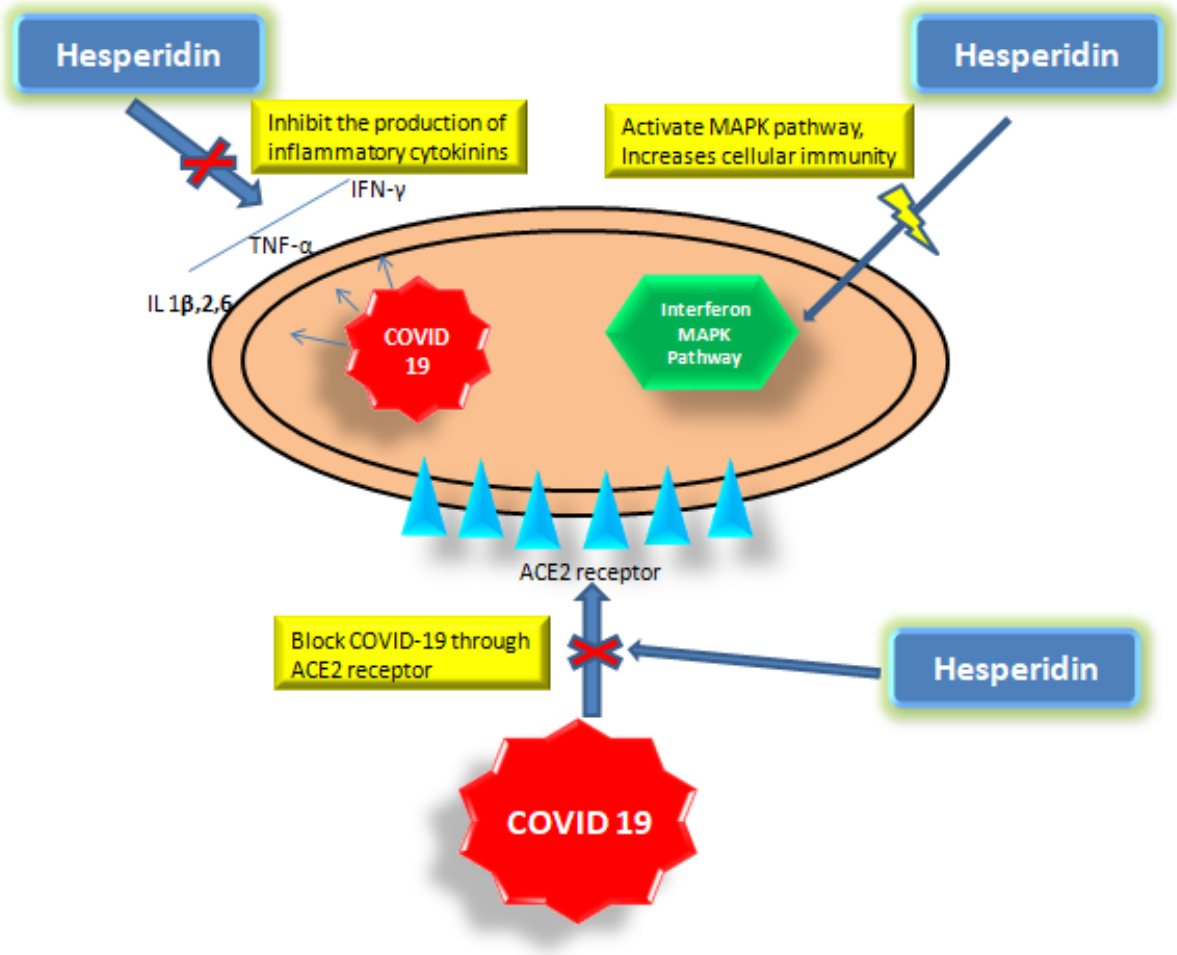


Fig. (3). Schematic diagram showing the effects of hesperidin in COVID-19. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2. Obesity

Obesity is one of the major public health concerns worldwide due to its continuously rising prevalence in recent years. According to a study, more than 30% of the population globally suffers from being overweight. Obesity occurs not only due to lifestyle factors, such as unhealthy eating and exercising, but it is also caused by genetic factors [13]. Lack of exercise, together with excess intake of fat, results in an accumulation of fatty cells in the body, known as hyperplasia or hypertrophy. Organ dysfunction is one of the problems that develop from obesity. Obesity will cause metabolic dysfunction when hypertrophy of fat cells prevents the storage of triglycerides, and this contributes to the infiltration of inflammatory cells into all parts of the body and leads to organ dysfunction. The buildup of visceral fatty tissues finally leads to the development of type-2 diabetes, cardiovascular disease, and hyperlipidemia [14].

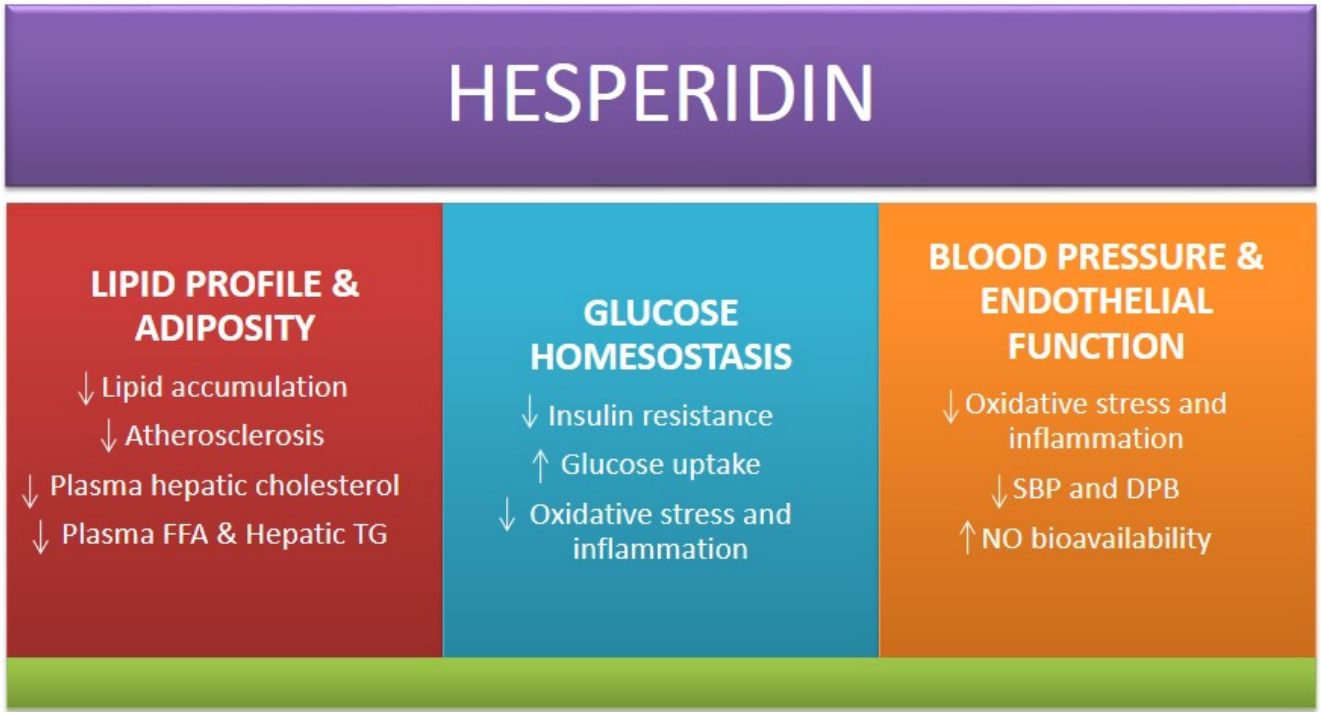


Fig. (4). Summary of the most significant effects of hesperidin and its derivatives on lipid profile, adiposity, glucose homeostasis, and cardiovascular risk parameters, including blood pressure and endothelial function. SBP: systolic blood pressure; DBP: diastolic blood pressure; NO: nitric oxide; FFA: free fatty acids; TG: triglycerides; Chol: cholesterol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Adipose tissue is a type of connective tissue mainly used for energy storage in lipid form. There are two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). The function of WAT is to store excess energy as triglycerides and release the energy in the form of fatty acid when the body is needed. BAT with a high quantity of mitochondria is involved in thermoregulation. It is important in regulating balanced body temperature and energy. Activation of BAT also improves glucose and lipid regulation, preventing lipid accumulation and obesity [15]. Previous studies proved that hesperidin-containing substances could turn WAT into BAT, which decreases the lipid concentration in blood and has beneficial effects on postprandial hyperglycemia [16].

Hesperidin can cause the release of cholecystokinin (CCK), which leads to the suppression of appetite and prevent obesity [17]. An *in vivo* study on rats showed that hesperidin in high concentrations upregulated adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) mRNA expression, which caused some changes to the signaling pathway of insulin, the substrate of insulin receptors, and genes responsible for the metabolism of lipid, thereby leading to the activation of PPAR-α mRNA expression. Moreover, it was found to prevent the accumulation of mature adipocytes by expressing messenger RNA through hormone-sensitive lipases [13]. Hesperidin decreases retinol transport from the hepatic to target tissue through retinol-binding protein (RBP). By regulating RBP, heart-type fatty acid-binding protein (H-FABP), and cutaneous type fatty acid-binding protein (C-FABP), hesperidin can prevent hypercholesterolemia by suppressing cholesterol synthesis and absorption [18]. It controls the systolic blood pressure (SBP), cholesterol concentration in the blood, and TG concentration. Fatty acid synthase is a protein responsible for fatty acid synthesis. Moreover, its anti-lipolytic activity is known to reduce fatty acid synthase, which causes an increase in HDL-C and a decrease in plasma LDL-C and VLDL-C levels (Fig. **4**) [13].

2.3. Depolarization of Pacemaker Potential

Hesperidin is a citrus flavonoid that can be found in many nutritious fruits. Hesperidin has been found to have a wide range of biological functions [19]. It has been used to treat a variety of ailments, including neurological, psychological, and cardiovascular problems. Hesperidin is used with other drugs, such as rikkunshito, as a combination to achieve the best results. Rikkunshito is a Japanese herbal remedy used in Japan to stimulate appetite and treat indigestion. Hesperidin promotes ghrelin secretion, while the combination of rikkunshito and hesperidin exerts a synergistic effect that yields a promising result [20]. In the gastrointestinal (GI) tract, interstitial cells of Cajal (ICC) act as pacemakers. The active pacemaker potential generated by ICC causes electrical and mechanical activity in smooth muscles [21]. Ca^{2+} activated Cl^{-} channels and non-selective cation channels are important for the activity of the pacemaker [19].

Muscarinic receptors play an important role in GI motility regulation. It has been observed that the potential of hesperidin remains unaffected by methoctramine or 4-DAMP. Moreover, the effect of hesperidin on ICC did not appear to be mediated by muscarinic receptors. Hesperidin depolarized pacemaker potentials of ICC in a dose-dependent manner

[22]. Furthermore, 5-HT is also important in GI motility regulation. Pacemaker activity is regulated by 5-HT through the 5-HT3, 5-HT4, and 5-HT7 receptors [23]. Hesperidin-induced effects on ICC were thought to be mediated by 5-HT4 receptors and G-protein and PLC/PKC pathways. Furthermore, hesperidin was found to increase GE and ITR. Therefore, hesperidin improved GI motility by depolarizing ICC pacemaker potential through 5-HT4 receptors, G protein, and PLC/PKC-dependent pathways [19]. Hence, hesperidin can be a promising new drug for controlling GI motility.

2.4. Chemopreventive Effect

Hesperidin is a bioflavonoid that is derived from its glycosidic linkage. Hesperidin is primarily used as an antioxidant that reduces the effects of oxidative stress by scavenging reactive oxygen species (ROS) and inhibiting oxidative injury in the cell. In cultured human polymorphonuclear neutrophils, hesperidin protects them from producing reactive oxygen species (ROS) and caspase-dependent apoptosis. It has been observed that hesperidin administration through the diet had no toxic effects in various tissues. Moreover, it also protects the liver and kidneys from oxidative stress caused by iron [24]. Using various hesperidin doses was reported to significantly lower the prevalence and the average number of tumors [25]. A recent study found that mice administered with hesperidin were less likely to develop benzo-a-pyrene-induced lung carcinoma. Hesperidin also entirely prevented C3H 10T1/2 fibroblasts from transforming into cancerous cells [23]. The inhibition of the initiation and promotion stages of carcinogenesis appears to be responsible for the chemopreventive effect of hesperidin. Reactive oxygen species are needed for cell proliferation and tumor progression in multistep carcinogenesis, especially during the promotion phase. The inflammatory response of TPA alters genome fidelity by inducing extra mutations in the cell, causing the initiated cell to proliferate and form tumors [26]. The growth of tumors after DMBA+TPA application may be due to increased oxidative stress and sustained inflammatory response, as evidenced by a sharp decrease in GSH, GST, CAT, and SOD actions, as well as higher MDA levels [27]. Hesperidin therapy decreased MDA levels and inhibited the DMBA+TPA-induced decrease in GSH, GST, CAT, and SOD, suggesting that hesperidin activity was important in reducing oxidative stress-mediated carcinogenesis [23]. Treatment of hesperidin in DMBA+TPA-treated mice decreased oxidative stress markedly, as evidenced by lower MDA levels, which may have resulted in a decrease in tumor production [28]. Previous studies revealed that certain flavonoids of *Opuntia humifusa* reduced MDA levels in skin tumors. MDA levels may have been reduced due to increased levels of antioxidant enzymes; hence, the antioxidants have been shown to have anti-cancer properties [23].

Inhibitory effects of hesperidin on DMBA+TPA-induced carcinogenesis were mediated by a number of different mechanisms. Hesperidin is thought to suppress free radical formation, and this action of hesperidin may prevent DMBA/TTPA-induced free radicals, lowering the mutagenic effect and, as a result, the occurrence of tumors. Lipid peroxidation is known to cause various types of DNA damage, which can result in mutagenesis and neoplastic transformation [29]. The rise in GSH content, GST, catalase, and SOD activity, as well as the decrease in lipid peroxidation values, may decrease DMBA/TPA-induced oxidative stress and inflammation, which are directly involved in the carcinogenesis process, thus decreasing tumor incidence. The activation of NF-B signaling has been linked to the development of skin cancer caused by DMBA+TPA. Hesperidin was reported to decrease the DMBA+TPA-induced expression of NF-B, RassF7, PARP, and Nrf2, which are known to be hyperactivated during inflammation, cell proliferation, and carcinogenesis, reducing tumor occurrence. NF-B and COX-II activation have been shown to be inhibited by hesperidin and naringin [29].

Hesperidin can prevent the proliferation of cancer cells in oral cancer. It inhibits the expression of proteins involved in EMT and members of the matrix metallopeptidase protein (MMP) family, which can prevent cancer cell invasion [30]. Hesperidin causes A549 cells to die by activating mitochondrial apoptosis proteins and limiting the expression of cell cycle-related molecules. It also induces apoptosis in colon cancer cells by enhancing caspase-9 and caspase-3 activities. Hesperidin activates the ERK1/2 signaling pathway and causes apoptosis of HepG2 cells, while it suppresses the growth of cancer cells by inducing apoptosis in NCI-H358 and A549 cells [31].

Hesperidin is found to have low cytotoxicity in MRC-5 cells, which is a type of normal lung fibroblast. It has been shown to increase caspase-3 enzyme expression and decrease MMP levels, both of which are linked to apoptosis. Hesperidin therapy reduced the effectiveness of NSCLC cell tumor volume and colony formation by improving miR-132 expression and reducing ZEB2 expression [32]. Additionally, ZEB2, an inhibitor of E-cadherin transcription, has been reported to have a significant role in EMT and is a direct target of miR-132. Furthermore, ectopic expression of miR-132 greatly decreased the invasiveness of CRC cells and inhibited their EMT process, among several targets for miR-132 in cancer [30].

2.5. Effect on Skin Health

In recent years, environmental pollution has caused severe ozone depletion worldwide. Ozone layer functions as a natural filter of ultraviolet (UV) light rays emitted from the Sun, specifically UV type B (UV-B) [33]. Since the output of UVB from the Sun is always constant, the depleted ozone layer will allow more UVB to pass through the Earth. UVB is known to have a carcinogenic effect on human skin. By inducing thymine-thymine dimer in the DNA, UVB is notorious for causing skin cancer [34]. Furthermore, frequent exposure to UVB results in the generation of ROS, increasing oxidizing stress and ultimately damaging DNA, protein, and lipids [35].

In a study conducted by Petrova *et al.* [36], it was found that honeybush (a plant native to South Africa) presented a photoprotective effect, preventing photodamage from the UVB rays on human skin. They have found that honeybush contains numerous antioxidant polyphenols. Polyphenols, particularly hesperidin, are responsible for absorbing the ROS produced by exposure to UVB [36]. In another study conducted on mice, Martinez *et al.* found that a topical for-

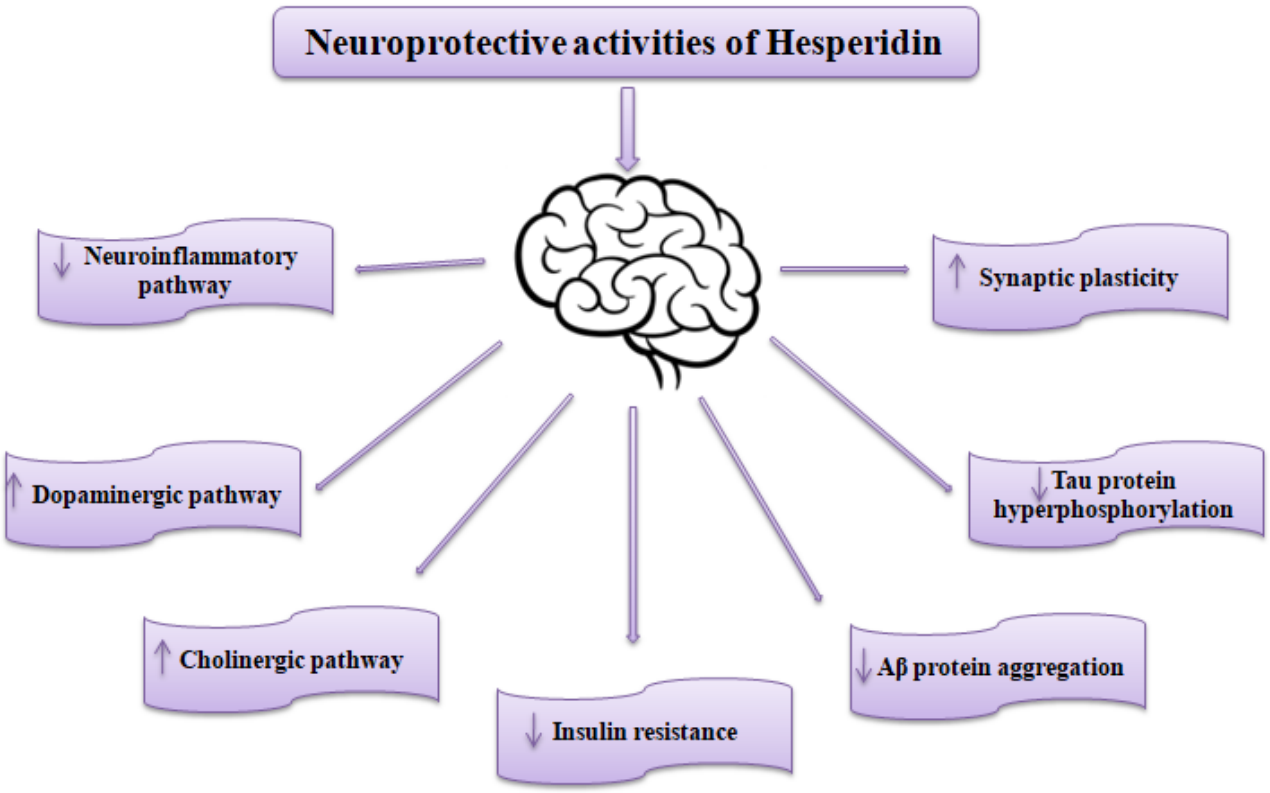


Fig. (5). Schematic diagram showing neuroprotective effects of hesperidin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

mulation containing hesperidin derivative, hesperidin methyl chalcone, potentially had a protective effect on the mice's skin. The compound was found to reduce ROS and inflammation caused by UVB. The anti-inflammatory effect is possibly due to the inhibition of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β, interleukin-6, and interleukin-10, which are generated due to UVB irradiation [37].

Besides the potential skin protective effect, hesperidin also demonstrated an excellent wound-healing effect. A study by Bagher *et al.* reported that adding hesperidin to alginate/chitosan (Alg/Chit) hydrogels further enhanced the wound healing capability and antimicrobial activity at the site of skin damage. The addition of 10% hesperidin to the Alg/Chit improved cell proliferation in the wounded skin. The anti-inflammatory effect of hesperidin also contributes to wound healing, mainly due to the suppression of several cytokines [38]. Moreover, hesperidin also scavenges free radicals and thus speeds up the process of wound healing [38]. Hence, due to its dermatological effect, hesperidin can be a potential agent that can be examined in the future for skin protection and as a wound-healing aid.

2.6. Neuroprotective Effect

Several neurodegenerative diseases, namely Alzheimer's disease, Parkinson's disease, multiple sclerosis, *etc*., are known to be caused by the progressive loss of brain and spinal cord cells [39]. Progressively worsening these chronic disorders can cause several dysfunctions, such as ataxia and dementia, and ultimately brain cell death or brain atrophy [40]. Moreover, the locomotion, motor behavior, and cognitive function of the patient are also affected [41]. Some factors leading to neurodegeneration include the accumulation of ROS, inflammation in the brain, and malfunctioned apoptosis. The accumulation of ROS in the brain or spinal cord is likely to be caused by either overproduction or poor metabolism. ROS accumulation will increase oxidative stress and, eventually, cell damage [39]. Inflammation, on the other hand, causes brain cell damage by the glial cells and cytokines. It has been observed that patients experiencing Alzheimer's disease (AD), whose cognitive function and memory are damaged, would suffer from dementia [42].

Hesperidin is a potent antioxidant that scavenges ROS, which is useful in the case of neurodegeneration due to oxidative stress. In a study conducted by Wang *et al.* [43], hesperidin was found to be capable of increasing anti-oxidative defense and thus help in cognitive function. Hesperidin administration for 16 weeks at 100 mg/kg per day showed improvement in cognitive function and locomotion. In research, hesperidin was reported to improve mitochondrial complex I-IV enzyme activities and inhibit the activity of glycogen synthase kinase-3β (GSK-3β) [43]. The function of GSK-3 is to regulate glycogen and protein synthesis, where GSK-3β phosphorylates tau. However, overexpression of GSK-3β can cause tau hyperphosphorylation, apoptotic neuronal death,

and reactive astrocytosis, which, in turn, causes Alzheimer's disease [44].

In addition to AD, Parkinson's disease (PD) also affects most elderly patients, which occurs highly due to the loss of dopaminergic neurons. The accumulation of ROS is one of the causes of dopaminergic neuron degeneration, followed by mitochondrial dysfunction [45]. PD patient usually shows mood disturbances, depression, insomnia, *etc.* Hesperidin was found to be effectively alleviated the symptoms of PD, and it acts on the kappa-opioid and serotonin receptors [40, 46]. Hesperidin also prevents dopamine depletion, mitochondrial activation, and ROS inhibition, exerting a neuroprotective effect. In addition, researchers suggested that hesperidin is also likely to alter adrenaline, noradrenaline, and serotonin levels in the body, thus exhibiting a neuroprotective effect (Fig. **5**) [47].

3. LIMITATIONS OF HESPERIDIN

Hesperidin is a crystalline powder that is white to yellow in color and has a low water solubility [48]. Its limited aqueous solubility limits its dissolving rate in water, resulting in low *in vivo* bioavailability [49]. It is also known to be insoluble in the majority of physiologically safe organic solvents used in the development of pharmaceutical dosage forms. Natural bioactive chemicals have limited water solubility and bioavailability, making formulation development difficult [50]. Natural bioactive chemicals are extracted from their respective plant sources using unsafe or physiologically harmful solvents, such as methanol, chloroform, and ether [51-56]. Due to regulatory and toxicological concerns, these organic solvents are not suited for formulation development.

Hesperidin may also interfere with medications like celiprolol [57] and diltiazem [58], preventing them from being absorbed. It also improves the absorption of certain medicines, such as verapamil, which increases the drug's effects [59]. Hesperidin may make the exporter pumps less active, allowing more drugs like etoposide, paclitaxel, vinblastine, and vincristine to be absorbed by the body. This could cause negative effects by increasing the amount of some drugs in the body. However, there is little information to determine whether this is a major risk [60]. Hesperidin may help prevent blood coagulation, and if it is used with drugs that reduce blood coagulation, it may raise the risk of bruising, bleeding, and other complications [61]. It might cause sleepiness and drowsiness when used with sedative medicines [62].

CONCLUSION

In conclusion, despite many doubts about the actual benefits of hesperidin due to the lack of evidence, the fact that it has a major contribution to the medical field is incredible. Hesperidin contains antioxidant and radical scavenging properties, which could explain its medicinal effects. It was observed to restore the antioxidant enzymes' defense system. Hesperidin and its analogs have anti-cancer properties due to apoptosis and cytotoxic actions. It suppresses a wide range of inflammatory mediators and their expressions. It also inhibits the action of several enzymes. Its anti-diabetic and anti-hypertensive properties have been extensively researched. In addition to animal studies, numerous research works on humans have indicated its anti-obesity, anti-hyperlipidemic, and anti-hemorrhagic properties. Hesperidin can also bind to the SARS-CoV-2 "spike" protein, which results in a prophylactic action that prevents the SARS-CoV-2 from latching onto the cells lining of the lungs. This unique ability of hesperidin is not found in any other flavonoids. Hesperidin also has antiviral activity against influenza through the MAPK pathway, which controls the spread of the virus. Its effects on appetite suppression and cardio risk management are also significant to the extent of being cardioprotective and a supplement for obesity. Moreover, hesperidin has been consumed in the human diet as its side effects are negligible compared to its benefits. Flavonoids are involved in a protective mechanism for plants against pests, thus explaining its cytotoxicity; however, its multiple health potentials and benefits are worth more research to be carried out on this compound. As a result, hesperidin might be considered an essential phytochemical that requires further research to establish an effective safety profile in humans and provide therapeutic advantages.

LIST OF ABBREVIATIONS

BAT	=	Brown Adipose Tissue
ICC	=	Interstitial Cells of Cajal
SARS-CoV-2	=	Severe Acute Respiratory Syndrome
TNF-α	=	Tumor Necrosis Factor- α

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

None.

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