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HESPERIDIN EFFECT ON HEART DISORDER

Mahnoor Fatima[1] and Muhammad Umair Azam[2]

[1,2] National Institute of Food Science and Technology, University of Agriculture, Faisalabad, 38000, Pakistan.

*Corresponding author: (mahnooralvi142@gmail.com); (Umair522000@gmail.com)

ABSTRACT

Citrus fruits are a rich source of hesperidin, a flavonoid that has shown promise in supporting cardiovascular health. It's lipid-lowering, anti-inflammatory, and antioxidant qualities have been emphasized by several preclinical and clinical investigations. Mechanistically, hesperidin reduces pro-inflammatory cytokines and oxidative stress indicators by modulating important signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway. The development of atherosclerosis, hypertension, and myocardial infarction are all significantly influenced by these processes, which also help to improve endothelial function, control blood pressure, and lessen vascular remodeling. Supplementing with hesperidin has produced positive changes in lipid profiles, lower blood pressure, and lower levels of inflammatory mediators in both human and animal models. The evidence for hesperidin's cardioprotective actions, both in vitro and in vivo, is thoroughly assessed in this review. According to the clinical results, hesperidin may be a useful adjunct therapy in the management and prevention of cardiovascular illnesses, especially when taken as a targeted supplement or as part of a diet high in flavonoids.

***Keywords*:** Flavonoid, Hesperidin, anti-oxidation, anti-inflammation, heart disease

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1. INTRODUCTION

Hesperidin (HSP) is a flavanone glycoside found in citrus fruits. HSP markedly improves vascular function in living organisms with vascular hypertension and inhibits renin-angiotensin system over activity (Apaijit *et al*., 2022a). HES belongs to the group of polyphenolic bioflavonoid flavanone glycosides and is widespread in their citrus peels such as that of orange and tangerine in addition to grapefruits among others Citrus rinds contain a large amount of hesperidin, where tangerines peel (Citrus reticulata) may have 5%–10% hesperidin of their dry mass. This F ratio was first isolated from spongy tissue in 1828 by Leverton. Hesperides orange peels the inner part of which has a shape like round and cylinder. The pathogen also later showed up in lemons isolate with neo-hesperidin from citrus fruits, and some other plants. That it was named HES which has a meaning, the term 'Hesperidium', which is citrus fruits. Due to its status as a bound form of hesperitin, is also known Vitamin P, which may be referred to due to their comparable properties with vitamins of wound healing being used as part of the medical regimen combination in the treatment of scurvy with Vitamin C (Pla-Paga *et al*., 2019). HES could improve myocardial function by inhibiting oxidative stress, inflammation, cardiac remodeling, myocardial hypertrophy, and fibrosis (Zhang *et al*., 2020). HES play its impactful role when it is taken in the diet. HSP is a flavonoid found in citrus fruit. As citrus fruits are known as a rich source of antioxidants which reduce the inflammation in the body. It is termed as the most important factor in reducing the hypertension, myocardial infarction, ischemic heart disease and stroke. HSP alongside with other flavonoids perform a key role in reducing endothelial dysfunction and the prevention of cardiovascular diseases. HSP show antithrombotic effects in order to minimize the thrombosis in the vessels to that there will be no blockage in the blood vessels and it will reduce the blockage of arteries which will prevent cardiac arrest and eliminate the chances of developing heart diseases (Hashemzaei *et al*., 2020). HSP is a polyphenolic bioflavonoid flavanone glycoside that is dominantly found in orange peels and other citrus fruits like tangerine and grapefruits. Smashed dried tangerine contains 5-10% of HSP. Leverton isolated it first in 1828 from the spongy inner portion of orange peel of the family Hesperides. It was given the name HES, which comes from the term 'Hesperidium', meaning citrus fruits. Also, it is referred to as hesperetin-7- rutinoside. HSP is the food-bound form of hesperidin, and was earlier referred to as Vitamin P due to its vitamin-like properties of wound healing and was used in combination with Vitamin C for the treatment of scurvy (Tejada *et al*., 2020).

The main reason for its biological activity is its antioxidant ability which can be penetrate the phospholipid bilayers to scavenge free oxygen radicals. HSP has a protective effect in cardiovascular disease (Liu *et al*., 2021a). Release of different inflammatory cytokines is reduced by interleukin 1-β (IL-1β), interleukin-6 (IL-6),

interleukin 18 (IL-18), and tumor necrosis factor-alpha (TNF-α) can protect against cardiac tissue inflammation (Zaafar *et al*., 2022).

HSP is shown to possess antihypertensive, anti-inflammatory, and antioxidant activity along with a potential to boost Nrf2. These features tend it to be an ideal candidate to treat hypertrophy. However, there is no ample scientific evidence to prove its efficacy and mechanism of action in the oxidative stress-mediated pathological conditions like cardiac hypertrophy. The protective role of HSP in preventing isoproterenol-induced cardiac hypertrophy and to signaling pathway responsible for this cardio protective effect (Velusamy *et al*., 2020). HSP reduces elevated vessel resistance by inhibiting NADPH oxidase or by promoting NO production, resulting in a reduction in Blood Pressure (Gao *et al*., 2020). Selection and collection of data was based on the actual diagnosis of effects on rats as they were the lab animals.

This review is designed to explore available scientific and evidence-based data on HSP efficacy against different heart disease in various forms, to interpret their study outcome for the improvement and stability effect of hesperidin. Their 'therapeutic effect' in health promotion and various diseases' prevention are also evaluated in this review. Therefore, recent accessible experiments on the safe and effective use for blood pressure regulation and increase the stability of heart. For data collection, an advanced search option on Google Scholar, Science Direct, Elsevier and Scopus was performed from 2018 to November 2024 with keywords selected as 'hesperidin' OR 'heart disease'.

Mechanism of action

The protective role of HSP in preventing isoproterenol-induced cardiac hypertrophy. As shown in figure 1 it is to depict that the signaling pathway is responsible for this cardio-protective effect (Velusamy *et al*., 2020). HES reduces elevated vessel resistance by inhibiting NADPH oxidase or by promoting NO production, resulting in a reduction in Blood Pressure (Gao *et al*., 2020). HES could reduce Ang II-induced cardiac fibrosis and inflammation (Zhang *et al*., 2020). HES is sufficient to effectively limit Ang II-induced myocardial hypertrophy and remodeling because it can significantly improve Ang II-induced systolic dysfunction and reduce hypertension, myocardial hypertrophy, fibrosis, superoxide dismutase production, and inflammation. HSP can reduce heart hypertrophy brought on by Ang II, and it may do so by inhibiting the hypertrophy signaling pathway as well as oxidative stress and inflammation (Zhang *et al*., 2020). As shown in figure 2 hesperidin help in preventing heart disease in various ways by protecting it from antioxidants.

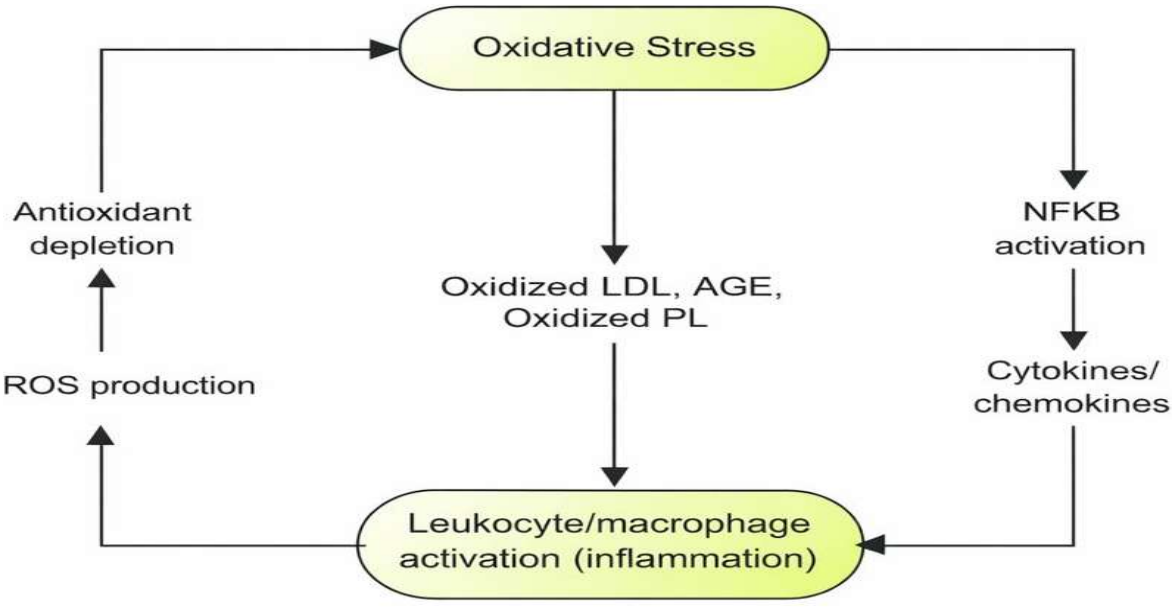

Figure 1. Management of Oxidative Stress by Leukocyte

HSP preventive action against drugs harmful cardiovascular effects may be mediated by many methods. HSP could prevent drugs -aggravated atherosclerotic plaque formation by reversing the higher ox LDL net absorption in macrophages, which raises the risk for cardiovascular events –p3linked to atherosclerotic plaque formation. HSP may therefore be a candidate drug for reducing the elevated risk for cardiovascular diseases (Koga *et al*., 2020). As a result, it is believed that HES may be able to reduce the increased risk of cardiovascular disease caused by drug (Koga *et*

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al., 2020). Cardiac hypertrophy is the heart's adaptive increase in cardiac mass in response to various types of stress. The reactivation of the fetal gene program a rise in myocardial cell size, a higher degree of sarcomere organization, changes in gene transcription and translation that result in increased protein synthesis are the molecular characteristics of cardiac hypertrophy. One of the main variables that contribute to the development and progression of cardiac hypertrophy is oxidative stress. The heart size and HW/BW ratio in the isoproterenol-administered rats were significantly reduced by pretreatment with hesperidin (Velusamy *et al*., 2020).

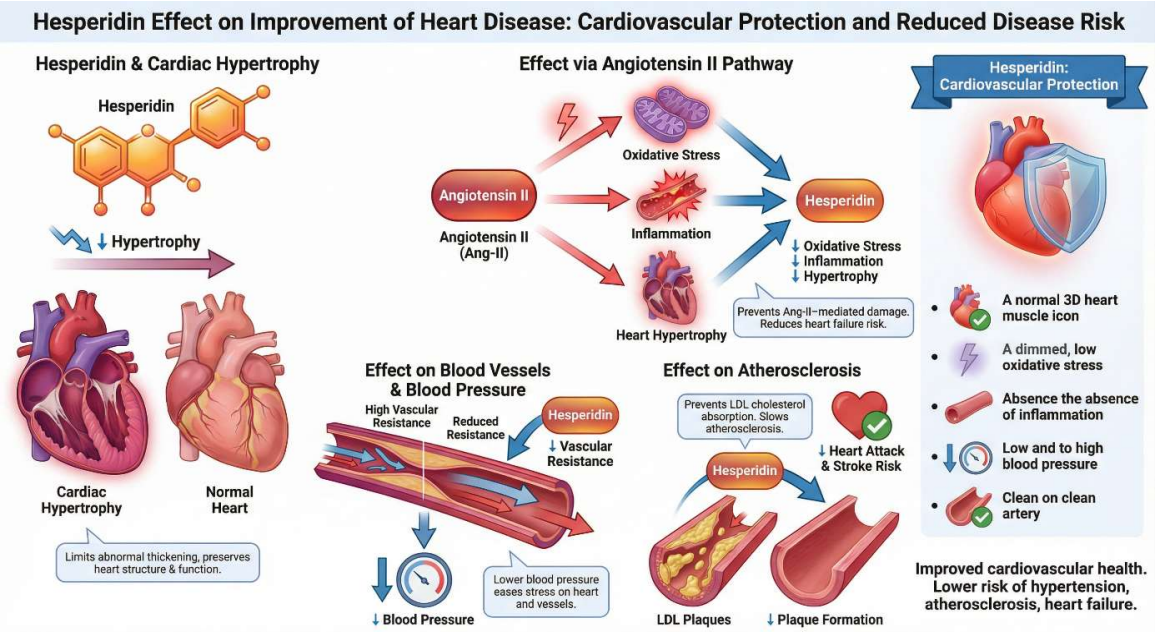

Figure 2. Hesperidin effect on improvement of heart disease

Heart remodeling is caused by the adaptive process of heart hypertrophy. While pathological hypertrophy is visible in response to diseases like hypertension, endocrine imbalance, and myocardial infarction, healthy hypertrophy is induced by pregnancy and exercise. Long-term hypertrophy is linked to a rise in the death rate from cardiovascular disease. In diabetic rats, HES also have cardio protective effects against ischemic heart disease through a PPAR route (Bhargava *et al*., 2019). Reactive oxygen species (ROS) can function as second messengers to control common cellular functions like signal transduction, gene expression, and homeostasis. Produced ROS in the vascular system can result in the development of additional mercurial nitrogen classes which can result in cardiovascular problems and a loss of vascular wall integrity. HSP performs its antioxidant function by specifically scavenging free radicals and enhancing the antioxidant defense of cells. As a result, it guards against tissue damage from both internal (from oncogenes) and external (from radiation, inflammation, and toxins) (Olumegbon *et al*., 2022).

HSP causes vasodilation through nitric oxide (NO)-mediated hypotension (Hashemzaei *et al*., 2020). Small compounds known as natural products are created by living things as primary and secondary metabolites. They have a number of beneficial effects, including those that are anti-oxidant and anti-inflammatory. The main source of death across the globe is cardiovascular disease. The main contributing factor to these diseases is hypertension. Because of their lower expense and fewer side effects, the use of medicinal herbs is particularly important.

Therapeutic Effect of Hesperidin on CVS

The purpose of this study is to investigate any potential cardio protective effects of HSP on isoproterenol (ISO)-induced myocardial ischemia. Myocardial architectural changes were evaluated using an electrocardiogram and heart histological changes. Using kits, it was possible to measure the levels of inflammatory cytokines as well as their activity as markers of oxidative stress (Liu *et al*., 2021a). Increased oxidative stress, particularly reactive oxygen species (ROS), which are crucial in the pathogenesis of oxidative myocardial damage and subsequent cardiac dysfunction, is highly associated with IHD. HSP modulates oxidative stress, inflammation, and apoptosis via Sirt1/Nrf2 pathway activation to counteract ISO-induced myocardial ischemia (Liu *et al*., 2021a). HSP preventive action against unknown harmful cardiovascular effects may be mediated by many methods. HSP could prevent aggravated atherosclerotic plaque formation by unknown factor by reversing the higher ox LDL net absorption in

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macrophages, which raises the risk for cardiovascular events linked to atherosclerotic plaque formation. HSP may therefore be a candidate drug for reducing the elevated risk for cardiovascular events (Koga *et al*., 2020). The development and progression of cardiac hypertrophy is oxidative stress. Isoproterenol (5 mg/kg body weight) subcutaneous injections were given for seven days to induce cardiac hypertrophy (Velusamy *et al*., 2020). The heart size and HW/BW ratio in the isoproterenol-administered rats were significantly reduced by pretreatment with hesperidin (Velusamy *et al*., 2020). HSP defend against cardiotoxicity brought on by ATO by preventing oxidative stress, along with the ensuing inflammation and apoptosis. The underlying findings have a strong connection to the control of the p62-Keap1-Nrf2 signaling pathway (Jia *et al*., 2021). Hesperidin treatment, on the other hand, caused a significant reduction in vascular congestion, perivascular inflammation, and hemorrhage in the alcohol-fed group, indicating an ameliorative impact. However, additional research is necessary to confirm the value of this flavonoid as a cardio protective and therapeutic agent as well as to specify its optimal application circumstances and doses. HSP may have a possible cardio protective impact in persistently ethanol-induced cardiotoxicity (Gaballah *et al*., 2019). Natural substances are regarded as cutting-edge therapeutic agents for the treatment of cardiovascular diseases, and they have attracted a lot of interest (Hashemzaei *et al*., 2020).

Hesperidin and Atherosclerosis

Atherosclerosis is a vascular pathology that is the cause of the majority of cardiovascular ischemic events occur silently as a chronic illness. The integrity of the endothelial barrier is determined by the presence of intercellular junction complexes i.e. junctional adhesion molecules (Tejada *et al*., 2020). A popular and efficient medication for quitting smoking is varenicline. Experimental data demonstrating varenicline raises the risk of cardiovascular events was previously reported by us. In apolipoprotein E knockout (ApoE KO) mice, varenicline advances the formation of atherosclerotic plaque. Hesperidin prevented worsening effects on ApoE KO mice's whole aorta, aortic arch, and aortic root. Hesperidin also blocked the upregulation of CD36 and LOX-1 scavenger receptors and downregulation of ABCA1 and ABCG1 cholesterol efflux transporters in RAW 264.7 cells, providing protection against varenicline-enhanced oxLDL net absorption (Koga *et al*., 2020). HSP preventive action against varenicline's harmful cardiovascular effects may be mediated by many methods. HSP could prevent varenicline-aggravated atherosclerotic plaque formation by reversing the higher oxLDL net absorption in macrophages, which raises the risk for cardiovascular events linked to atherosclerotic plaque formation. HSP may therefore be a candidate drug for reducing the elevated risk for cardiovascular events associated with varenicline (Koga *et al*., 2020). Citrus flavonoid hesperidin has many health benefits, including being anti-oxidant, anti-inflammatory, anti-diabetic, cardioprotective, neuroprotective, and anti-cancer. As a result, we believe that HSP may be able to reduce the increased risk of cardiovascular disease caused by varenicline (Koga *et al*., 2020).

Myocardial and Ischemic Heart Disease

Cardiac hypertrophy is the heart's adaptive increase in cardiac mass in response to various types of stress. The re activation of the fetal gene program, a rise in myocardial cell size, a higher degree of sarcomeric organization, changes in gene transcription and translation that result in increased protein synthesis are the molecular characteristics of cardiac hypertrophy. One of the main variables that contribute to the development and progression of cardiac hypertrophy is oxidative stress. Isoproterenol (5 mg/kg body weight) subcutaneous injections were given for seven days to induce cardiac hypertrophy (Velusamy *et al*., 2020). There were four groups of animals: (1) rats pretreated with hesperidin (received hesperidin suspended in 0.5% methyl cellulose orally for 30 days), (2) hypertrophy-induced rats (received isoproterenol hydrochloride 5 mg/kg body weight, subcutaneously for 7 days), (3) control rats (received vehicle alone), and (4) rats given isoproterenol 5 mg/kg body weight, subcutaneously for 7 days. The heart size and HW/BW ratio in the isoproterenol-administered rats were significantly reduced by pretreatment with hesperidin (Velusamy *et al*., 2020). HSP suppresses inflammation after ischemia and prevents coronary heart disease and stroke (Alikhani *et al*., 2022). HSP naturally has the capacity to scavenge oxygen radicals and iron atoms. HSP suppresses post-ischemic inflammation and guards against arterial heart disease and stroke (Alikhani *et al*., 2022). Myocardial infarction continues to be the leading cause of mortality world-wide. In this regard, the cardio- protective role of HSP on isoproterenol-induced myocardial ischemia has been reported. It reduced lipid peroxidation and antioxidant status in experimental animals that were exposed to subcutaneous injections of isoproterenol (Sharifi-Rad *et al*., 2020).

Hesperidin and Hypertension

HSP is an important natural flavonoid that finds most of its origin in plants. By the deferment of HSP hydrolysis. It is also said to be widely present in citrus fruits, which are historically known for usage as they have a high vitamin content. Biological properties flavonoids. In recent years, HSP is said to have anti-oxidative, other pharmacological effects such as anticancer and much more anti-atherogenic activities. According to previous

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research, the protective effect of HSP against cardiovascular disease is its major property. This is due to the antioxidant nature of it thus making its biological activity depend on its ability as an readily penetrate the phospholipid bilayers to detect and destroy free oxygen radicals (Liu *et al*., 2021b). HSP has been evaluated for its anti-hypertensive effects because hypertension is a risk factor of cardiovascular disease. Several studies have demonstrated experimental that hesperidin could regulate blood pressure by vasodilation, RAS modulation and enhancing endothelial function.

A group of physiological and metabolic disorders known as the metabolic syndrome (MS) include insulin resistance, central obesity, hypertension etc. In order to make a clinical diagnosis of MS, at least three of these anomalies must be present. HSP is a significant flavanone glycoside and a type of flavonoid that is primarily present in all citrus fruits. Numerous studies assert that there is proof of hesperidin's positive effects on health (Prasatthong *et al*., 2021). Hesperidin could reduce Ang II-induced cardiac fibrosis and inflammation (Zhang *et al*., 2020). Hesperidin is sufficient to effectively limit Ang II-induced myocardial hypertrophy and remodeling because it can significantly improve Ang II-induced systolic dysfunction and reduce hypertension. HSP can reduce heart hypertrophy brought on by Ang II, and it may do so by inhibiting the hypertrophy signaling pathway as well as oxidative stress and inflammation. HSP was effective in reducing signs of Metabolic syndromes which include hypertension and improvement in cardiac activity by reducing hypertrophy. These beneficial effects on the heart were associated with the restoration of the cardiac health by the active effects of hesperidin. The ROS are removed by taking HSP and preventing the body against certain health issues. Studies confirmed that oxidative stress and inflammation are close relation heart toxicity and that HSP possess ameliorative effects against toxicity. The modulatory effects of HSP are likely owing to the alleviation of oxidative stress, inflammation and markers of cardiotoxicity (Zhang *et al*., 2020).

Among the glycosides of flavonoids, hesperidin as a main flavanone has demonstrated antihypertensive property along with anti-oxidant and therapeutic actions. In order to reveal uncertainty of the disease caused by the reaction. HSP remarkable suppression of Metabolic changes with venous endothelial dysfunction and remodeling. HSP significantly reduced the development of oxidative stress and inflammation due to HFFD by decreasing plasma level and aortic superoxide anion production, as well as by inhibiting the tumor necrosis factor expression of in the thymus, spleen. Endothelial nitric oxide synthase andAdipoR1 metabolite. HSP also showed an increase in eNOs protein expression. These findings indicated that HSP has an ameliorative effect on the vascular dysfunction and remodeling observed in rats with oral hyper insulinemia N1. The possible underlying mechanism could include a decrease in the generation of reactive oxygen species and subsequent inflammation, while bringing back expression levels of eNOS expression(Apaijit *et al*., 2022a).

Hesperidin and Cardiac Hypertrophy

Cardiac hypertrophy is the heart's adaptive increase in cardiac mass in response to various types of stress. The re activation of the fetal gene program, a rise in myocardial cell size, a higher degree of sarcomere organization, changes in gene transcription and translation that result in increased protein synthesis are the molecular characteristics of cardiac hypertrophy. One of the main variables that contribute to the development and progression of cardiac hypertrophy is oxidative stress. Isoproterenol (5 mg/kg body weight) subcutaneous injections were given for seven days to induce cardiac hypertrophy (Velusamy *et al*., 2020). The heart size and HW/BW ratio in the isoproterenol-administered rats were significantly reduced by pretreatment with hesperidin (Velusamy *et al*., 2020).

Dietary intake of HSP is linked with the decreased incidence of coronary heart disease. Different mechanisms are considered to be involved in broad and nonspecific effects of flavonoids on the cardiovascular system (Sharifi-Rad *et al*., 2020). The formation of new fragile and leaky vessels that invade the expanding intima contributes to enlarge the necrotic core increasing the vulnerability of the plaque. The lesion along with the main morphological characteristics that predispose to plaque rupture, and discuss the multifaceted mechanisms which did platelet activation and subsequent thrombus formation (Tejada *et al*., 2020).

Anti-Inflammation and Anti-Oxidant

The orange peel contains the flavonoid glycoside hesperidin (HSP), which is an antioxidant (Jia *et al*., 2021). 50 mice were divided into five groups at random. Mice received intraperitoneal injections of 7.5 mg/kg/day of ATO and concurrent oral administration of HSP at doses of 100 or 300 mg/kg/day. For analysis, blood and heart tissues were taken. In addition, evaluated in heart tissues were the levels of reactive oxygen species (ROS). HSP have the ability to remove ROS and free radicals that are linked to a number of illnesses and tissue damage, including cancer, ageing, and atherosclerosis. HSP has been shown to have anti-inflammatory, anti-carcinogenic, anti-oxidant, and anti-allergic properties (Varışlı *et al*., 2022). HSP is a naturally occurring flavonoid that is derived from citrus fruits and has been shown to have numerous anti-inflammatory and antioxidant actions. In addition to lowering high blood pressure (BP), HSP also reduced the expression of TNF-, As it is can be seen in table.

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Table 1. Hesperidin effect on different study objects, Route of Exposure and Results

Study Object	Disorder	Route of exposure /Dose	Methodology	Result	References
Mice	Iron overload-induced cardiac dysfunction	IP, 100 mg/kg/day × 2 weeks	N=84, low/high HSP groups	HSP reduced inflammation & protected heart	(Alikhani *et al.*, 2022)
Male Sprague-dawley rats	HFFD-induced vascular dysfunction	Oral, 30 mg/kg/day	HFFD + fructose, 16 wks	HSP alleviated vascular dysfunction & remodeling	(Apaijit *et al.*, 2022a)
Mice	Ang II-induced cardiac hypertrophy	Infusion, 1000 ng/kg/min	4 groups (Sham, HSP, Ang-II, HSP+Ang-II)	HSP inhibited hypertrophy, fibrosis, oxidative stress	(Zhang *et al.*, 2020)
Adult male Kunming mice	Isoproterenol-induced cardiac injury	Injection, 25–50 mg/kg/day	5 groups incl. control & HSP	HSP protected via Sirt1/Nrf2, anti-apoptotic effect	(Liu *et al.*, 2021a)
ApoE KO mice	Atherosclerosis (varenicline-induced)	High-fat diet	ApoE KO (8 wk)	HSP reduced oxLDL uptake, protected against plaques	(Koga *et al.*, 2020)
Spontaneously hypertensive rats	Hypertension	Oral, 50 mg/kg/day, 20 wks	Mikan tea with HSP	↓ SBP (~60 mmHg), no receptor changes	(Gao *et al.*, 2020)
Male Wister rats.	ISO-induced hypertrophy	Subcutaneous, 5 mg/kg × 7 d	HSP intervention	HSP enhanced Nrf2, reduced remodeling	(Velusamy *et al.*, 2020)
Male kunning Mice	ATO-induced cardiotoxicity	Oral HSP (100–300 mg/kg) + ATO IP	5 groups	HSP ↓ oxidative stress & inflammation, ↑ antioxidants	(Jia *et al.*, 2021)
Albino Rats	Ethanol-induced cardiotoxicity	Oral HSP	Control, ethanol, ethanol+HSP groups	HSP cardioprotective vs ethanol	(Gaballah *et al.*, 2019)
male albino Wister rats	ISO-induced cardiac hypertrophy	Oral HSP (200 mg/kg) ± enalapril	6 groups	HSP + enalapril protective effect	(Bhargava *et al.*, 2019)
Rats	Radiation-induced cardiac injury	Oral HSP (100 mg/kg)	4 groups, pre-radiation	HSP reduced troponin-I, protected heart	(Sajadi *et al.*, 2021)
Swiss mice	Sorafenib-induced cardiotoxicity	Oral HSP (50 mg/kg)	4 groups	HSP mitigated toxicity (TLR4/NLRP3)	(Zaafar *et al.*, 2022)
Wister rats	Exercise-induced oxidative stress	Oral HSP (200 mg/kg)	Exhaustion test	HSP improved antioxidant status, performance	(Estruel-Amades *et al.*, 2019)
Male Sprague–Dawley rats	HFD-induced metabolic syndrome	Oral HSP (30 mg/kg)	HFD model	HSP reduced LV hypertrophy & dysfunction	(Prasatthong *et al.*, 2021)
Wister rats	DEP-induced cardiac stress	Oral HSP (200 mg/kg)	8 groups	HSP protected vs oxidative stress & inflammation	(Olumegbon *et al.*, 2022)
Rats	NaF-induced cardiotoxicity	Oral gavage	10–12 wk rats	HSP ↑ antioxidants, ↓ lipid peroxidation	(Varışlı *et al.*, 2022)
Rats	Renal artery stenosis-induced HTN	Oral HSP (50 mg/kg)	Supplementation	HSP ↓ BP via anti-inflammatory effects	(Khidr *et al.*, 2020)
Male Sprague Dawley rats	DOX-induced cardiomyopathy	Oral HSP (50 mg/kg) ± Vit E	7 groups	HSP improved cardiac histology	(Donia *et al.*, 2019)
Healthy male amateur cyclists	Athletic performance	Oral, 500 mg	18–50 yrs	HSP improved anaerobic effort	(Martínez-Noguera *et al.*, 2019)
Male wistar rats	HFD-induced hypertension	Oral HSP (200 mg/kg) ± crocin	7 weeks	HSP ↓ SBP; crocin no effect	(Hashemzaei *et al.*, 2020)

COX-2, and PG-E2 and lessened oxidative stress by raising glutathione reductase (GSH) and lowering malondialdehyde (MDA). HSP works to reduce inflammation and oxidative stress, two processes that can damage many cells and organs (Khidr *et al*., 2020). ROS generation has been associated with activating pro-inflammatory and stress signaling pathways. Among these NF-κB signaling has been reported as the main signal transduction pathway involved in the regulation of the genes and activation of some of the pro-inflammatory cytokines containing TNF-α and iNOS. Studies confirmed that oxidative stress, inflammation, apoptosis and autophagy are close relation with NaF induced heart toxicity and that HSP possess ameliorative effects against this NaF-induced toxicity. The modulatory effects of HSP are likely owing to the alleviation of oxidative stress, apoptosis, autophagy, inflammation and markers of cardiotoxicity (Varışlı *et al*., 2022). HSP is a flavonoid present in high concentration in citrus species and has numerous biological properties, principally antioxidant and anti-inflammatory. Several studies have been performed in order to evaluate the effects of hesperidin as anti-inflammatory agent using cellular and animal models and few clinical trials. HSP treatment decreased inflammatory mediators and exerted significant antioxidant effects. The molecular basis for its anti-inflammatory effects seems to be mediated by signaling pathways especially the nuclear factor κβ pathway.

Hesperidin effect on heart

Iron overload in the heart may lead to ventricular dilatation, systolic dysfunction, arrhythmias, diastolic dysfunction etc. Patients suffering from cardiac diseases or those in need of blood transfusion get special consideration. In this study it is investigated the quenching activity of HSP, against iron-induced oxidative damage

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in the hearts of mice with iron overload. In this case, 84 mice were prepared by injecting iron into all except the control group, which helped to induce iron overload. Lastly, the concentration of antioxidant enzymes such as superoxide dismutase and catalase were checked in the removed hearts mouse. Additionally, the level of malondialdehyde, which reflects the extent of lipid peroxidation, was recorded as well. The structural changes in cardiac actomyosin. HSP performed better as an iron chelator chemical than desferal. By lowering the quantity of iron deposited, hesperidin—the best antioxidant compound—was able to increase the activity of antioxidant enzymes (Alikhani *et al*., 2022). HSP, the flavanone glycoside, has been demonstrated to be good for lowering high blood pressure, controlling free radicals, and decreasing inflammation. Male Sprague- Long-Evans rats got a high dose of fructose at a rat concentration of 15% in drinking water along with high-fat diet for 16 weeks. HFFD-fed rats were taking antithrombotic medication, hesperidin (30 mg/kg/day), or the control drug, for the last 4 weeks (Apaijit *et al*., 2022b). The term 'hesperidin' (HSP) refers to a natural active compound from citrus peel and some other citrus fruits that has been found having many protective effects. Among such protective effects are potent antioxidant and anti-inflammatory actions. The final objective is to assess the restorative role of HSP in attenuating RVH by utilizing an in-vitro 2K1C RAS model and evaluating whether reparation of renal cell injury is possible by targeting oxygen free radicals. Oral Supplementation of HSP in rats whose renal artery is stenosed (50 mg/kg body weight). Blood pressure measurement used and a few other oxidative stress markers and inflammatory mediators such as tumor necrosis factor-α (TNF-α), cyclooxygenase- 2(COX-2) and prostaglandin-E2 (PG-E2) were taken. Results: The BP was down-regulated after the nervous system was stabilized and the expressions of HSP, TNF-α, COX-2 and PG-E2 also decreased, while the anti-oxidative stress effect was demonstrated by the increase of glutathione reductase (GSH) and decrease of malondialdehyde (MDA). The results indicate that hesperidin is able to inhibit inflammation and oxidation processes, fight the ones which lead to many damage on a cell and organ level *(*Khidr *et al*., 2020). There have been reports of toxicities to the brain, thyroid, kidney, liver, and testicular tissues resulting from excessive fluoride ingestion. HSP is an antioxidant with anti-inflammatory, anti-allergenic, and anti-carcinogenic properties. Studies on the harmful effects of sodium fluoride (NaF) on cardiac tissue are now being conducted at the biochemical and molecular levels are constrained. The purpose of this study was to assess the protective effects of HSP against the toxicity of NaF on rats' hearts in vivo by looking at changes in pro-inflammatory markers, oxidative injury markers, and GSH), expressions of apoptotic genes, levels of autophagic markers, expression levels of cardiological markers. Treatment with HSP reduced the NaF-induced cardiotoxicity (Varışlı *et al*., 2022).

Air particle matter exposure increases oxidative stress and the inflammatory response; it has been related to cardiovascular disease and atherosclerosis. The purpose of this investigation is to ascertain whether using hesperetin (HSP) as a therapeutic agent may lessen the pro-inflammatory and oxidative effects of diesel exhaust particles on the cardiovascular system in Wistar rats. DEP was n-hexane fraction (hDEP) was extracted from an Iveco freight engine truck. Eight groups were created from forty Wistar strains of male albino rats that were six weeks old: The other groups received either the Standard Reference Material 2975 (0.064 mg/kg hSRM) or the n-hexane extract of DEP (0.064 or 0.640 mg/kg hDEP) in the presence or absence of 200 mg/kg HSP. In addition, inflammatory cytokines, PCSK-9, low-density lipoproteins, antioxidant and thrombosis also play provoked role. The messenger RNA transcription for specific genes from heart and aorta were looked into by RT-PCR. In this approach, the protein-protein interaction is examined using the target molecular interaction in the computer system. Furthermore, fish extracts of DEP caused a significant ($p < 0.001$) elevation in serum lipid levels as well as, they significantly decreased the serum HDL levels. It also has effect on the CDs` and MDA levels, but it`s good news for the GSH. Similarly, the components present in the particulate extracts were the key contributors in the significant ($p < 0.001$) increase in the expressions of the pro-inflammatory genes in the heart and the aorta as well as significant decrease in the expressions of the IL-10 and LDL-R genes. The inclusion of HESP before treatment could reverse all the presented alterations. Research suggests that HSP is able to counteract the DEPs damage by decreasing the levels of oxidative stress and inflammation in the cardiovascular system (Olumegbon *et al*., 2022).

This study aimed to determine the ability of hesperidin, a flavonoid found naturally, to reduce the harm of myocardial ischemia and reperfusion (I/R) in diabetic rats. The male Wistar-rats who were diabetic were assigned to the 5 groups among them and the saline solution, healing (100 mg/kg/day; IR-Hesperidin), and GW9662 (PPAR-c receptor antagonist) were given as oral administration once daily for 14 days. On the 15th day, both IR-control and IR-treatment group rats underwent LAD coronary artery occlusion for 45 minutes and then one hour of reperfusion. Heart rate, blood pressure, and breathing rate were registered. Rats were sacrificed; hearts were harvested for biochemical, histopathological, ultrastructural and immunohistochemistry analysis. In IR-control group, pathological ventricular dysfunctions were noted along with a greater than normal protein Bax expression. The cardiac injury markers reduced with decreased lactate dehydrogenase activity and increased levels of CK-MB. Besides, the markers of lipid peroxidation thiobarbituric acid reactive substances and TNF-a also increased. A significant reduction in mean arterial pressure, a decrease in left ventricular end-diastolic pressure, and the improvement of not only inotropic and lusitropic function of the heart but also both systems) were observed in

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Hesperidin pre-treatment as compared to the IR-control.

HSP treatment further showed a significant reduction in the amount of thiobarbituric acid reactive substances (TBARS), and restored the value of lactate dehydrogenase (LDH) to its normal level. Among the apoptotic pathways, it was found that HSP inhibited the Bcl-2 protein and stimulated the Bax protein expression. Also the histopathological and the ultrastructural studies confirmed the beneficial action of hesperidin again (Agrawal *et al*., 2014). HSP anti-hypertensives effects behind the consumption of Mikan tea have been evaluated and found to be as good or better than existing drugs. Checking out the effect of magnolia bark in 8-week-old SHRs (spontaneously hypertensive rats) at a dose of 50mg/kg body weight for both, over 20 weeks. The probe is over, outcomes from our group denote a reduction of pressure which is impressive and significant ($P < 0.05$) on the systolic blood pressure level of the participants. The treating of the trained SBP (SBP = ~60 mmHg) in the SHR volunteers through the intake of hesperidin and Mikan tea was recorded. The one having participated in running and cycling activities showed a different heart rate from those who did not. HSP induced the improved vascular response via the NO and KrC mechanisms.

In 28-week-old SHRs. Efforts toward receptor expression revealing the driver of mitogen-guided vascular activity are needed. The work over by Torra *et al*. in 2021 clearly indicated that the same research group had found out that the expression of Mas receptor (MasR) in the aorta of hesperidin-administered SHRs was upregulated. However, no changes were observed in these receptors in angiotensin II-type1 and type 2. An increase in cAMP decreases of angiotensin II level in aorta were observed in sham-operated rats after hesperidin administration which sprung them into action again. HSP has the role of maintaining the regulation of vessels pathway through the increasing value of MascR/AMP axe.

2. CONCLUSION

In conclusion, this review paper presents a comprehensive evaluation of the existing literature on the potential effects of HSP on heart disease. Therapeutic effects of HSP are associated with increased adiponectin action and nitric oxide bioavailability and suppressed oxidative stress and inflammation. HSP is a natural flavonoid found in abundance of citrus fruits, and it shows interesting cardiovascular protective properties due to its antioxidant activities both anti-inflammatory activity and lipid lowering. Preclinical and clinical studies revealed putative cardio protective effects, including positive endothelial function, stopping of atherosclerosis as well as pressure normalization. Although hesperidin seems to be safe and tolerated by many people, further studies are needed regarding its long-term safety dosing in various populations. The use of HSP as an adjunctive tool to the conventional pharmacological cardiovascular interventions is promising in prevention and management of heart disease. HSP exhibits promising anti-oxidant, cardio protective and therapeutic properties through its various mechanisms of action, which contribute to the prevention and management of heart disease. HSP supplementation improves exercise performance, maintains endogenous antioxidant defenses in anti-inflammation and prevents the oxidative stress. HSP shows its anti-hypertensive activity by elevating inflammation and oxidation process which occur in certain number of cells and damage in vital organ. However, further preclinical and clinical studies are needed to elucidate its optimal therapeutic dose, bioavailability, and long-term effects. Overall, HSP holds great promise as a natural compound for the prevention and treatment of heart disease, warranting continued research and exploration of its clinical potential. Natural Compounds such as hesperidin should be more in use as it prevents the body against acute and chronic diseases. Protect the body against different possible health effects which can disturb the normal physical health of the human being. HSP act as the protective shield and play an important role in carrying out certain activities. It filters the body the toxins from the body which do inflammation in the cell.

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