



Review Article

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A comprehensive review on the impact of hesperidin and its aglycone hesperetin on metabolic dysfunction-associated steatotic liver disease and other liver disorders

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Abstract

The purpose of this review is to examine the effects of hesperidin and hesperetin on liver disorders. Metabolic dysfunction-associated steatotic liver disease is a complicated disorder influenced by many factors, including inflammation, diabetes and obesity. Currently, the most prominent treatment method is lifestyle changes. If left untreated, it can progress to cirrhosis, liver fibrosis and liver cancer. Hesperidin, which is a flavanone glycoside polyphenolic plant compound, belongs to the flavanone class and was first isolated from citrus peel. Hesperidin includes aglycone hesperetin and rutinose sugar. It is the most dominant form of flavonoid in citrus fruits. In our review, we discuss the effects of these phytochemicals on liver diseases, focusing on their relationship with inflammation, blood sugar regulation and blood lipids. Hesperidin and hesperetin are seen as promising agents for many diseases. Their antioxidant and anti-inflammatory properties support this view. Although their low water solubility limits their potential effects, many studies have demonstrated their benefits. They are thought to play an effective role in inflammatory processes, particularly in liver diseases. More studies are required to find the optimum dosage and to use them as a therapeutic agent for the liver.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously called non-alcoholic fatty liver disease, is a disease with a global prevalence around 25% and increasing⁽¹⁾. MASLD is caused by the accumulation of triacylglycerol in hepatocytes over time and is characterised by fatty liver (hepatic steatosis) without any significant signs of inflammation. MASLD is a disorder caused by a combination of sedentary lifestyle, high-calorie diet, genetic factors, physiological and metabolic factors⁽²⁾. Metabolic dysfunction-associated steatohepatitis (MASH) occurs with the progression of MASLD and the onset of an inflammatory process. The basis of the pathogenesis of MASH is the stress response to the excessive supply of nutrients to the liver, which promotes fibrosis and ultimately leads to cirrhosis⁽³⁾.

Hesperidin (HES), a polyphenolic plant compound, belongs to the flavanone class and was first isolated from citrus peel by the French chemist Lebreton in 1828⁽⁴⁾. Hesperidin, also known as hesperetin-7-*O*-rutinoside, is a flavanone consisting structurally of the aglycone form and the disaccharide rutinose⁽⁵⁾. The aglycone form is called hesperetin (HST)⁽⁶⁾. Various pharmacological effects of hesperidin are supported by different studies in the literature. Some of these effects are cardioprotective, anti-inflammatory, antidiabetic and antioxidant^(7–10).

In this review, we will discuss how hesperidin impacts liver health by examining its influence on inflammation, liver enzymes, lipid profile and blood sugar regulation, all of which are intricately linked to liver function.

Methods and materials

This narrative review is based on peer-reviewed articles. PubMed, Web of Science and Science Direct databases were used. Only animal studies were included in this review, covering the years between 2014 and 2024. The following keywords were used: 'hesperidin' OR 'hesperetin 7-*O*-rutinoside' OR 'hesperetin' OR 'hesperetin 7-*O*-glucoside' AND 'NAFLD' OR 'non-alcoholic fatty liver disease' OR 'liver fibrosis' OR 'NASH' OR 'fatty liver' OR 'non-alcoholic steatohepatitis'. The authors checked all parts of the article separately. In case of disagreement, the authors discussed for a common decision. As a result of this process, fourteen were identified (Table 2). Apart from these, some human studies related to the topic are also presented in Table 3.

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Table 1. Sources of hesperidin

Plant	Plant part	Concentration	Reference
<i>Citrus limonia</i>	Leaves and stems	3.2 g/kg	Soares <i>et al.</i> , 2015 ⁽¹⁰³⁾
<i>Citrus sinensis</i>	Leaves	13.8 g/kg	Soares <i>et al.</i> , 2015 ⁽¹⁰³⁾
<i>Mentha piperita</i>	Plant extract	504.2 mg/l	Najafian <i>et al.</i> , 2016 ⁽¹⁰⁴⁾
<i>Stevia rebaudiana</i>	Plant extract	493.4 mg/l	Najafian <i>et al.</i> , 2016 ⁽¹⁰⁴⁾
<i>Citrus limetta</i>	Pulp	0.62 mg/g	Damián-Reyna <i>et al.</i> , 2017 ⁽¹⁰⁵⁾
	Juice	27.3 mg/l	
	Seed	0.04 mg/g	
<i>Citrus reticulata</i>	Pulp	0.98 mg/g	Damián-Reyna <i>et al.</i> , 2017 ⁽¹⁰⁵⁾
	Juice	21.7 mg/l	
	Seed	0.09 mg/g	

Definition of hesperidin and hesperetin

Flavonoids are a group of polyphenolic structures present in citrus fruits, and they are divided into four groups: flavones, flavanols, flavanones and flavanols. Flavanones are predominantly present in citrus fruits such as oranges, grapefruits and lemons. Therefore, they are sometimes also referred to as citrus flavonoids or bioflavonoids⁽¹¹⁾.

The origin of the name hesperidin is based on the word 'hesperidium' used for citrus tree fruits⁽¹²⁾. Hesperidin is found in different concentrations in various foods⁽¹³⁾. Hesperidin is detected in citrus fruits, particularly in the peel parts such as zest and albedo, in larger amounts compared with seeds and juicy cells⁽⁴⁾. The predominant type of flavanone found in citrus fruits, HES, and its aglycone form HST are particularly abundant in sweet unripe oranges (*Citrus sinensis*) at high levels (1–2%)⁽¹⁴⁾. Hesperetin has similar values to hesperidin in plants because it is a metabolite of hesperidin. It is found in higher proportions in unripe fruits compared with ripe fruits. HES is also a bioflavonoid⁽⁴⁾.

Chemical properties of hesperidin

Hesperidin (hesperetin-7-rutinoside) is a polyphenolic compound of plant origin. Although it belongs to the flavonoid group, it is more specifically a flavanone⁽¹⁵⁾. Hesperidin is a flavanone glycoside that has an aglycone portion called hesperetin and a sugar portion called rutinoside (shown in Fig.1). In addition, hesperidin can be enzymatically converted to the aglycone hesperetin⁽¹⁴⁾.

Hesperidin is abundant in citrus fruits such as lemon, lime, tangerine, orange and grapefruit and is the most dominant flavonoid form in citrus fruits (Rutaceae family)^(5,16). Pure hesperidin is a tasteless and odourless molecule that occurs as long hair-like needles that are skin-coloured or light yellow. Its melting point is between 258°C and 262°C. Its molecular formula is C₂₈H₃₄O₁₅ and its molecular weight is 610.57 Da. It is slightly soluble in methanol and almost insoluble in chloroform, acetone and benzene⁽¹⁷⁾. However, it is easily soluble in pyridine. Since it

can form complex crystals with other glycosides of similar structure, its solubility and other physical properties are significantly affected. Therefore, it is not easy to obtain in pure form. For purification, it must be washed with hot water, extracted with 95% methyl alcohol and then crystallised.⁽¹⁸⁾

Glucosyl hesperidin (G-hes) is water soluble, being 10 000 times more soluble in water than hesperidin alone. In addition, it is absorbed much faster and more effectively⁽¹⁹⁾. This form, G-hes, was synthesised by Hijjiya⁽²⁰⁾ and colleagues using regioselective transglucosylation with cyclodextrin glucanotransferase from *Bacillus stearothermophilus*^(19,21). G-hes and hesperidin exhibit similar effects⁽²²⁾. For example, in one study, when HES and G-hes were administered to mice at equal doses, similar improvements were observed in serum cholesterol profiles⁽²³⁾. In another study, G-hes was found to have anti-obesity and antidiabetic effects. G-hes can easily convert to hesperidin via the α -glucosidase enzyme⁽¹⁹⁾.

Hesperidin can be easily isolated from products of citrus processing, making it economical. Conversely, in industry, hesperetin can be produced using bacterial enzymes to modify hesperidin. This results in a more complex aglycone (hesperetin) production process than obtaining hesperidin from the outset, thereby incurring production costs⁽¹⁴⁾.

Sources of hesperidin

Apart from citrus fruits, hesperidin has been detected in many different plant genera, including within the families Fabaceae and Betulaceae⁽¹⁸⁾. Hesperidin concentrations in some plant parts are summarised in Table 1.

The Mediterranean diet is also a high source of hesperidin and hesperetin. It is a diet rich in vegetables and fruits that is frequently recommended for patients with chronic diseases⁽²⁴⁾. Therefore, it is very rich in polyphenols, especially citrus bioflavonoids⁽²⁵⁾. Following consumption of the Mediterranean diet, an increase in the plasma levels of hesperidin, hesperetin, naringin and routine flavonoids was observed⁽²⁶⁾.

Stability of hesperidin

Majumdar *et al.* found that the concentrations of hesperidin aqueous solutions did not change for 2 months in the pH range between 1 and 7.4 in samples, unlike for samples with pH 9⁽²⁷⁾. The degradation rate constants, most likely by alkaline hydrolysis, were 0.03 and 23 at pH 9 at 25°C and 40°C, respectively. This indicates hesperidin can undergo alkaline hydrolysis when exposed to elevated pH levels and higher temperatures.

Zhang and colleagues studied how storage conditions and heat processing during pasteurisation affect hesperidin levels in orange juice⁽²⁸⁾. Although hesperidin levels decreased at both room temperature and 4°C, the decrease was faster at room temperature. The study concluded that, as the storage time of orange juice increases, hesperidin could precipitate, leading to a decrease in its concentration. It is noted that the decomposition of vitamin C may be responsible for the precipitation of hesperidin as the storage time prolongs.

A study on the stability of hesperidin was carried out by Bisega *et al.* Honey, onion and apple samples were used in the study⁽²⁹⁾. The apple matrix largely stabilised these compounds, while the highest degradation occurred in the honey samples. Therefore, it was concluded that hesperidin degradation may also be related to the food matrix.

Table 2. Effects of hesperidin and hesperetin on liver diseases

	Disease	Study group	Treatment	Time	Results
Li <i>et al.</i> , 2021 ⁽⁴⁸⁾	MASLD *induced with HFD	Male Wistar rats	Hesperetin • 100 mg/kg/d • 300 mg/kg/d Orally consumed	16 weeks	<ul style="list-style-type: none"> Hesperetin reduced oxidative stress. Hesperetin reduced TC, TG and LDL levels.
Xie <i>et al.</i> , 2022 ⁽⁶⁸⁾	MASLD *induced with HFD	SD rats	Hesperidin • 200 mg/kg Orally consumed	12 weeks	<ul style="list-style-type: none"> While hesperidin suppressed high-fat diet-induced body weight gain and hepatic steatosis, it did not affect serum TG, TC and LDL levels. Hesperidin reduced endoplasmic reticulum stress in THP-1 cells stimulated with high-fat diet.
Tang <i>et al.</i> , 2023 ⁽⁸³⁾	MASLD *induced with HFD	Wistar rats	Shuganzhi Tablet (SGZT) • SGZT (100 mg/kg/d) • SGZT (200 mg/kg/d) • SGZT (400 mg/kg/d) *Main metabolites in SGZT: Hesperidin, polydatin, naringin, emodin, specnuezhenide, saikosaponin A and resveratrol Orally consumed	12 weeks	<ul style="list-style-type: none"> Increased body weights after HFD decreased significantly with SGZT (200 and 400) treatment. No significant change was occurred in the SGZT-100 group. LDL-c and TG levels, which increased after HFD, decreased significantly with SGZT (200 and 400) treatment. HDL levels increased after treatment. In the SGZT 100, 200 and 400 treatment groups, hepatic steatosis was moderate or small. The circular vacuole was significantly reduced compared with the HFD group.
Li <i>et al.</i> , 2022 ⁽⁹⁰⁾	MASLD *induced with HFD	C57BL/6J mice	Hesperidin • LFD • HFD • HFD + hesperidin (%2- 1.6 g) Orally consumed	16 weeks	<ul style="list-style-type: none"> Mice receiving only the high-fat diet gained more weight than the other two groups. There was no significant difference between the final weights of the LFD and HFD + hesperidin groups. The lowest levels of TG, ALT, AST and LDL were found in LFD mice. The levels of the group receiving hesperidin were found to be lower than the HFD group. Hesperidin prevented fat accumulation in the liver.
Chen <i>et al.</i> , 2019 ⁽⁶⁹⁾	MASLD *induced with HFD	C57BL/6J mice	Hesperidin • HFD • HFD + hesperidin (150 mg/kg/d) • HFD + hesperidin (300 mg/kg/d) • Hesperidin (300 mg/kg/d) Orally consumed	12 weeks	<ul style="list-style-type: none"> There was no difference in weight between groups. Hesperidin treatment reduced TG and LDL levels but did not affect total cholesterol levels. Hesperidin treatment reduced liver steatosis. Hesperidin administration alone, without HFD, prevented fatty liver.
Nie <i>et al.</i> , 2024 ⁽⁹⁸⁾	MASLD *induced with HFD	C57BL/6J mice	Hesperidin • HFD • HFD + hesperidin (150 mg/kg/d) • HFD + hesperidin (300 mg/kg/d) • Hesperidin (300 mg/kg/d) Orally consumed	16 weeks	<ul style="list-style-type: none"> Body weight serum TG levels increased, TC, LDL, AST and ALT levels decreased and HDL levels increased with hesperidin treatment. Hesperidin showed a protective effect against MASLD by reducing hepatic fat accumulation.
Prasatthong <i>et al.</i> , 2021 ⁽¹⁰⁶⁾	Hepatic steatosis *induced with HFD	Rats with metabolic syndrome	<ul style="list-style-type: none"> Hesperidin <ul style="list-style-type: none"> o 15 g/kg o 30 mg/kg Metformin Metformin + hesperidin 	16 weeks	<ul style="list-style-type: none"> Less fat accumulation was observed in rats treated with hesperidin or metformin. Hesperidin and metformin ameliorated high-fat diet-induced dyslipidaemia and liver dysfunction in rats.
Li <i>et al.</i> , 2022 ⁽⁷⁴⁾	Liver fibrosis *induced with CCL4	C57BL/6J mice	Hesperetin derivative-16 • 25 mg/kg/d • 50 mg/kg/d • 100 mg/kg/d Orally consumed	4 weeks	<ul style="list-style-type: none"> HD-16 (25, 50 and 100 mg/kg) dose-dependently reduced collagen deposition caused by CCl4 treatment. HD-16 treatment increased SIRT3 expression in fibrotic livers.

(Continued)

Table 2. (Continued)

	Disease	Study group	Treatment	Time	Results
Chen <i>et al.</i> , 2017 ⁶¹	Liver fibrosis *induced with CCL4	C57BL/6J mice	Hesperetin derivative-14 <ul style="list-style-type: none"> • 25 mg/kg • 50 mg/kg • 100 mg/kg Orally consumed	Once every 2 weeks for 4 weeks	<ul style="list-style-type: none"> • HD treated mice with hepatic fibrosis dose-dependently inhibited hepatocyte necrosis, inflammatory cell infiltration and mouse liver fibrogenesis. • ALT, AST and ALP serum levels decreased. • Serum TGF-β1 and IL-1β levels decreased.
Zhu <i>et al.</i> , 2022 ¹⁰⁷	Liver fibrosis *induced with CCL4	C57BL/6J mice	Hesperetin derivative-14 <ul style="list-style-type: none"> • 25 mg/kg/d • 50 mg/kg/d • 100 mg/kg/d Orally consumed	6 weeks	<ul style="list-style-type: none"> • Hesperidin reduced CCL4-induced liver fibrogenesis. • Hesperidin reduced the expression of fibrogenic genes in activated hepatic stellate cells. • 50 and 100 mg/kg/d hesperidin treatments reduced ALT and AST levels.
Sukkasena <i>et al.</i> , 2021 ⁸⁵	Fatty liver disease *induced with HFD and ethanol	ICR mice	Intragastrically administered Hesperidin <ul style="list-style-type: none"> • 50 mg/kg/d • 200 mg/kg/d 	8 weeks (60 d)	<ul style="list-style-type: none"> • Hesperidin interventions reduced liver size and improved hepatic, morphological and histological features. • Both doses of intervention reduced TG levels. TG levels decreased more in the low-dose hesperidin group. • Hesperidin treatment suppressed inflammatory cytokines, improved mRNA expression of metabolic genes and improved the antioxidative system.
Yi <i>et al.</i> , 2023 ¹⁰⁸	Alcoholic liver disease *induced with ethanol	C57BL/6J mice	Citrus honey (CH) *contains 41 chemical components including hesperidin and hesperetin. Orally consumed <ul style="list-style-type: none"> • Low-dose CH (5 mg/kg) • Medium-dose CH (10 mg/kg) • High-dose CH (20 mg/kg) *Chow diet was applied for 13 weeks, followed by ethanol and CH treatment for 10 d.	10 d	<ul style="list-style-type: none"> • High- and medium-dose CH treatment led to improvements in ALT and AST levels. • Alcohol-induced liver damage was ameliorated by honey intake, and levels of cellular oedema and steatosis were reduced. • CH treatment (dose dependent) has shown some significant benefits in maintaining homeostasis of the gut microbiota and manipulating the gut microbiota to control the production of short-chain fatty acids.
Yuan <i>et al.</i> , 2023 ¹⁰⁹	Alcoholic liver disease *induced with ethanol	C57BL/6J mice	Hesperidin <ul style="list-style-type: none"> • 2 mg/d • 4 mg/d Orally consumed	10 d	<ul style="list-style-type: none"> • Hesperidin treatment decreased ALT, AST and TG levels. • Hesperidin reduced hepatic steatosis and inflammatory response in ethanol-exposed mice.
Ali <i>et al.</i> , 2023 ¹¹⁰	Hepatotoxicity *induced with Paclitaxel	Wistar rats	Hesperidin 10 mg/kg every other day Orally consumed	6 weeks	<ul style="list-style-type: none"> • ALT, AST, LDH, ALP and GGT levels, which increased after paclitaxel application, decreased with hesperidin treatment. • Hesperidin treatment reduced the increased lipid peroxidation in the liver. • The combination of hesperidin with rutin significantly reduced the damage caused by paclitaxel.

MASLD, metabolic dysfunction-associated steatotic liver disease; HFD, high-fat diet; LFD, low-fat diet; TC, total cholesterol; TG, triacylglycerol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; THP-1, the human leukaemia cell line-1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HD-16, hesperetin derivative-16; CCL4, carbon tetrachloride-4; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TGF- β 1, transforming growth factor beta 1; IL-6, interleukin-6; SIRT3, sirtuin 3.

Table 3. Randomised controlled studies of hesperidin and its effects on some diseases linked with MASLD

	Disease	Treatment	Time	Results
Cheraghpour <i>et al.</i> , 2019 ⁽⁸⁴⁾	MASLD	49 individuals with level 2 and 3 MASLD between the ages of 18 and 70 <ul style="list-style-type: none"> Intervention group ($n = 25$) = two capsules of hesperidin (each contains 500 mg), Control group ($n = 25$) = placebo (starch) *In addition, individuals were given healthy nutrition recommendations and physical activity recommendations.	12 weeks	<ul style="list-style-type: none"> Insulin and blood glucose levels decreased in both groups as a result of the interventions. However, there was no significant difference between the changes in the two groups. There were significant decreases in serum TG, total cholesterol and LDL levels in the hesperidin group. Compared with placebo, the reduction in serum TG and TC was significantly greater. Hepatic steatosis and fibrosis decreased in both groups, but there was a greater decrease in the hesperidin group.
Yari <i>et al.</i> , 2021 ⁽¹¹¹⁾	METs	98 adult participants <ul style="list-style-type: none"> Control group ($n = 25$) *those following the lifestyle intervention program (LIP) Flaxseed group ($n = 25$) *Those who consume 30 g/d of ground brown flaxseed and follow LIP Hesperidin group ($n = 24$) *those who consume 2 500 mg hesperidin capsules per day and follow LIP Flaxseed-hesperidin group ($n = 24$) *Those consuming 30 g/d ground brown flaxseed + two 500 mg hesperidin capsules and following LIP 	12 weeks	<ul style="list-style-type: none"> Serum TG levels decreased significantly compared with the baseline value in all groups except the control group. There was no difference in BMI between the groups. Flaxseed-hesperidin group was found to be significantly effective on glucose parameters. The combination of hesperidin and flaxseed has been found to have positive effects on METs.
Osama <i>et al.</i> , 2023 ⁽¹¹²⁾	T2DM	Patients older than 18 years using oral antidiabetic agents *Diabetic patients who have had symptomatic peripheral neuropathy for at least one month and have a Michigan Neuropathy Screening Instrument (MNSI) physical examination score of ≥ 2.5 . <ul style="list-style-type: none"> Control group ($n = 33$) Hesperidin group ($n = 32$) *500 mg twice a day Diosmin group ($n = 32$) *500 mg twice a day Hesperidin + diosmin group ($n = 32$) * 500 mg twice a day for each *For 7 d before the start of the study and throughout the study, the subjects continued their normal lifestyle and foods rich in citrus flavonoids were restricted.	12 weeks	<ul style="list-style-type: none"> Fasting plasma glucose decreased in all groups. Hesperidin and diosmin combination group showed the most significant decrease. The decrease in LDL levels was most clearly observed in the hesperidin and diosmin group. There was no significant difference between the groups in the increase in HDL levels. There was a significant decrease in MNSI in the hesperidin group ($p = 0.003$), diosmin group ($p = 0.015$) and hesperidin and diosmin combination group ($p < 0.001$).
Homayouni <i>et al.</i> , 2017 ⁽¹¹³⁾	T2DM	64 participants aged 30–65, who had diabetes for at least 3 years, who used oral antidiabetics, and whose BMI was greater than 30 kg/m ² . <ul style="list-style-type: none"> Control group ($n = 32$) *placebo capsule Intervention group ($n = 32$) * 500 mg hesperidin/d 	6 weeks	<ul style="list-style-type: none"> Hesperidin treatment improved antioxidant capacity and glycaemic control in patients with T2DM. Hesperidin reduced hyperglycaemia-induced oxidative stress. MDA levels decreased significantly in the hesperidin group.
Yari <i>et al.</i> , 2020 ⁽¹¹⁴⁾	MET	49 participants <ul style="list-style-type: none"> Hesperidin group *500 mg capsules twice a day ($n = 25$) Placebo group ($n = 24$) Patients were also recommended lifestyle intervention.	12 weeks	<ul style="list-style-type: none"> Hesperidin reduced serum TNF-α levels. Hesperidin improved oxidative stress and inflammation. Hesperidin significantly reduced fasting glucose levels and increased insulin sensitivity.

MASLD, metabolic dysfunction-associated steatotic liver disease; MET, metabolic syndrome; T2DM, type 2 diabetes; TC, total cholesterol; TG, triacylglycerol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; MDA, malondialdehyde; TNF- α , tumour necrosis factor- α .

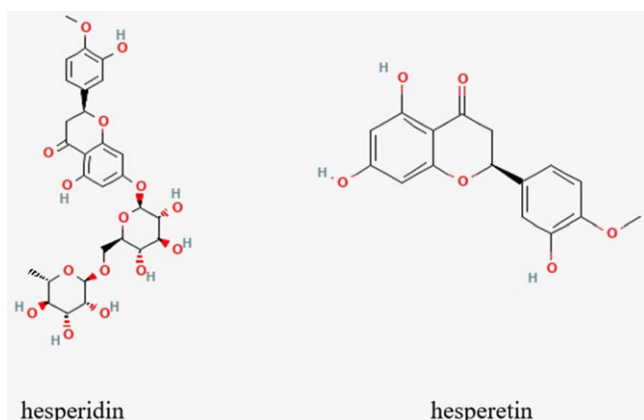


Figure 1. Chemical structures of hesperidin and hesperetin. This figure was created by PubChem.

Metabolism of hesperidin

Absorption and transport of hesperidin

The absorption and metabolism of citrus flavonoids in the intestine vary depending on their chemical structure; This significantly affects their bioactivity⁽³⁰⁾. The presence of polyphenols in the form of glycosides, where one or more sugar moieties are attached, contributes to their variable bioavailability⁽⁶⁾.

Hesperidin is a β -glucoside, whereas hesperetin is its aglycone form⁽¹⁴⁾. Absorption of glycosides and aglycones is different. The sugar residues markedly influence the absorption because free aglycones can be absorbed in the stomach, whereas the entire glycoside may not be absorbed⁽¹¹⁾. Flavonoid aglycones such as hesperetin are moderately hydrophobic and are relatively easier and faster to absorb from the lumen compared with flavonoid glycosides (hesperidin)⁽³⁰⁾. In studies in which hesperetin and hesperidin were consumed by healthy human subjects, the peak concentration in plasma occurred 4 h after consuming hesperetin, whereas for hesperidin-rich juices, the peak concentration was achieved after 7 h. This indicates faster absorption of hesperetin^(31,32).

The main absorption sites for flavanones are the small intestine and colon. In a study where naringenin was injected into different parts of the rat intestines to observe flavanone absorption, the absorption rates of naringenin were found to be similar in the duodenum (47%), jejunum (39%) and ileum (42%). The colon had the highest absorption rate (68%)⁽³³⁾.

The non-detection of hesperidin in human plasma or urine after oral consumption of hesperidin-rich orange juice supports the idea that hesperidin is broken down to hesperetin and related metabolites during absorption⁽³⁴⁾.

The reason that most ingested hesperidin is not hydrolysed by small-intestinal β -glucosidases is due to the presence of a routine component that requires its metabolism and absorption in the colon⁽³⁵⁾. It has been suggested that the rutinose molecule, hesperetin-7-rutinoside, is hydrolysed by the intestinal microbiota in the large intestine⁽⁶⁾. Hesperidin is absorbed in the colon via the microbiota, where it is converted into the aglycone form, hesperetin. This is then metabolised and hydrolysed⁽³⁶⁾.

Summary of studies in the literature indicate that hesperidin, also known as hesperidin-7-rutinoside, when orally consumed by

humans or animals, is absorbed either by removal of the rutinose portion to convert it to the aglycone (hesperetin) form or by conversion of hesperidin to hesperetin 7-glucoside by bacterial enzymes (β -glucosidases) produced by enterobacteria in the intestine^(34,37). It is believed that, after absorption, it is converted into glucuronidated and sulphated metabolites and released into the bloodstream (shown in Fig.2)^(5,38). Following the cleavage of hesperidin to hesperetin, the passage of aglycone hesperetin into enterocytes occurs via proton-dependent active transport and passive diffusion⁽¹¹⁾.

There are two hypotheses regarding how flavonoid glycosides are absorbed in the small intestine⁽³⁹⁾ Firstly, the glycoside may undergo hydrolysis by lactase-phlorizin hydrolase, after which the free aglycone diffuses passively or with facilitation through the epithelial cells. Secondly, the glycoside molecule might be transported into enterocytes via SGLT1 carrier and subsequently glycosylated by β -glucosidase enzymes found in intestinal cells. Both ways lead to intracellular aglycones that are conjugated to glucuronides or sulphates⁽³¹⁾.

In a study conducted with human subjects, individuals were orally given low-dose orange juice containing hesperidin, high-dose orange juice containing hesperidin and orange juice with added hesperidinase, thereby containing hesperetin-7-glucoside⁽³¹⁾. Concentration of hesperetin-7-glucoside was measured in plasma and urine. Subjects consuming orange juices containing low and high doses of hesperidin achieved similar plasma peak concentrations at approximately 7 h. However, in the group consuming orange juice containing hesperidinase, the peak concentration was achieved after 4 h. This finding supports the notion that flavonoids with rutinose groups are absorbed following hydrolysis by colonic microflora⁽³¹⁾. An animal study showed that the disaccharide portion of hesperidin was removed by intestinal bacteria and absorbed as hesperetin in the intestine. This study demonstrated that hesperetin undergoes immediate glucuronidation in the intestinal epithelium, converting it into hesperetin glucuronides⁽¹⁸⁾. Matsumoto *et al.*⁽³⁴⁾ showed that, after oral intake of hesperidin, it is converted into hesperetin glucuronides in the intestinal epithelium and then reaches the liver. This molecule undergoes deglucuronidation, demethylation, remethylation and reglucuronidation in the liver, leading to the release of hesperetin conjugates such as hesperetin-7-O- β -D-glucuronide (HPT7G) and hesperetin-3-O- β -D-glucuronide (HPT3G), as well as homoeriodictyol conjugates into the plasma. It was also reported in this study that HPT7G was found in higher amounts than HPT3G. In another animal study, the influence of hesperidin metabolites on endothelial function and blood pressure was investigated, and intravenous administration of HPT7G reduced blood pressure similarly to hesperetin, exhibiting vasodilatory and anti-inflammatory effects. Meanwhile, HPT3G had little effect on these parameters^(5,16).

Numerous studies indicate that, after oral consumption, hesperidin is hydrolysed to its aglycone form by β -glucosidases and then converted to glucuronides and sulphates in the colon. Subsequently, absorbed hesperetin undergoes immediate metabolism into glucuronide and sulphate conjugates in the intestinal epithelium and liver^(5,19,34). Three hours after intake, hesperetin appears in the plasma primarily as glucuronides, accounting for 87% of the total. The remaining portion consists of sulfoglucuronides. It reaches peak concentration between 5 and 7 h⁽⁴⁰⁾.

However, hesperidin exhibits low solubility in water (0.01%) and limited bioavailability^(37,41,42). Different methods such as micronisation and encapsulation have been proposed, especially

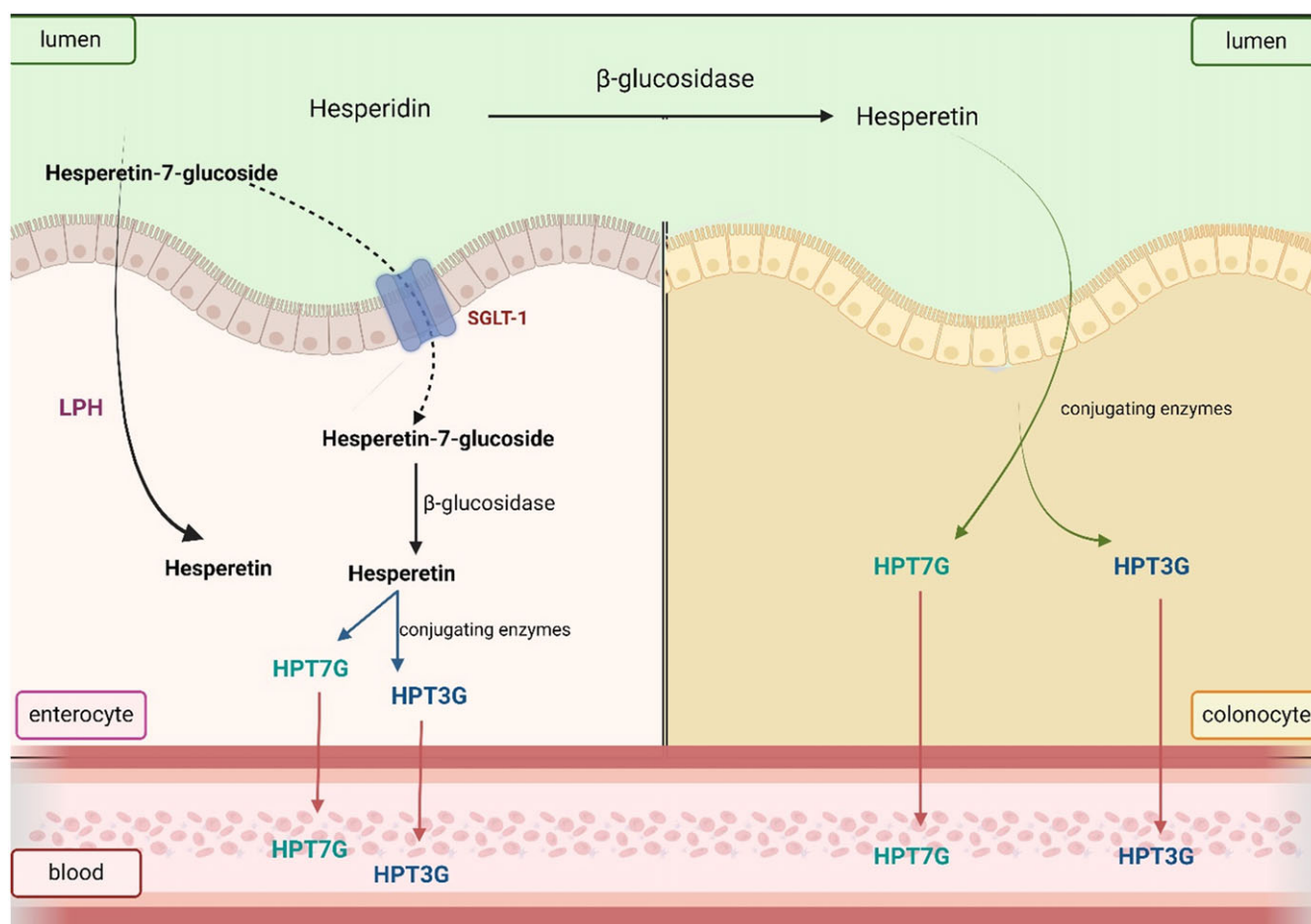


Figure 2. Absorption pathways of hesperidin and hesperetin. This figure was created with BioRender.com. The aglycone form, hesperetin, is absorbed more easily than hesperidin. Hesperidin is first converted to hesperetin with the help of lactase-phlorizin hydrolase or absorbed into enterocytes via SGLT-1. LPH, lactase-phlorizin hydrolase; SGLT1, sodium/glucose cotransporter 1; HPT3G, hesperetin-3-O- β -D-glucuronide; HPT7G, hesperetin-7-O- β -D-glucuronide.

in pharmaceutical production. With these methods, it is possible to increase the bioavailability and stability of hesperidin^(42,43).

Bioavailability of hesperidin

The bioavailability of polyphenols varies significantly. One of the primary factors influencing human absorption is the glycoside structure of the polyphenols present in plants. This glycoside structure, in which polyphenols are attached to one or more sugar molecules, is considered one of the primary factors determining the absorption level in humans. The general bioavailability of hesperidin, also known as hesperetin-7-O-rutinoside, is comparatively low owing to a rutinoside molecule in its structure⁽⁶⁾. In a study aimed at increasing the bioavailability of hesperidin, the rutinoside molecule was enzymatically removed from hesperidin under *in vitro* conditions, resulting in the production of hesperetin-7-O-glucoside. The study reported that the bioavailability of hesperetin was approximately tripled⁽³¹⁾.

In another study conducted to screen and identify metabolites of hesperidin and hesperetin, and to determine similarities and differences in pharmacodynamics and pharmacokinetics, Sprague-Dawley rats were orally administered equal amounts of hesperidin and hesperetin. It was shown that the bioavailability of hesperetin exceeded that of hesperidin⁽⁴⁴⁾.

Examining the factors associated with hesperidin and MASLD

Effects on inflammation – possible mechanisms

The combined causes of MASLD include a sedentary life and a high-calorie diet that also causes obesity, environmental factors, genetic elements, and physiological and metabolic factors. Consumption of Western-style diets, particularly elevated intake of simple sugars and saturated fats, obesity, hyperlipaemia and insulin resistance increase the prevalence of MASLD. Lifestyle modifications for the management of MASLD and comorbid diseases and elimination of the underlying causes of the disease are the issues that the scientific perspective focuses on^(45–47).

Despite the complex and uncertain pathogenesis of MASH, oxidative stress is widely known as a main reason. In healthy liver tissue, there exists a dynamic balance between oxidation and antioxidant systems. Hepatocytes have the ability to effectively neutralise ROS by using antioxidant mechanisms⁽⁴⁸⁾.

In MASH, ROS production in mitochondria increases and the activity of ROS scavenging mechanisms decreases, leading to ROS overproduction and oxidative stress, resulting in the formation of toxic lipid peroxides 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA)⁽⁴⁹⁾. Consequently, the accumulation of ROS and lipid peroxides negatively affects protein production following

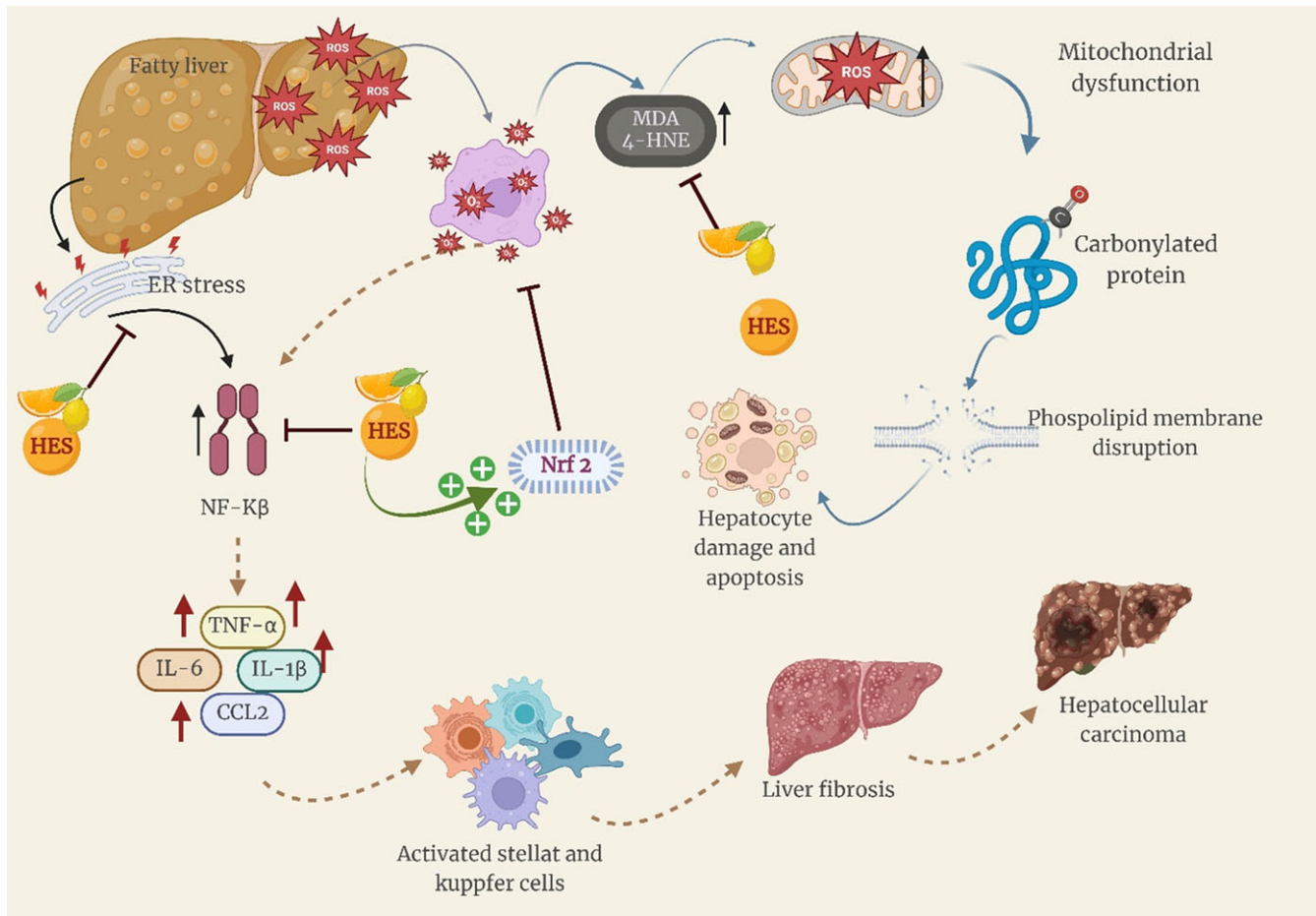


Figure 3. Summary of the effect of hesperidin on inflammatory pathways. This figure was created with BioRender.com. HES, hesperidin; ER, endoplasmic reticulum; ROS, reactive oxygen species; MDA, malondialdehyde; 4-HNE, 4-hydroxy-2-nonenal; NF- κ B, nuclear factor- κ B; TNF- α , tumour necrosis factor alpha; IL-6, interleukin-6; IL-1 β , interleukin-1 β ; CCL2, chemokine ligand 2; Nrf2, nuclear factor erythroid 2-related factor.

mitochondrial dysfunction. Protein carbonylation and destruction of phospholipid membranes result in hepatocyte damage and apoptosis. In hepatocytes, overaccumulation of ROS can activate the nuclear factor- κ B (NF- κ B)-mediated inflammatory pathway. NF- κ B is a transcription factor that regulates liver inflammation and modulates the inflammation–fibrosis–cancer axis in liver disorders. Chemokines and cytokines increase with NF- κ B increase (shown in Fig.3). Activation of hepatic stellate cells and Kupffer cells plays an important role in the development of liver fibrosis. This activation may be mediated by the release of inflammatory cytokines^(50,51). Chronic inflammation and subsequent continuous increase in NF- κ B and cytokines may also trigger hepatic carcinogenesis (shown in Fig.3)⁽⁵²⁾. There are studies in the literature showing that the phytochemical hesperidin is effective in stopping cell growth and preventing apoptosis by inhibiting NF- κ B^(53,54). In addition, in a study, rats with carbon tetrachloride (CCL4)-induced liver cirrhosis significantly reduced MDA levels after hesperidin treatment, indicating its antioxidant effect. In this study, the levels of NF- κ B increased 11-fold in rats with CCL4-induced liver cirrhosis compared with the control group, but administration of hesperidin treatment inhibited NF- κ B and transforming growth factor beta 1 (TGF- β) expression. Interestingly, in this study, administering hesperidin to non-cirrhotic normal rats lowered NF- κ B levels to a level below the control values⁽⁵⁵⁾.

In another study, rats with liver cancer induced by diethyl nitrosamine and CCL4 were treated with hesperidin, and MDA levels decreased significantly⁽⁵⁶⁾. The levels of TNF- α , TGF- β 1 and Smad3 in these rats also decreased significantly. In addition, very low levels of collagen accumulation were observed in the groups receiving hesperidin treatment. Consistently, in another study, hesperidin treatment showed a protective effect against ethanol-induced damage by reducing MDA levels⁽⁵⁷⁾.

In summary, activated Kupffer cells increase liver damage by generating several metabolites that lead to cellular injury. Some of these metabolites are superoxide radicals and pro-inflammatory cytokines⁽⁵⁸⁾. Eventually, this condition evolves from a simple fatty liver disease to NASH. Therefore, controlling oxidative stress and excessive ROS production in the liver is a critical strategy to prevent NASH⁽⁴⁸⁾.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a protein which has a vital role in antioxidant system and controls the transcription of various antioxidant genes, providing protection from oxidative damage induced by inflammation⁽⁵⁹⁾. Nrf2 is the main controller of antioxidant stress systems. The Nrf2/ARE signalling pathway plays a significant role in combatting continuous oxidative stress in cellular defence, regulating the expression of antioxidant genes. When oxidative stress increases, Nrf2 moves to the nucleus and attaches to the antioxidant response element (ARE). This starts the down-regulation of antioxidant

gene transcription, resulting in a decrease in intracellular ROS content and inhibition of oxidative stress⁽⁶⁰⁾. One study showed that Nrf2 deficiency leads to NF- κ B activation and increases oxidative stress, thereby worsening liver steatosis and injury, and then leads to fibrosis in mice with MASLD⁽⁶¹⁾. Other studies have also shown that hesperidin has an anticarcinogenic effect by activating the Nrf2/ARE/HO-1 signalling pathway^(56,62,63). Increasing evidence suggests that the activation of Nrf2 may protect hepatocytes from oxidative stress and, thus, lipotoxicity, thereby attenuating MASLD. Considering these aspects, Nrf2 has been considered as a new focus to reduce oxidative stress in the liver and treat the disease⁽⁴⁸⁾.

One of the important pathways in NF- κ B activation is activated by endoplasmic reticulum (ER) stress⁽⁶⁴⁾. The ER regulates protein synthesis, proper folding and post-translational modification. It is susceptible to the build-up of unfolded or misfolded proteins in its lumen, disrupting ER homeostasis. If the accumulation of these unproper protein cargo exceeds the ER's folding capacity, the unfolded protein response (UPR) is triggered⁽⁶⁵⁾. One of the main pathways regulated by ER membrane receptors during UPR is the pancreatic ER kinase-like ER kinase (PERK) pathway. Under ER stress, PERK phosphorylates the α subunit of eukaryotic translation initiation factor-2, which in turn activates the NF- κ B pathway. Subsequently, activated NF- κ B increases the synthesis of TNF- α and IL-6^(66,67). One study showed that hesperidin could attenuate liver ER stress in NEFA-stimulated human THP-1 cells⁽⁶⁸⁾.

Hepatic fibrosis, which represents a response to the chronicity of liver injury, is marked by the deposition of extracellular matrix particularly α -SMA, collagen I. Permanent fibrosis usually results in cirrhosis or liver failure^(69,70). Activation of hepatic stellate cell is one of the key factors responsible for the accumulation of extracellular matrix. The persistent activation of hepatic stellate cells results in the continuous production of inflammatory cytokines, such as TGF- β 1, and the development of liver fibrosis. Inhibiting this activation appears to be an effective therapeutic strategy to prevent liver fibrosis. The adenosine 5-monophosphate activated protein kinase (AMPK) pathway is associated with fibrosis of liver⁽⁷¹⁾. AMPK inactivation increases hepatic fibrogenesis. Sensitivity to AMPK phosphorylation reduces liver fibrosis. SIRT3, a regulator belonging to the histone deacetylase family, is located in mitochondria. It contributes to homeostasis and stress response, which are some of the physiological activities of the cell. With the up-regulation of AMPK/SIRT3 signalling, mitochondrial function can improve and the progression of the disease slows down^(72,73). In one study, mice with CCl₄-induced liver fibrosis were given hesperetin-16 (HD-16), an increased water-soluble form of hesperetin, and hesperetin-16 reduced inflammation and fibrogenesis in the liver by moderating the AMPK/SIRT3 pathway. In the same study, HD-16 treatment of TGF- β -activated LX-2 cells decreased the expression of genes involved in fibrogenesis, indicating its antifibrotic effect⁽⁷⁴⁾.

Another study focusing on fibrosis of liver highlights that one of the significant factors leading to fibrosis is the Hedgehog signalling pathway⁽⁷⁵⁾. It is suggested that activation of the Hedgehog-Glioma pathway increases the transformation of quiescent stellate cells into fibrogenic myofibroblasts. This pathway is associated with several cellular responses, including proliferation, differentiation and cell viability. Abnormal activation of this pathway is often shown by the up-regulation of Gli-1 and plays a role in liver cancer⁽⁷⁶⁾. In this study, the mRNA levels of fibrotic genes decreased in hepatic stellate cells isolated from mice treated with a derivative of hesperetin compared to hepatic fibrosis mice⁽⁷⁷⁾. These findings indicate that hesperetin interferes with the onset of

liver fibrogenesis in mice. In addition, it has been shown that Gli-1 levels in hepatic stellate cells isolated from mice treated with hesperetin decreased compared with hepatic fibrosis mice^(77,78).

Sarcopenia is a severe condition in the elderly, marked by muscle loss and increased inflammation, including elevated pro-inflammatory cytokines and ROS⁽⁷⁹⁾. One of the main elements of the disease is the increase in inflammation and, thus, the increase in pro-inflammatory cytokines and ROS. A study investigating the link between sarcopenia and inflammation found that daily administration of hesperidin to animals for 8 weeks improved muscle strength in older mice⁽⁸⁰⁾. At the end of the study, the muscle fibres and strength of elderly mice treated with hesperidin increased. This result was achieved by improving the M1/M2 macrophage imbalance through the anti-inflammatory properties of hesperidin. Moreover, hesperidin reduced muscle protein degradation, increased protein synthesis and promoted myogenesis, leading to stronger muscle fibres. In addition, there are shared mechanisms involved in developing sarcopenia and MASLD, and the two may coexist in the elderly. In one study, people with MASLD were found to have consistently lower muscle mass than healthy people over a 12-year period⁽⁸¹⁾.

The impact of hesperidin on lipid profile and liver enzymes

We mentioned above that there is no definitive treatment method for MASLD. Lifestyle change is still considered the most current treatment approach⁽⁸²⁾. In one study, an *in vitro* model of lipid accumulation related to NEFA was created, and this cell line was treated with hesperidin. There was a decrease in lipid accumulation in the cells⁽⁸³⁾. In a study with human subjects with MASLD, there were positive effects of dietary intervention and physical activity on the treatment of the disease. In addition to these interventions, the group receiving hesperidin supplementation showed significantly greater reductions in liver enzyme levels, serum triacylglycerol (TG) and total cholesterol levels, and hepatic steatosis and fibrosis amounts compared with the control group⁽⁸⁴⁾. In an animal study, hesperidin treatment improved serum TG levels in a MASLD mouse⁽⁸⁵⁾. In another animal study, high-dose hesperidin lowered serum Alanine transaminase (ALT), Aspartate transaminase (AST) and total and direct bilirubin levels, while low-dose hesperidin had no effect on liver enzymes⁽⁸⁶⁾. There are promising studies in the literature regarding the effect of hesperidin on blood lipids. For example, in a randomised controlled trial conducted with obese individuals, hesperidin intervention was added to calorie restriction. The hesperidin intervention did not affect body weight when combined with calorie restriction, but it did lead to notable decreases in LDL-cholesterol and total cholesterol levels. Liver enzymes (ALT, AST, Alkaline phosphatase (ALP), and Gamma-glutamyl transferase (GGT)) decreased in both groups compared with baseline, but there was no significant difference between the two groups. Total antioxidant capacity (TAC) and MDA levels were also evaluated in this study. The TAC and MDA levels of both groups decreased compared with baseline, but hesperidin intervention did not cause a greater decrease than the calorie-restricted group⁽⁸⁷⁾. A randomised controlled study showed that G-hes decreased serum total cholesterol levels⁽⁸⁸⁾.

In an animal study, pre-treatment with hesperidin was protective against the toxic effects of cadmium and ameliorated the impaired lipid profile caused by cadmium. Hesperidin increased HDL-cholesterol levels while decreasing LDL-cholesterol and total cholesterol levels⁽⁸⁹⁾. However, whether the hesperidin treatment impacts the lipid profile is controversial. In

an animal study, although hesperidin reduced the appearance of steatosis the liver, it did not affect the lipids⁽⁶⁸⁾.

Hesperidin intervention can reduce fat accumulation in the liver. In one study, hesperidin prevented the increase of lipid deposition in the liver. In addition, due to a selective enrichment of a group of intestinal bacteria such as Bacteroidota proven to improve obesity and metabolic syndrome symptoms, and the promotion of arginine synthesis by these bacteria, hesperidin is considered a therapeutic agent for MASLD⁽⁹⁰⁾.

The effects of hesperidin on plasma glucose

Although its frequency is increasing day by day and it has a significant prevalence in the world, the pathogenesis is not completely understood⁽⁹¹⁾. Thus, MASLD has become an important public health problem within the scope of metabolism and liver disorders. MASLD, a multisystem metabolic disease, is often accompanied by type 2 diabetes (T2DM) and metabolic syndrome (MET), which together promote disease progression⁽⁹²⁾. The liver has a fundamental role in lipogenesis and gluconeogenesis, including cholesterol metabolism. Metabolic dysfunctions in the diseased liver can lead to various pathological conditions. The increasing prevalence of obesity, T2DM and MET promotes the pathophysiological changes that lead to MASLD. MASLD is thought to be the most common liver disorder in western communities⁽⁹³⁾. Changes in insulin response associated with obesity, metabolic syndrome and diabetes can lead to progression of liver damage due to imbalance in β -oxidation, lipid metabolism and autophagy. Therefore, these diseases are thought to be interconnected⁽⁹⁴⁾. For instance, it is known that, in the presence of diabetes, increased glucose auto-oxidation and protein glycation lead to increased formation of free radicals. The increase in free radicals also leads to an increase in lipid peroxidation⁽⁹⁵⁾. The accumulation of MDA leads to permanent damage in hepatocytes. The contribution of the accumulation of lipid peroxidation products in liver damage is inevitable. Therefore, diabetes and liver diseases can trigger each other's occurrence directly or indirectly^(48,96).

Disruptions exceeding a certain limit in glucose metabolism can lead to MASLD; thus, there is an interconnection between the disorder, glucose homeostasis and lipid metabolism. Some studies in the literature indicate that hesperidin can positively affect glucose metabolism and insulin activity^(87,97). In one animal study, elevated blood glucose and insulin levels were reduced with hesperidin treatment. In the same study, a group of mice was given glucose intraperitoneally followed by hesperidin administration. Hesperidin is thought to reduce increased blood sugar levels and thereby reduce glucose tolerance^(98,99).

Hesperidin is thought to regulate blood glucose levels by modulating enzymes in glucose metabolism such as glucose-6-phosphatase. In one study, administration of hesperidin to mice reduced the levels of glucose-6-phosphate dehydrogenase and fatty acid synthase enzymes. In addition, after hesperidin treatment, significant increases in glucokinase mRNA levels were noted. In this study, hesperidin caused a significant decrease in hepatic GLUT2 expression while increasing adipocyte GLUT4 levels compared with the control group⁽¹⁰⁰⁾. Other studies suggest that another effect of hesperidin on glucose metabolism may occur via glucose transporters^(101,102).

Conclusion

Hesperidin and hesperetin are being investigated as promising treatments for many diseases. They are thought to play an effective

role in inflammatory processes, particularly in liver diseases, but further studies are needed to determine the optimum dosage. In addition, their low water solubility limits their potential benefits. We believe that deriving water-soluble forms could enhance their beneficial effects. Although we consider them as promising agents in preventing and treating liver diseases, especially due to their anti-inflammatory and lipid-lowering effects, it is important to note that more research is required. Based on their effects in *in vivo* and *in vitro* studies, we must emphasise the necessity for further investigation.

Author contributions. A.S: methodology, investigation, writing, visualisation; Z.G: conceptual design, methodology, review & editing, supervision.

The authors have reviewed and approved the final version of the manuscript.

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References

1. Cotter TG, Rinella M (2020) Nonalcoholic fatty liver disease 2020: the state of the disease. *Gastroenterology* **158**, 1851–1864.
2. Wei S, Wang L, Evans PC, *et al.* (2024) NAFLD and NASH: etiology, targets and emerging therapies. *Drug Discov Today* **29**, 103910.
3. Harrison SA, Allen AM, Dubourg J, *et al.* (2023) Challenges and opportunities in NASH drug development. *Nat Med* **29**, 562–573.
4. Roohbakhsh A, Parhiz H, Soltani F, *et al.* (2015) Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. *Life Sci* **124**, 64–74.
5. Choi SS, Lee SH, Lee KA (2022) A comparative study of hesperetin, hesperidin and hesperidin glucoside: antioxidant, anti-inflammatory, and antibacterial activities *in vitro*. *Antioxidants (Basel)* **11**, 1618.
6. Actis-Goretta L, Dew TP, Lévêques A, *et al.* (2015) Gastrointestinal absorption and metabolism of hesperetin-7-O-rutinoside and hesperetin-7-O-glucoside in healthy humans. *Mol Nutr Food Res* **59**, 1651–1662.
7. Welbat JU, Naewla S, Pannangrong W, *et al.* (2020) Neuroprotective effects of hesperidin against methotrexate-induced changes in neurogenesis and oxidative stress in the adult rat. *Biochem Pharmacol* **178**, 114083.
8. Ahmadi A, Shadboorestan A (2016) Oxidative stress and cancer; the role of hesperidin, a citrus natural bioflavonoid, as a cancer chemoprotective agent. *Nutr Cancer* **68**, 29–39.
9. Hanchang W, Khamchan A, Wongmanee N, *et al.* (2019) Hesperidin ameliorates pancreatic β -cell dysfunction and apoptosis in streptozotocin-induced diabetic rat model. *Life Sci* **235**, 116858.
10. Alharbi FK, Alshehri ZS, Alshehri FF, *et al.* (2023) The role of hesperidin as a cardioprotective strategy against doxorubicin-induced cardiotoxicity: The antioxidant, anti-inflammatory, antiapoptotic, and cytoprotective potentials. *Open Vet J* **13**, 1718–1728.
11. Najmanová I, Vopršalová M, Saso L, *et al.* (2020) The pharmacokinetics of flavanones. *Crit Rev Food Sci Nutr* **60**, 3155–3171.
12. Stanisic D, Liu LHB, dos Santos RV, *et al.* (2020) New sustainable process for hesperidin isolation and anti-ageing effects of hesperidin nanocrystals. **25**, 4534.
13. Tayal R, Munjal K, Gauttam VK, *et al.* (2023) Potential role of hesperidin in lifestyle disorders: A scoping review. *S Afr J Bot* **161**, 542–554.
14. Wdowiak K, Walkowiak J, Pietrzak R, *et al.* (2022) Bioavailability of hesperidin and Its aglycone hesperetin-compounds found in citrus fruits as a parameter conditioning the pro-health potential (neuroprotective and antidiabetic activity)-mini-review. *Nutrients* **14**, 2647.
15. Imperatrice M, Cuijpers I, Troost FJ, *et al.* (2022) Hesperidin functions as an ergogenic aid by increasing endothelial function and decreasing exercise-induced oxidative stress and inflammation, thereby contributing to improved exercise performance. *Nutrients* **14**, 2955.

16. Yamamoto M, Jokura H, Hashizume K, *et al.* (2013) Hesperidin metabolite hesperetin-7-O-glucuronide, but not hesperetin-3'-O-glucuronide, exerts hypotensive, vasodilatory, and anti-inflammatory activities. *Food Funct* **4**, 1346–1351.
17. Calomme M, Pieters L, Vlietinck A, *et al.* (1996) Inhibition of bacterial mutagenesis by citrus flavonoids. *Planta Med* **62**, 222–226.
18. Garg A, Garg S, Zaneveld LJ, *et al.* (2001) Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytother Res* **15**, 655–669.
19. Yamada M, Tanabe F, Arai N, *et al.* (2006) Bioavailability of glucosyl hesperidin in rats. *Biosci Biotechnol, Biochem* **70**, 1386–1394.
20. Hijiya HaM, T. (1991), vol. European Patent 0402049.
21. Sugasawa N, Katagi A, Kurobe H, *et al.* (2019) Inhibition of atherosclerotic plaque development by oral administration of α -Glucosyl Hesperidin and water-dispersible hesperetin in apolipoprotein E knockout mice. *J Am Coll Nutr* **38**, 15–22.
22. Ohtsuki K, Abe A, Mitsuzumi H, *et al.* (2003) Glucosyl hesperidin improves serum cholesterol composition and inhibits hypertrophy in vasculature. *J Nutr Sci Vitaminol* **49**, 447–450.
23. Yoshida H, Tshako R, Sugita C, *et al.* (2021) Glucosyl hesperidin has an anti-diabetic effect in high-fat diet-induced obese mice. *Biol Pharm Bull* **44**, 422–430.
24. Mayr HL, Tierney AC, Kucianski T, *et al.* (2019) Australian patients with coronary heart disease achieve high adherence to 6-month Mediterranean diet intervention: preliminary results of the AUSMED Heart Trial. *Nutrition* **61**, 21–31.
25. Guasch-Ferré M, Merino J, Sun Q, *et al.* (2017) Dietary polyphenols, mediterranean diet, prediabetes, and type 2 diabetes: a narrative review of the evidence. *Oxid Med Cell Longevity* **2017**, 6723931.
26. Al-Aubaidy HA, Dayan A, Deseo MA, *et al.* (2021) Twelve-week mediterranean diet intervention increases citrus bioflavonoid levels and reduces inflammation in people with type 2 diabetes mellitus. *Nutrients* **13**, 1133.
27. Majumdar S, Srirangam R (2009) Solubility, stability, physicochemical characteristics and *in vitro* ocular tissue permeability of hesperidin: a natural bioflavonoid. *Pharm Res* **26**, 1217–1225.
28. Zhang L, Ling W, Yan Z, *et al.* (2020) Effects of storage conditions and heat treatment on the hesperidin concentration in Newhall navel orange (*Citrus sinensis* Osbeck cv. Newhall) juice. 85, 103338.
29. Biesaga M, Pyrzyńska K (2013) Stability of bioactive polyphenols from honey during different extraction methods. *Food Chem* **136**, 46–54.
30. Wang M, Zhao H, Wen X, *et al.* (2021) Citrus flavonoids and the intestinal barrier: Interactions and effects. *Compr Rev Food Sci Food Saf* **20**, 225–251.
31. Nielsen ILF, Chee WSS, Poulsen L, *et al.* (2006) Bioavailability is improved by enzymatic modification of the citrus flavonoid hesperidin in humans: a randomized, double-blind, crossover trial. *J Nutr* **136**, 404–408.
32. Kanaze FI, Bounartzi MI, Georarakis M, *et al.* (2007) Pharmacokinetics of the citrus flavanone aglycones hesperetin and naringenin after single oral administration in human subjects. *Eur J Clin Nutr* **61**, 472–477.
33. Xu H, Kulkarni KH, Singh R, *et al.* (2009) Disposition of naringenin via glucuronidation pathway is affected by compensating efflux transporters of hydrophilic glucuronides. *Mol Pharmacol* **6**, 1703–1715.
34. Matsumoto H, Ikoma Y, Sugiura M, *et al.* (2004) Identification and quantification of the conjugated metabolites derived from orally administered hesperidin in rat plasma. *J Agric Food Chem* **52**, 6653–6659.
35. Borges G, Lean ME, Roberts SA, *et al.* (2013) Bioavailability of dietary (poly)phenols: a study with ileostomists to discriminate between absorption in small and large intestine. *Food Funct* **4**, 754–762.
36. Pereira-Caro G, Fernández-Quirós B, Ludwig IA, *et al.* (2018) Catabolism of citrus flavanones by the probiotics *Bifidobacterium longum* and *Lactobacillus rhamnosus*. *Eur J Nutr* **57**, 231–242.
37. Ávila-Gálvez M, Giménez-Bastida JA, González-Sarrias A, *et al.* (2021) New insights into the metabolism of the flavanones eriocitrin and hesperidin: a comparative human pharmacokinetic study. *Antioxidants (Basel, Switzerland)* **10**, 435.
38. Aschoff JK, Riedl KM, Cooperstone JL, *et al.* (2016) Urinary excretion of citrus flavanones and their major catabolites after consumption of fresh oranges and pasteurized orange juice: A randomized cross-over study. *Mol Nutr Food Res* **60**, 2602–2610.
39. Manach C, Scalbert A, Morand C, *et al.* (2004) Polyphenols: food sources and bioavailability. *Am J Clin Nutr* **79**, 727–747.
40. Pla-Pagà L, Companys J, Calderón-Pérez L, *et al.* (2019) Effects of hesperidin consumption on cardiovascular risk biomarkers: a systematic review of animal studies and human randomized clinical trials. *Nutr Rev* **77**, 845–864.
41. Manach C, Morand C, Gil-Izquierdo A, *et al.* (2003) Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. *Eur J Clin Nutr* **57**, 235–242.
42. Vallejo F, Larrosa M, Escudero E, *et al.* (2010) Concentration and solubility of flavanones in orange beverages affect their bioavailability in humans. *J Agric Food Chem* **58**, 6516–6524.
43. Crescenti A, Caimari A, Alcaide-Hidalgo JM, *et al.* (2022) Hesperidin bioavailability is increased by the presence of 2S-diastereoisomer and micronization—a randomized, crossover and double-blind clinical trial. *Nutrients* **14**, 2481.
44. Jiao Q, Xu L, Jiang L, *et al.* (2020) Metabolism study of hesperetin and hesperidin in rats by UHPLC-LTQ-Orbitrap MSn. *Xenobiotica* **50**, 1311–1322.
45. Hassani Zadeh S, Mansoori A, Hosseinzadeh M (2021) Relationship between dietary patterns and non-alcoholic fatty liver disease: A systematic review and meta-analysis. *J Gastroenterol Hepatol* **36**, 1470–1478.
46. Risi R, Tozzi R, Watanabe M (2021) Beyond weight loss in nonalcoholic fatty liver disease: the role of carbohydrate restriction. *Curr Opin Clin Nutr Metab Care* **24**, 349–353.
47. Morshedzadeh N, Ramezani Ahmadi A, Behrouz V, *et al.* (2023) A narrative review on the role of hesperidin on metabolic parameters, liver enzymes, and inflammatory markers in nonalcoholic fatty liver disease. *Food Sci Nutr* **11**, 7523–7533.
48. Li J, Wang T, Liu P, *et al.* (2021) Hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD. *Food Funct* **12**, 3898–3918.
49. Serviddio G, Bellanti F, Vendemiale G (2013) Free radical biology for medicine: learning from nonalcoholic fatty liver disease. *Free Radical Biol Med* **65**, 952–968.
50. Lee J, Park JS, Roh YS (2019) Molecular insights into the role of mitochondria in non-alcoholic fatty liver disease. *Arch Pharm Res* **42**, 935–946.
51. Liu W, Baker RD, Bhatia T, *et al.* (2016) Pathogenesis of nonalcoholic steatohepatitis. *Cell Mol Life Sci* **73**, 1969–1987.
52. Goldberg JE, Schwertfeger KL (2010) Proinflammatory cytokines in breast cancer: Mechanisms of action and potential targets for therapeutics. *Current Drug Targets* **11**, 1133–1146.
53. Lee KH, Yeh MH, Kao ST, *et al.* (2010) The inhibitory effect of hesperidin on tumor cell invasiveness occurs via suppression of activator protein 1 and nuclear factor-kappaB in human hepatocellular carcinoma cells. *Toxicol Lett* **194**, 42–49.
54. Ghorbani A, Nazari M, Jeddi-Tehrani M, *et al.* (2012) The citrus flavonoid hesperidin induces p53 and inhibits NF- κ B activation in order to trigger apoptosis in NALM-6 cells: involvement of PPAR γ -dependent mechanism. *Eur J Nutr* **51**, 39–46.
55. Pérez-Vargas JE, Zarco N, Shibayama M, *et al.* (2014) Hesperidin prevents liver fibrosis in rats by decreasing the expression of nuclear factor- κ B, transforming growth factor- β and connective tissue growth factor. *Pharmacology* **94**, 80–89.
56. Mahmoud AM, Mohammed HM, Khadrawy SM, *et al.* (2017) Hesperidin protects against chemically induced hepatocarcinogenesis via modulation of Nrf2/ARE/HO-1, PPAR γ and TGF- β 1/Smad3 signaling, and amelioration of oxidative stress and inflammation. *Chem Biol Interact* **277**, 146–158.
57. El-Sisi AE-DE-S, Sokar SS, Shebl AM, *et al.* (2017) Antifibrotic effect of diethylcarbamazine combined with hesperidin against ethanol induced liver fibrosis in rats. *Biomed Pharmacother* **89**, 1196–1206.

58. Chen X, Ding HW, Li HD, *et al.* (2017) Hesperetin derivative-14 alleviates inflammation by activating PPAR- γ in mice with CCl₄(4)-induced acute liver injury and LPS-treated RAW264.7 cells. *Toxicol Lett* **274**, 51–63.
59. Itoh K, Chiba T, Takahashi S, *et al.* (1997) A Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem Biophys Res Commun* **236**, 313–322.
60. Aleksunes LM, Manautou JE (2007) Emerging role of Nrf2 in protecting against hepatic and gastrointestinal disease. *Toxicol Pathol* **35**, 459–473.
61. Liu Z, Dou W, Ni Z, *et al.* (2016) Deletion of Nrf2 leads to hepatic insulin resistance via the activation of NF- κ B in mice fed a high-fat diet. *Mol Med Rep* **14**, 1323–1331.
62. Chen M, Gu H, Ye Y, *et al.* (2010) Protective effects of hesperidin against oxidative stress of tert-butyl hydroperoxide in human hepatocytes. *Food Chem Toxicol* **48**, 2980–2987.
63. Subramanian P, Anandan R, Jayapalan JJ, *et al.* (2015) Hesperidin protects gentamicin-induced nephrotoxicity via Nrf2/HO-1 signaling and inhibits inflammation mediated by NF- κ B in rats. *J Funct Foods* **13**, 89–99.
64. Di Conza G, Ho PC (2020) ER stress responses: an emerging modulator for innate immunity. *Cells* **9**, 695.
65. Han J, Back SH, Hur J, *et al.* (2013) ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. *Nat Cell Biol* **15**, 481–490.
66. Bi M, Naczki C, Koritzinsky M, *et al.* (2005) ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth. *EMBO J* **24**, 3470–3481.
67. Yoshida H, Matsui T, Yamamoto A, *et al.* (2001) XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell* **107**, 881–891.
68. Xie Q, Gao S, Lei M, *et al.* (2022) Hesperidin suppresses ERS-induced inflammation in the pathogenesis of non-alcoholic fatty liver disease. *Aging (Albany NY)* **14**, 1265–1279.
69. Chen X, Li X-F, Chen Y, *et al.* (2019) Hesperetin derivative attenuates CCl₄-induced hepatic fibrosis and inflammation by Gli-1-dependent mechanisms. *Int Immunopharmacol* **76**, 105838.
70. Jung YK, Yim HJ (2017) Reversal of liver cirrhosis: current evidence and expectations. *Korean J Intern Med* **32**, 213–228.
71. Yang J-J, Yang Y, Zhang C, *et al.* (2020) Epigenetic silencing of lncRNA ANRIL enhances liver fibrosis and HSC activation through activating AMPK pathway. **24**, 2677–2687.
72. Han L, Li J, Li J, *et al.* (2020) Activation of AMPK/Sirt3 pathway by phloretin reduces mitochondrial ROS in vascular endothelium by increasing the activity of MnSOD: Via deacetylation. *Food Funct* **11**, 3073–3083.
73. Wang Y, Li C, Gu J, *et al.* (2020) Celastrol exerts anti-inflammatory effect in liver fibrosis via activation of AMPK-SIRT3 signalling. *J Cell Mol Med* **24**, 941–953.
74. Li JJ, Jiang HC, Wang A, *et al.* (2022) Hesperetin derivative-16 attenuates CCl₄-induced inflammation and liver fibrosis by activating AMPK/SIRT3 pathway. *Eur J Pharmacol* **915**, 174530.
75. Yang J-J, Tao H, Li J (2014) Hedgehog signaling pathway as key player in liver fibrosis: new insights and perspectives. *Expert Opin Ther Targets* **18**, 1011–1021.
76. Kim HY, Cho HK, Hong SP, *et al.* (2011) Hepatitis B virus X protein stimulates the Hedgehog–Gli activation through protein stabilization and nuclear localization of Gli1 in liver cancer cells. *Cancer Lett* **309**, 176–184.
77. Chen X, Li XF, Chen Y, *et al.* (2019) Hesperetin derivative attenuates CCl₄ (4)-induced hepatic fibrosis and inflammation by Gli-1-dependent mechanisms. *Int Immunopharmacol* **76**, 105838.
78. Iredale JP, Benyon RC, Pickering J, *et al.* (1998) Mechanisms of spontaneous resolution of rat liver fibrosis. Hepatic stellate cell apoptosis and reduced hepatic expression of metalloproteinase inhibitors. *J Clin Invest* **102**, 538–549.
79. Tarantino G, Sinatti G, Citro V, *et al.* (2023) Sarcopenia, a condition shared by various diseases: can we alleviate or delay the progression? *Intern Emerg Med* **18**, 1887–1895.
80. Oh H-J, Jin H, Lee B-Y (2023) Hesperidin ameliorates sarcopenia through the regulation of inflammaging and the AKT/mTOR/FoxO3a signaling pathway in 22–26-month-old mice. *Cells* **12**, 2015.
81. Lee JH, Lee HS, Lee BK, *et al.* (2021) Relationship between muscle mass and non-alcoholic fatty liver disease. *Biology (Basel)* **10**, 122.
82. Mokhtari Z, Gibson DL, Hekmatdoost A (2017) Nonalcoholic fatty liver disease, the gut microbiome, and diet. *Adv Nutr (Bethesda, Md)* **8**, 240–252.
83. Tang J, Wang L, Shi M, *et al.* (2023) Study on the mechanism of Shuganzhi Tablet against nonalcoholic fatty liver disease and lipid regulation effects of its main substances *in vitro*. *J Ethnopharmacol* **316**, 116780.
84. Cheraghpour M, Imani H, Ommi S, *et al.* (2019) Hesperidin improves hepatic steatosis, hepatic enzymes, and metabolic and inflammatory parameters in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled, double-blind clinical trial. **33**, 2118–2125.
85. Sukkasem N, Chatuphonprasert W, Jarukamjorn K (2021) Hesperidin, a novel candidate for the successful treatment of high fat diet plus ethanol-induced fatty liver disease in mice. *J Physiol Pharmacol: An Official J Polish Physiol Soc* **72**, 217–224.
86. Kong R, Wang N, Luo H, *et al.* (2018) Hesperetin mitigates bile duct ligation-induced liver fibrosis by inhibiting extracellular matrix and cell apoptosis via the TGF- β 1/Smad pathway. *Curr Mol Med* **18**, 15–24.
87. Ribeiro C, Dourado G, Cesar T (2017) Orange juice allied to a reduced-calorie diet results in weight loss and ameliorates obesity-related biomarkers: A randomized controlled trial. *Nutrition* **38**, 13–19.
88. Katada S, Oishi S, Yanagawa K, *et al.* (2021) Concomitant use of tea catechins affects absorption and serum triglyceride-lowering effects of monoglucosyl hesperidin. *Food Funct* **12**, 9339–9346.
89. Aja PM, Ekpono EU, Awoke JN, *et al.* (2020) Hesperidin ameliorates hepatic dysfunction and dyslipidemia in male Wistar rats exposed to cadmium chloride. *Toxicol Rep* **7**, 1331–1338.
90. Li X, Yao Y, Wang Y, *et al.* (2022) Effect of hesperidin supplementation on liver metabolomics and gut microbiota in a high-fat diet-induced NAFLD mice model. *J Agric Food Chem* **70**, 11224–11235.
91. Riazi K, Azhari H, Charette JH, *et al.* (2022) The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* **7**, 851–861.
92. Rong L, Zou J, Ran W, *et al.* (2022) Advancements in the treatment of non-alcoholic fatty liver disease (NAFLD). *Front Endocrinol (Lausanne)* **13**, 1087260.
93. Feldstein AE (2010) Novel insights into the pathophysiology of nonalcoholic fatty liver disease. *Semin Liver Dis* **30**, 391–401.
94. Bechmann LP, Hannivoort RA, Gerken G, *et al.* (2012) The interaction of hepatic lipid and glucose metabolism in liver diseases. *J Hepatol* **56**, 952–964.
95. Kumawat M, Sharma TK, Singh I, *et al.* (2013) Antioxidant enzymes and lipid peroxidation in type 2 diabetes mellitus patients with and without nephropathy. *N Am J Med Sci* **5**, 213–219.
96. Dokumacioglu E, Iskender H, Musmul A (2019) Effect of hesperidin treatment on α -Klotho/FGF-23 pathway in rats with experimentally-induced diabetes. *Biomed Pharmacother* **109**, 1206–1210.
97. Jung UJ, Lee MK, Jeong KS, *et al.* (2004) The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. *J Nutr* **134**, 2499–2503.
98. Nie T, Wang X, Li A, *et al.* (2024) The promotion of fatty acid β -oxidation by hesperidin via activating SIRT1/PGC1 α to improve NAFLD induced by a high-fat diet. *Food Funct* **15**, 372–386.
99. Ahmed OM, Mahmoud AM, Abdel-Moneim A, *et al.* (2012) Antidiabetic effects of hesperidin and naringin in type 2 diabetic rats. **41**.
100. Jung UJ, Lee M-K, Park YB, *et al.* (2006) Effect of citrus flavonoids on lipid metabolism and glucose-regulating enzyme mRNA levels in type-2 diabetic mice. *Int J Biochem Cell Biol* **38**, 1134–1145.
101. Kerimi A, Gauer JS, Crabbe S, *et al.* (2019) Effect of the flavonoid hesperidin on glucose and fructose transport, sucrase activity and glycaemic response to orange juice in a crossover trial on healthy volunteers. *Br J Nutr* **121**, 782–792.

102. Shen W, Xu Y, Lu YH (2012) Inhibitory effects of citrus flavonoids on starch digestion and antihyperglycemic effects in HepG2 cells. *J Agric Food Chem* **60**, 9609–9619.
103. Soares MS, da Silva DF, Forim MR, *et al.* (2015) Quantification and localization of hesperidin and rutin in *Citrus sinensis* grafted on *C. limonia* after *Xylella fastidiosa* infection by HPLC-UV and MALDI imaging mass spectrometry. *Phytochemistry* **115**, 161–170.
104. Najafian S, Moradi M, Sepehrimanesh M (2016) Polyphenolic contents and antioxidant activities of two medicinal plant species, *Mentha piperita* and *Stevia rebaudiana*, cultivated in Iran. *Comp Clin Path* **25**, 743–747.
105. Damián-Reyna AA, González-Hernández JC, Maya-Yescas R, *et al.* (2017) Polyphenolic content and bactericidal effect of Mexican *Citrus limetta* and *Citrus reticulata*. *J Food Sci Technol* **54**, 531–537.
106. Prasatthong P, Meechat S, Rattanakanokchai S, *et al.* (2021) Hesperidin ameliorates signs of the metabolic syndrome and cardiac dysfunction via IRS/Akt/GLUT4 signaling pathway in a rat model of diet-induced metabolic syndrome. *Eur J Nutr* **60**, 833–848.
107. Zhu S, Chen X, Chen SY, *et al.* (2022) Hesperetin derivative decreases CCl₄-induced hepatic fibrosis by Ptch1-dependent mechanisms. *J Biochem Mol Toxicol* **36**, e23149.
108. Yi S, Zhang G, Liu M, *et al.* (2023) Citrus honey ameliorates liver disease and restores gut microbiota in alcohol-feeding mice. *Nutrients* **15**, 1078.
109. Yuan F, Xia GQ, Cai JN, *et al.* (2023) Hesperitin attenuates alcoholic steatohepatitis by regulating TLR4/NF- κ B signaling in mice. *Anal Biochem* **682**, 115339.
110. Ali YA, Soliman HA, Abdel-Gabbar M, *et al.* (2023) Rutin and hesperidin revoke the hepatotoxicity induced by paclitaxel in male Wistar rats via their antioxidant, anti-inflammatory, and antiapoptotic activities. *Evid Based Complement Alternat Med* **2023**, 2738351.
111. Yari Z, Cheraghpour M, Hekmatdoost A (2021) Flaxseed and/or hesperidin supplementation in metabolic syndrome: an open-labeled randomized controlled trial. *Eur J Nutr* **60**, 287–298.
112. Osama H, Hamed EO, Mahmoud MA, *et al.* (2023) The effect of hesperidin and diosmin individually or in combination on metabolic profile and neuropathy among diabetic patients with metabolic syndrome: a randomized controlled trial. *J Diet Suppl* **20**, 749–762.
113. Homayouni F, Haidari F, Hedayati M, *et al.* (2017) Hesperidin supplementation alleviates oxidative DNA damage and lipid peroxidation in Type 2 diabetes: a randomized double-blind placebo-controlled clinical trial. *Phytother Res* **31**, 1539–1545.
114. Yari Z, Movahedian M, Imani H, *et al.* (2020) The effect of hesperidin supplementation on metabolic profiles in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. *Eur J Nutr* **59**, 2569–2577.