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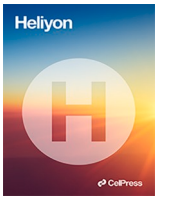

Review article

Hesperidin : a citrus plant component, plays a role in the central nervous system

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ABSTRACT

Hesperidin is a kind of flavonoids, which has the biological activities of antioxidation, anti-inflammation, antibacterial, anti-virus, anti-allergy, anti-cancer, heart protection and neuro-protection. More and more studies have begun to pay attention to the therapeutic prospect of hesperidin in central nervous system (CNS) diseases. This paper describes its current role in the treatment of central nervous system diseases, especially stroke, and discusses its bioavailability, so as to provide a theoretical basis for the clinical application of hesperidin.

In botany, Citrus generally refers to the citrus genus in the Rutaceae family, including grapefruit, lemon, orange, tangerines and so on. In China, Citrus is rich in resources and variety, which has both edible and medicinal value. One of the most important bioactive components in Citrus fruits is flavonoid hesperidin (HSD), also known as hesperitin 7-rutinoside [1]· It has the biological activities of antioxidant, anti-inflammation, antibiosis, anti-viral, anti-allergic, anti-cancer, cardioprotection and neuroprotection [2]. Flavonoids are one of the most common polyphenols, and a large number of flavonoids have been evaluated for their beneficial effects on human health in the form of free or glycosides [3]. This paper mainly expounds the source, physical and chemical properties, biological activity of HSD and the protective role of HSD in central nervous system diseases, in order to provide theoretical support for the further development and utilization of HSD in clinic.

1. Source and physicochemical properties

HSD mainly exists in the peel of navel orange, and its content can reach 1.4 % of the fresh weight of peel. Although navel orange in China has a wide planting area, only a small portion are made into traditional Chinese medicine tangerine peel, and most of the peel is discarded [46]. HSD is a white crystalline powder with molecular formula $C_{28}H_{34}O_{15}$, molecular weight about 610.56, melting point 258 °C–262 °C, solubility 1g in 50L water, soluble in dimethylformamide and formamide at 60 °C, soluble in dilute alkali and pyridine, insoluble in common organic solvents, slightly soluble in ethanol [47,48]. After hydrolysis of HSD, hesperitin and rutinose can be obtained, and hesperitin is the aglycone form of HSD.

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2. Biological activity

2.1. Anti-inflammation

Inflammation is a complex and necessary component of the response to biological, chemical, or physical stimuli and can be caused by several different causes, including blood clots, immune system disorders, cancer, infections, chemical exposure, physical injuries, or neurological diseases [49,50]. Adefegha et al. when treating arthritis rats induced by Freund's complete adjuvant with HSD, they found that HSD can reduce the inflammatory response of arthritis in rats and is a natural anti-inflammatory drug [4]. Clinical study on the effect of HSD supplementation on blood pressure and inflammatory markers in patients with type 2 diabetes. In this research, 64 patients were randomly assigned to take 500 mg/day HSD or placebo capsules for 6 weeks. It was found that HSD may have anti-hypertensive and anti-inflammatory effects on type 2 diabetes [5]. The central mediator of inflammatory response is NF- κB. The activation of NF- κB depends on its phosphorylation state, which is regulated by the cascade of mitogen activated protein kinase (MAPK) [3]. In a randomized, double-blind, placebo-controlled clinical study of HSD in the treatment of non-alcoholic fatty liver disease (NAFLD), it was found that HSD in combination with lifestyle changes improved NAFLD-related risk factors at least in part by inhibiting NF- κB activation and improving lipid and insulin sensitivity [6]. Mahmoud et al. in animal experiments with HSD to prevent cyclophosphamide-induced hepatotoxicity, it was found that HSD played its role by up-regulating PPARγ and reducing oxidative stress and inflammation, while PPARγ could effectively inhibit the transcriptional activity of NF-κB in a time and dose dependent manner [7] (Fig. 1) Table 1.

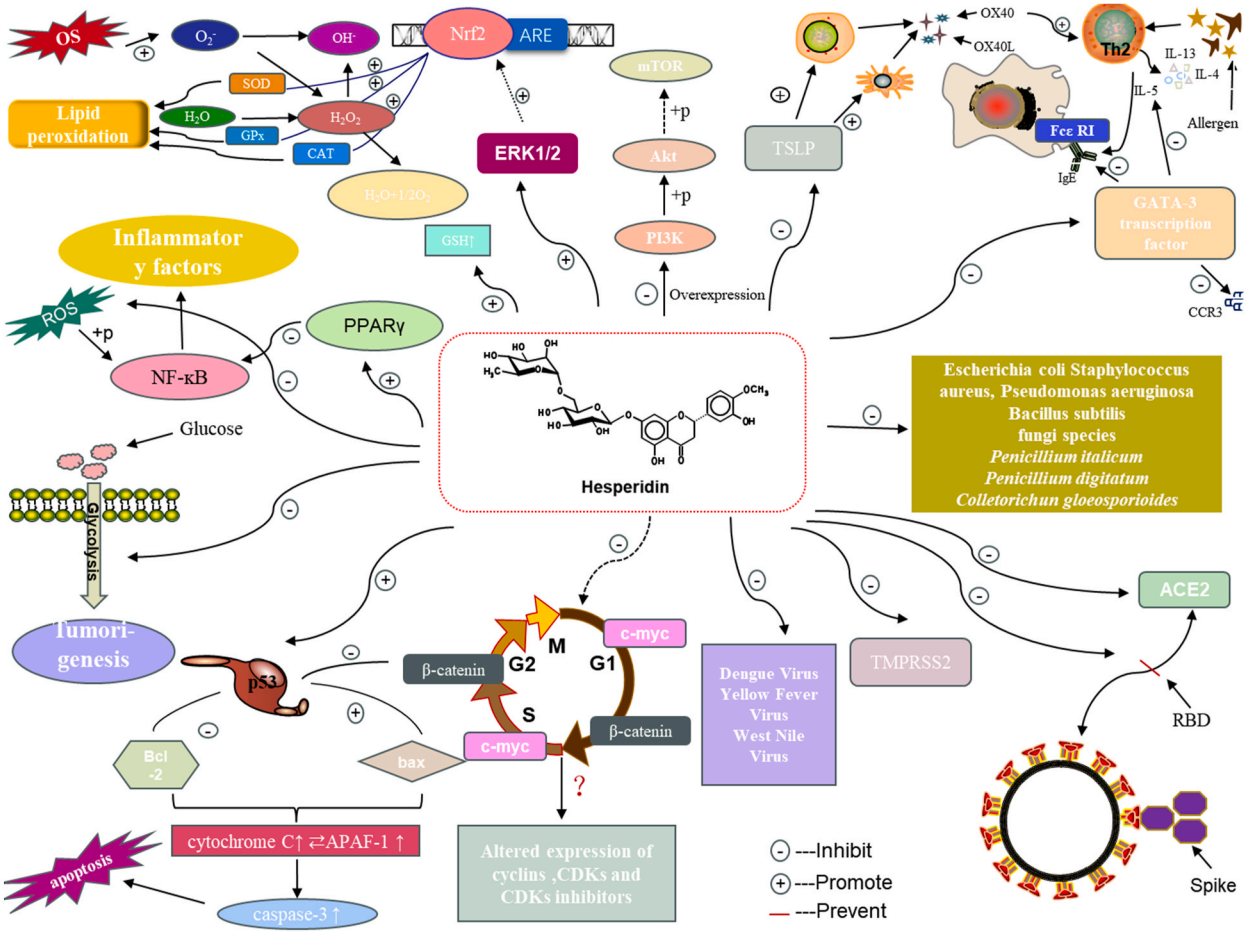

Fig. 1. ROS: reactive oxygen species NF-κB: nuclear factor kappa-B PPARγ: peroxisome proliferator-activated receptor γ SOD : superoxide dismutase CAT : catalaseGPx : glutathioneperoxidase OS: oxidative stress Nrf2 : nuclear factor erythroid-2-related factor 2 ARE: antioxidant response element ERK1/2: extracellular regulated protein kinases PI3K: phosphatidylinositol 3-kinase mTOR: mechanistic target of rapamycin TSLP: recombinant thymic stromal lymphopoietin OX40L: OX40 ligand Th2: T helper cell type 2 Fcε RI: Fc epsilon RI IgE: immunoglobulin EIL4/IL5/IL13: interleukin-4/ interleukin-5/ interleukin-13 ACE2: angiotensin converting enzyme 2 RBD: Spike-receptor binding domain TMPRSS2: transmembrane serine protease 2 c-myc: c-myc oncogene Bcl2: B-cell lymphoma-2 Bax: BCL2-associated X proteinp53: tumor protein 53 CCR3: chemokine (C-C motif) receptor 3

Table 1
A brief overview of the studies carried out using hesperidin.

Biological Activity	Model of Study	Treatment Dose	Mechanism of Action of Hesperidin	Ref.
Anti-inflammation	Wistar rats	40, 80 mg/kg/d; 0.2 mg/kg/d dexamethasone	mitigated inflammation & apoptotic process, activated cell cycle arrest, modulated adenosine nucleotides and nucleoside hydrolysing enzymes and levels, intracellular ROS↓	[4]
	Patients of type 2 diabetes	500 mg/day/d; 6 weeks	systolic blood pressure (SBP)↓, diastolic blood pressure↓, serum total antioxidant capacity (TAC)↑, TNF-α↓, IL-6↓, high-sensitivity C-reactive protein (hs-CRP)↓	[5]
	NAFLD patients	1 g hesperidin capsul; 12 weeks	Hesperidin & healthy lifestyle habits : alanine aminotransferase (AST)↓, γ-glutamyltransferase (GGT)↓, total cholesterol↓, triglyceride↓, hepatic steatosis↓, hs-CRP↓, TNF-α↓, NF-κB↓	[6]
	Wistar rats	25, 50 mg/kg/d; 11 days	Peroxisome proliferator activated receptor gamma (PPARγ) ↑,NF-κB & inducible nitric oxide synthase (iNOS) mRNA expressions↓	[7]
Antioxidation	J774A.1 cells; C57BL/6 mice	Cell : 24.42, 48.84, 97.7 μg/mL; Mouse : 10, 25, 50 mg/kg	Reduced the recruitment of inflammatory cells to the airways, oxidative damage and the formation of CCL-2↓, IL-12↓. Especially 50 mg/kg increased activity of enzymatic antioxidants↑	[8]
	SD rats	100 mg/kg/d; 7 days	Catalase (CAT)↑, superoxide dismutase (SOD)↑, glutathione peroxidase (GPx)↑, antioxidant↑, nitric oxide↑, blood urea nitrogenand↓, serum creatinine↓	[9]
Antibacterial activity	Water extract of Isatidis Radix, water extract of bergamot, bergamot essential oil, hesperidin against *Escherichia coli* (EC), *Staphylococcus aureus* (SA), *Pseudomonas aeruginosa* (PA) and Bacillus subtilis (BS)	The concentration of Hesperidin : 0.4 mg/mL	Water extract of bergamot, bergamot essential oil and hesperidin on these four bacteria were stronger than the water extract of Isatidis Radix, Hesperidin had the best antibacterial effect on SA, its MIC is 0.05 mg/mL and MBC is 0.2 mg/mL. Under the action of hesperidin, the growth of SA was slow, extracellular soluble proteins↑, extracellular nucleic acids↑	[10]
	The peel of Subgenus *Citrus*	The average content of hesperidin determined by HPLC was 22.7173 mg/g, accounting for 74.49 % of the total flavanones	Correlation analysis showed that the contents of total phenols, total flavonoids were positively correlated with hesperidin and vanillin, and there was also a certain correlation also between the contents of total phenols and total flavonoids; The hyphae of Penicillium↓, green mold ↓, anthrax↓	[11]
Antivirus	The human Beas 2B lung cell; the human NCI-H460 lung cancer cell; monkey VeroE6 kidney cells	/	Disrupted the interaction of ACE2 and SARS-CoV-2 S protein and the protein expressions of ACE2↓ and TMPRSS2↓	[12]
Anti-cancer	A549 cells	LC50: 12.5, 25 μM; 24h	The protein expressions of β-catenin↓, c-Myc↓, PCNA↓, cyclin D↓, cdk 4↓, Bcl-2↓; The expression levels of p53↑, p21↑,Bax↑,APAF-1↑,caspase-3↑, cytochrome *c*↑; Induced apoptosis	[13]
	A549, H460, H1975 cells	25, 37.5, 50, 62.5 μg/mL; 0,24,48,72h	CXCR-4↓; SDF-1↓; Vimentin↓; MMP-9↓; CK-19↑; the inhibition of EMT; promoted the activation of the NF-κB signaling pathway	[14]
	Female Wistar rats	200 mg/kg	Tumor occurrence↓, tumor volume↓, survival rate↑; Malondialdehyde (MDA)↓; TNF-α↓; NF-κ B↓; IL-6↓; Ki67↓; oxidative stress↓; reduce the organ toxicity associated with administration of Dox; comparable anticancer activity as that of doxorubicin alone	[2]
	The human breast epithelial cell lines MCF-7,MDA-MB-231	IC50 of MCF-7 cells : 30 μM; IC50 of MDA-MB-231 cells : 20 μM	Prevent S phase cell division; upregulate the Bax/Bcl-2 pathway in the MCF-7 breast cancer cell line; downregulated it in the MDA-MB-231 breast cancer cell line	[15]
	HEK-293, HepG2, SH-SY5Y cell lines	IC50 of HepG2: 47 μM; IC50 of SH-SY5Y: 75 μM; HEK293:/0, 25, 50, 75 μM; 24 h	Inhibit the HepG2 and SH-SY5Y cells proliferation; MMP↓; the mitochondrial	[16]

(*continued on next page*)

Table 1 (*continued*)

Biological Activity	Model of Study	Treatment Dose	Mechanism of Action of Hesperidin	Ref.
			membrane depolarization↓; caspase-3↑; Bax↑; inhibit the kinase activity of CAMKIV	
	PC3, DU145 cells	0, 2, 5, 10, 20, 50 μM; 24h	Regulate the increase of intracellular $Ca2^{+}$; inhibit the phosphorylation of proteins involved in the PI3K (AKT, P70S6K), MAPK (ERK1/2, P90RSK, P38); oxidative stress↑; mitochondrial membrane disruption↑; proliferation of cells↓;	[17]
	DU145, PNT1A cells	IC50 of DU145: 10 μM; 24 h IC50 of PNT1A: 150 μM	G2/M cell cycle arrest; necrosis-like cell death; ROS↑; MMP↓; control prostate cancer metastasis;	[18]
	The HN6 and HN15 of human Oral squamous cell carcinoma	HN6: 50 μM HN15: 25 μM, 50 μM	PD-L1↓; inhibit up-regulated PD-L1 protein expression by IFN-γ via the STAT1 and the STAT3 signaling molecules; viability↓, proliferation↓, migration↓, invasion ↓	[19]
	HeLa cancer cells	Selective doses of hesperidin; 12 h	Jab1↓; p27↑; ROS↑; caspase-3↑; G0/G1 phase arrest accompanied with reduction in S and G2/M cell cycle phases; induced nuclear fragmentation in HeLa cells; MMP↓	[20]
	HCT-116 human colon cancer cells	IC30:≈129 μm; IC50:≈303 μm; 24h	At IC50 and IC30 concentration reduced notch target gene mRNA (Hes-1, Hey-1) levels & stemness/self-renewal markers (CD44, c-Myc, ALDH1, Gli 1); reduced sphere formation in colon cancer stem-like cells	[21]
	Albino rats	25 mg/kg; twice a week for 2 weeks	Inhibit the progression of colonic ACF; suppresses the transformation of preneoplasia to malignant neoplasia; Induce tumor tissue necrosis; Smad4↑; inhibit epithelial cell transformation and hyper proliferation; activin A↑; ROS↓	[22]
Anti-allergy	Female BALB/c mice	1, 5 mg/kg; 3 times a week for the last 5 weeks	Suppressed eosinophil infiltration, allergic airway inflammation, airway hyper-responsiveness (AHR); Th2 cytokines (IL-5)↓; IL-17↓; OVA-specific IgE↓; GATA-3↓; Th2 cytokine (IL-4) (5 mg/kg); eosinophil CCR3↓	[23]
	Female NC/Nga mice	AIN-93M diet with 0.1 % hesperidin (1 g/kg diet); AIN-93M diet with 0.13 % αG-hesperidin-containing diet (1.3 g/kg diet); 8 weeks	IL-17↓; skin lesions; Tribbles homolog 3 (TRIB3)↓, nuclear protein 1 (NUPR1)↓, activating transcription factor (ATF5)↓, RORγt↓, Foxp3↑, CTLA4 (αG-hesperidin)↑; enhance Treg activity; improved Th17/Treg balance; the inhibitory activity of αG-hesperidin was more potent than that of hesperidin	[24]
	BALB/c mice	100 mg/kg/d; began on the 18th day and lasted for 28 days	The symptoms of rhinitis↓; pathological damage of nasal mucosa↓; serum histamine & Ig E returned to normal; IL-4↓; IL-5↓; IFN- γ↑; IL-2↑; Th1/Th2 tend to be normal; inhibit TSLP/OX40L/OX40 pathway; GATA3↓	[25]
	Female ICR strain mice	Prednisolone:0.1 ml/10 g body weight of mouse/day, day 0 to day 5 for 6 days; CU-ext and hesperidin:0.2 ml/10g body weight of mouse/day, day −1 to day 5 for 7 days	The combination group (Hesperidin:20 and 50 mg/kg for 7 days & prednisolone:0.2 and 1 mg/kg for 6 days) inhibits ear swelling in a dose-dependent inhibitory effects; In combination group (Hesperidin:5 mg/kg & prednisolone: 0.2 mg/kg) thymus weight was reduced; CU-ext inhibits ear swelling during the induction and effector phases of PC-CD	[26]
Cardiovascular protection	Overweight male volunteers, 50–65 y of age	500 mL orange juice; 2 capsules (=500 ml orange juice),3 periods of 4 week	Diastolic BP(DBP)↓; uric acid↓; improve postprandial microvascular endothelial reactivity; vitamin C and b-cryptoxanthin were higher in fasted plasma after 4 weeks consumption of orange juice	[27]
	Male wistar albino rats	100,200 mg/kg; 14 d	NF-κB↓; TNF-α↓; IL-1β↓; Beclin↓; LC3A↓; LC3B↓; LDH↓; CK-MB↓; SOD↑; CAT↑; GPx↑; GSH↑; PI3K↑; AKT↑; mTOR↑; mRNA level of BAX↓, NF-κB↓, CAS-6↓, mTOR↓, CAS-6↓, AKT↓, p53↓, CAS-9↓, PI3KA↓; mRNA level of Bcl-2↑	[28]
	C57BL/6J ApoE KO mice	Hesperidin:3 mg/kg/d & varenicline:0.5 mg/kg/d; 3 weeks	Remarkably decreased varenicline-aggravated aortic plaque formation in the	[29]

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Table 1 (*continued*)

Biological Activity	Model of Study	Treatment Dose	Mechanism of Action of Hesperidin	Ref.
			whole aorta, aortic arch, and aortic root; reduce the varenicline-increased macrophage-rich area to 104 % of vehicle; CD36↓; LOX-1↓; reverse the enhanced oxLDL net uptake in macrophages	
	C57BL/6 male mice	50, 100 mg/kg; 2 weeks	Heart weight/body weight ratio↓; CK-MB↓; infarct size↓; TNF-α↓; IL-1β↓; IL-6↓; MCP-1↓; ICAM-1↓; MDA↓; SOD↑; CAT↑; caspase-3↓; caspase-9↓; p53↓; Bax/Bcl-2↓; PPAR-γ↑;	[30]
	Male Sprague-Dawley rats induced by N-nitro-L-arginine methyl ester (L-NAME)	15,30 mg/kg; 5 weeks	The left ventricular hypertrophy↓; fibrosis↓; TGF-β1↓; TNF-R1↓; inhibit vascular remodeling; oxidative stress↓; NO bioavailability↑; plasma NOx level↑; prevent development of hypertension	[31]
	Male albino Wistar rats of cardiac hypertrophy induced by isoproterenol (ISO)	200 mg/kg/d; 28 d	ISO-induced myocardial hypertrophy (HW/BW ratio, cardiomyocyte area)↓; GSH↑; SOD↑; CAT↑; TNF-α↓; IL-6↓; NF-κB↓; JNK↓; p-JNK↓; PPAR-γ↑; caspase-3↓; Bcl-2↑;	[32]
Neuroprotection: stroke	Male wistar rats	50, 100 mg/kg; 7 d	Improve neurobehavioral alterations (neurological score, locomotor activity, resistance to lateral push and hanging wire latency); oxidative damage↓; restore antioxidant, mitochondrial complex enzyme activities in cortex and in striatum;	[33]
	Institute of Cancer Research (ICR) micez; bEnd.3 cells	Animal:10 mg/kg, 24 h; Cell:10, 30 μg/mL	TJs↓ (claudin-5 and ZO-1); TEER (cell)↓; DPPH radical scavenging activity; FoxO3a translocation↓; mMP 3/9↓; inhibit ROS increase	[34]
	Male C57BL/6 mice	/; 12 h	AKT phosphorylation↓; MST4↓; LC3-II↓; brain edema↓; improve neurological deficits	[35]
	Patients with ischemic stroke	4 mg/kg body weight (400 mg maximum); 24 h, 7 d, 2 month	TGF-β1↓; MMP-2↓; MMP-9↓; the incidence rate of SIH following rt-PA↓; improve the transcranial Doppler ultrasonography (TCD), NIH Stroke Scale (NIHSS)	[36]
Neuroprotection: Neurodegenerative diseases	Neural progenitor; neuronal morphogenesis	10 μM; 48 h	DAPI labelled cells increase 71 %; b-tubulin III positive cells increase 80 %; The number of neurons↑; nitrite production reduce 50 %; activate the PI3K and MAPK pathways; Pools of astrocyte and oligodendrocyte progenitors were not affected	[37]
	female C57 BL/6 mice (18 mo old)	50 mg/kg/d; 28 d	Antioxidant; attenuate depressive-like behavior inferred from TST; impairment of cognitive performance based on the Morris water maze task; increased ROS levels; decreased GSH levels and TRAP; inhibition of GPx and CAT activity and rises in GR activity; decreased DA, DOPAC and HVA levels	[38]
	The Homosapien Bone Marrow Neuroblastoma (SH-SY5Y) cell line; Wildtype AB strain zebrafish	Cell:12.5, 25 μM;/Zebrafish:10, 20, 40 μM; 72 h	Cell:ROS↓; CAT↑; GSH↑; SOD↑; improve the MMP; Zebrafish: lrrk2↓; gsk3 β↓; casp 9↓; polg↓;	[39]
	neural stem cells (NSCs) from five familial AD (5xFAD) mice	50 μM; 24 h	AMPK↑; CREB↑; affects cell proliferation rather than cell differentiation; increase the number of newborn neurons; mediate AMPK/BDNF/TrkB/CREB signaling; memory impairment↓; increase NSC proliferation and the number of mature neuronal cells	[40]
	Male Wistar rats	100 mg/kg (10 ml/kg); 5 d	Pretreatment with hesperidin 1h can reduce spontaneous locomotor activity, deficit in PPI of startle response, oxidative stress, multiple histological and cellular abnormalities, iNOS; attenuate the disruption elicited by 3-NP through free radical scavenging, increased oxidative defense, decreased NO levels and increased SDH activity; MDA↓; CAT↑	[41]
	Drosophila melanogaster model of Parkinson-like disease induced by iron (Fe) exposure	10 μM; 10 d	Attenuate motor and non-motor alterations, such as motor coordination, memory deficits and anxiety-like behaviors, monoaminergic deficits, and lowered Fe levels in the head of flies; may can sedation, myorelaxation, and	[42]

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Table 1 (*continued*)

Biological Activity	Model of Study	Treatment Dose	Mechanism of Action of Hesperidin	Ref.
			analgesia; extend the flies' lifespan; iron chelation	
Neuroprotection: Depression	Male Sprague-Dawley (SD) rats	20, 50, 100 mg/kg; 14 d	Inhibit SPS-induced increases in plasma CORT levels; restoration of grooming behavior in the open field; displaying freezing behavior was reduced; reduce immobility time in the FST and the occurrence of anxiety-like behaviors; improve depression-like behaviors in an SPS-induced PTSD model by inhibiting decreases in hippocampal 5-HT; inhibited SPS-induced increases in hippocampal NE, suggesting that HSD may regulate the central adrenergic system as well as indirectly altering the synthesis of monoamines, such as DA, in the brain	[43]
	Male NMRI mice	50 mg/kg/d; 14 d	anti-depressant-like effects; immobility time induced by mTBI↓; the latency to feed↓; BDNF↑; MDA↓; TNF-α↓; IL-1β↓;	[44]
	Male Sprague Dawley rats	20, 50, 100 mg/kg/d; 28 d	IL-1β↓; IL-6↓; TNF-a↓; NLRP3↓; caspase-1↓; ASC↓; improve the anhedonia-like state in the SPT; ameliorate depressant-like states; diminish the effects of activation in LPS-treated cells	[45]

2.2. Antioxidation

Oxidative stress (OS) refers to the imbalance of reactive oxygen free radicals or/and lack of antioxidant system in cells [51]. Oxidative stress can be caused by many factors, such as environmental conditions, lifestyle choices, disease status and genetic susceptibility [52]. Oxidative stress has been shown to be associated with many diseases, including atherosclerosis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease and cancer, revealing multiple mechanisms of oxidant-induced cell damage [53]. Souza et al. proved that HSD can play a beneficial role in lung injury caused by mechanical ventilation by regulating oxidative stress and inflammation in vivo and in vitro [8]. HSD is a kind of flavonoids, some studies have shown that flavonoids have good free radical scavenging activity. Literature has pointed out that the antioxidant capacity of HSD can be quantified through such as the 2,2-diphenyl-1-pyridine hydrazide (DPPH) radical scavenging test or the oxygen radical absorbance capacity (ORAC) test, and its IC50 value (concentration required to scavenge 50 % of radicals) is between 10 and 100 μM. Malondialdehyde (MDA) levels is a marker of lipid peroxidation. HSD can significantly reduce MDA levels by 50 % during oxidative stress, increase mitochondrial ATP production by 30 % and reduce mitochondrial ROS levels by 40 % [54]. Park et al. used HSD to treat acute renal ischemia-reperfusion (I/R) injury in SD rats. The results showed that the expression levels of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the HSD treatment group were significantly higher than those in the untreated group, reflecting the antioxidant capacity of HSD [9]. Some studies have shown that the antioxidant activity of HSD is not only limited to free radical scavenging activity, but also enhances the defense of antioxidant cells through ERK/Nrf 2 signal pathway [55,56] (Fig. 1) Table 1.

2.3. Antibacterial activity

Polyphenolic compounds are a class of plant nutrients with diverse structures, and flavonoids (flavonols, flavanones, flavanols-3-ols, anthocyanidins, isoflavones and flavones) are one of them [57]. In the biological function of flavonoids, the antibacterial activity has been widely studied [58]. HSD, as a kind of flavonoids, naturally attracts much attention. Wang et al. by studying the active ingredient HSD of bergamot, it was found that the minimum inhibitory concentration (MIC) of HSD against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and Bacillus subtilis was 0.05 mg/mL (≤7.81 mg/mL), indicating that HSD was highly sensitive to Gram-positive and Gram-negative bacteria and had good antibacterial activity. The minimum bactericidal concentration (MBC) of HSD to the above four bacteria was 0.2 mg/mL, and HSD had the strongest germicidal efficacy compared with water extract of Isatidis Radix, water extract of bergamot, bergamot essential oil [10]. The study of antibacterial mechanism found that HSD may change the cell membrane permeability and make the intracellular protein and nucleic acid macromolecules leak out of the cell through the cell membrane, thus affecting the growth of bacteria and achieving bacteriostatic effect [59]. Zuo detected polyphenols in the pericarp of subgenus Citrus by HPLC and analyzed the correlation. It was found that HSD also inhibited the mycelial growth of Penicillium, Green mold and anthracnose to a certain extent [11] (Fig. 1) Table 1.

2.4. Antivirus

COVID-19 (Corona Virus Disease 2019) was once a global pandemic disease. In fact, novel coronavirus is still in constant variation, and its treatment is imminent. Some studies have shown that HSD may be used to prevent and treat COVID-19.The pathogen of COVID-

19 is severe acute respiratory syndrome coronavirus 2(SARS-CoV-2).SARS-CoV-2 uses its spike protein (Spike, S) to bind to the host receptor angiotensin converting enzyme 2 (ACE2) to mediate the virus [60]. Some studies have established the database of 78 commonly used antiviral drugs by virtual ligand screening. This study shows that natural HSD is the only compound that can target the interface between SARS-CoV-2S protein and ACE2 human receptor [61]. Based on virtual screening, HSD may disrupt the interaction between ACE2 and the RBD of SARS-CoV-2, thereby preventing its entry into lung cells [61]. Cheng et al. confirmed that HSD not only destroys the interaction between ACE2 and SARS-CoV-2S protein, but also inhibits the expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) protein, thus reducing SARS-CoV-2 infection, indicating that HSD can be used as a potential drug for prevention and treatment of COVID-19 [12]. According to reports, hesperidin disrupted the essential protein-protein interactions required for virus attachment and entry by forming hydrogen bonds, hydrophobic interactions, electrostatic interactions, and pi-stacking interactions with critical residues of the spike protein. This prevented the virus from effectively binding to the human ACE2 receptor, thereby hindering viral infectivity. This mechanism involves recognizing specific residues, occupying binding sites, and comprehensively inhibiting viral fusion and replication [54]. In addition, studies have shown that HSD can help combat COVID-19 virus replication by activating host immunity, thus improving the prognosis of patients [62]. Other studies have shown that HSD and its aglycone hesperitin may inhibit dengue virus, yellow fever virus by inhibiting NS2B/NS3 protease [63,64] Table 1.

2.5. Anti-cancer

Cancer is the main cause of death in China and developed countries [65]. Bioflavonoids have attracted wide attention in cancer treatment because of their strong antioxidation and biological activity [66]. HSD, as a flavonoid, is one of the most important bioactive components with anticancer potential, and can affect a variety of molecular targets involved in the mechanism of tumor cell survival, division and death [1]. HSD can block cell cycle progression in G1, G2 and M or S phases [67]. The cell cycle arrest mediated by HSD may be related to the regulation of cell cycle regulatory proteins, including CDK inhibitors, cyclin-dependent kinases and cyclins [67]. It has been pointed out that cancer cells usually show an increase in glycolysis efficiency, and HSD and its aglycones can show anticancer effect by inhibiting glucose uptake in different cancer cell lines [66,68]. For human lung cancer A549 cells, some researchers found that HSD inhibits cell proliferation and prevents the progression of the cell cycle by downregulating the expression of C-MYC and β-catenin, and activates p53-related pathways, reducing the ratio of Bcl-2/Bax, leading to the release of cytochrome C, apaf-1 complex and activation of caspases 3, and ultimately leading to apoptosis-induced cell death [13]. In another study, researchers found that HSD inhibits the migration and invasion of human lung cancer A549 cells by mediating the SDF-1/CXCR-4 signaling cascade [14]. In addition, because of the anti-cancer properties of HSD, many in vivo and in vitro studies have applied it to cancer treatments such as breast cancer [2,15], liver cancer [16], prostate cancer [17,18], neuroblastoma [16], oral cancer [19], cervical cancer [20], colon cancer [21,22], and other cancer treatments and confirmed that HSD exerts anti-cancer properties through different mechanisms of action (Fig. 1) Table 1.

2.6. Anti-allergy

Allergic diseases include allergic rhinitis, allergic bronchial asthma ("asthma"), atopic dermatitis, food allergy, etc., which have been listed as one of the six most common chronic diseases by WHO and become the focus of research and prevention in the 21st century [69]. Allergic reaction refers to the tissue damage or dysfunction of the immune-producing body when it is stimulated by the same antigen again [70]. After exposure to allergens, atopic individuals activate allergen specific Th2 cells, which secrete cytokines (IL-4, IL-5, IL-13) and produce allergen specific IgE antibodies [71]. IgE passes through FcεRI receptor binding, enveloping mast cells, and subsequent exposure to the same allergen leads to mast cell degranulation, release of mediators, and induction of related allergic manifestations [71]. It is reported that HSD can significantly inhibit airway inflammation in asthmatic mice by inhibiting GATA-3 transcription factors, reducing the production of Th2 cytokines (IL-5), OVA-specific IgE and the expression of eosinophil CCR3 [23]. In another study, the researchers found that HSD and αGHSD (transglycosylation synthesis using cyclodextrin glucan transferase) could inhibit the development of atopic dermatitis-like skin lesions in NC/Nga mice by inhibiting Th17 activity and enhancing Treg activity, and the inhibitory activity of αGHSD was more effective than that of HSD [24]. Domestic researcher Li Wei et al. found through animal experiments that HSD may reduce Th2 immune response and improve nasal mucosal allergic reaction in mice with allergic rhinitis by inhibiting the activation of TSLP/OX40L/OX40 signal [25]. HSD can also cooperate with other drugs to play an anti-allergic effect. Fujita et al. studied the therapeutic effects of 50 % ethanol extract of Fructus Aurantii (CU-ext) and HSD, the main component of CU-ext, on ear swelling in mice with contact dermatitis (PC-CD) induced by trichloropyridine. The results showed that subcutaneous injection of prednisolone and/or oral CU-ext could inhibit ear swelling during PC-CD induction and effect period, and subcutaneous injection of prednisolone and/or oral HSD could inhibit ear swelling during PC-CD induction [26]. And the effect of combined use is better than that of single use [26]. It was also found that the combination of CU-ext and prednisolone and the combination of HSD and prednisolone had synergistic effect and did not enhance the adverse reactions of steroids [26] (Fig. 1) Table 1.

2.7. Cardiovascular protection

Cardiovascular disease is the leading cause of disease and death worldwide, and the prevalence of related deaths has increased from 12.1 million in 1990 to 18.6 million in 2019, and is estimated to reach 24 million by 2030 [72]. The development of cardiovascular disease is usually related to the existence of many risk factors, and diet is a major external factor in the development of cardiovascular disease [73]. As one of the most important bioactive components in citrus, HSD plays an important role in human health. HSD has

beneficial effects on different biomarkers of cardiovascular risk in both animal and human studies [74]. A study on healthy volunteers showed a decrease in uric acid concentration and an increase in plasma vitamin C concentration after drinking orange juice or pure HSD capsules for 4 weeks, which may be associated with cardiovascular disease morbidity and mortality [27]. In animal experiments, Varışlı et al. studied the cardioprotective effect of HSD on rats induced by sodium fluoride. The results showed that HSD could inhibit lipid peroxidation by increasing the activities of SOD, CAT, GPx and the level of GSH; reverse the changes of apoptosis, autophagy and inflammation; regulate the gene expression level of PI3K/Akt/mTOR signal pathway and the level of cardiac markers (LDH, CK-MB), thus play a protective role in cardiotoxicity [28]. Varenicline is an effective drug to quit smoking, but it has the side effect of increasing the risk of cardiovascular disease. Koga et al. found that HSD can prevent valencine from aggravating atherosclerotic plaque formation by reversing the increased net uptake of oxidized low-density lipoprotein by macrophages [29]. In addition, some studies have found that HSD can regulate the occurrence of acute myocardial infarction [30], cardiovascular remodeling [31] and myocardial hypertrophy [32] through different signal pathways, reflecting the application prospect of HSD in the treatment of cardiovascular diseases (Fig. 1) Table 1.

3. Application in central nervous system diseases

3.1. Stroke

According to data published by GBD 2019, there were 12.2 million stroke cases and 101 million stroke epidemics in 2019 alone, 143 million disability-adjusted life expectancy due to stroke and 6.55 million stroke deaths [75]. Stroke remains the second leading cause of death and the third leading cause of death and disability worldwide [75]. Stroke is divided into ischemic stroke and hemorrhagic stroke. According to a case statistics on stroke in China, also in 2019, there were 2818875 cases of ischemic stroke, accounting for 82.6 %; 485474 cases of cerebral hemorrhage, accounting for 14.2 %; and 106819 cases of subarachnoid hemorrhage, accounting for 3.1 % [76]. This shows the impact of stroke epidemic on China and the world. The occurrence of ischemic stroke and hemorrhagic stroke will activate various signal pathways, and then cause damage to brain tissue or protect neurological function, among which the pathophysiology of ischemic stroke, mainly involves cell excitotoxicity, oxidative stress, cell death process and nerve inflammation; hemorrhagic stroke, like the pathophysiology of cerebral hemorrhage, is mainly related to oxidative stress, inflammation, siderotoxicity, thrombin formation and so on [77,78].

Blood-brain barrier (BBB) is a dynamic brain barrier between brain and peripheral circulation, which is composed of cerebral capillary endothelial cells, pericytes and astrocyte end-feet, effectively protecting the brain from harmful toxins and pathogens from bloodstream [79]. The BBB regulates microenvironment through its ion channels and transporters, maintains ion homeostasis and nutrition needed by the brain, regulates the level of neurotransmitters in the brain, and limits the penetration of plasma proteins and neurotoxins into the brain [80]. The mechanism of BBB destruction caused by stroke includes tight junction (TJ) protein phosphorylation, transporter expression regulation, neuroinflammation and abnormal enzyme function [81]. TJs consists of complete membrane and cytoplasmic accessory proteins, including occludin, claudin, JAMs, ZO proteins and cingulin. The permeability of BBB is related to the redistribution of occludin, ZO1, ZO-2 and claudin-5, IL-1 is related to the induction of endothelial cell adhesion molecules during ischemic stroke, and the increase of paracellular permeability of BBB induced by IL-β is related to the deletion of occludin and ZO-1 in junction complex [81]. After stroke, MMPs are related to the decrease of BBB integrity through tight junction and basement membrane degradation. Specifically, MMP-2 is involved in the initial stage of BBB permeability after ischemic stroke, while MMP-9 is involved in the later stage after stroke, which leads to BBB rupture and neuronal damage by destroying tight junction, increasing the infiltration of inflammatory mediators, inducing neurotoxicity and aggravating the consequences of stroke. Among them, oxidative stress in acute cerebral ischemia, especially through the secretion of MMP-9, negatively promotes the migration of peripheral cells, aggravates brain damage, and leads to the rupture of BBB [82].

It is confirmed by the cellular blood-brain barrier model that flavonoids and their metabolites are transported across human brain microvascular endothelial cells in a time-dependent manner. In other words, flavonoids can cross the blood-brain barrier and play a direct role in the central nervous system [83]. As a kind of flavonoids, HSD can also cross the blood-brain barrier. Gaur et al. found that pretreatment with 50 mg/kg and 100 mg/kg HSD significantly improved the neurobehavioral changes of rats, alleviated oxidative damage, and restored the levels of antioxidant enzymes SOD and CAT in the striatum and cortex and the activity of mitochondrial complex enzyme [33]. Lee et al. by making mouse MCAO model and blood-brain barrier endothelial cell model in vitro and intervening with HSD, they found that HSD inhibited the degradation of claudin-5 and the redistribution of ZO-1 through its antioxidant activity, thus alleviating the dysfunction of blood-brain barrier during hypoxia [34]. Many studies have found that the increase of blood-brain barrier permeability induced by oxidative stress is generally related to the changes of claudin-5 and ZO-1 [34]. Wu et al. reported that HSD is an effective selective inhibitor of MST4 kinase, and found that it can inhibit autophagy through MST4/AKT pathway and improve brain edema and neurological impairment in mice with intracerebral hemorrhage [35]. In clinical practice, it is mainly used for the side effect of symptomatic cerebral hemorrhage caused by the use of tissue plasminogen activator (t PA) after stroke. Studies have shown that the combination of HSD and recombinant tissue plasminogen activator (rt PA) significantly improves the treatment effect within 1 day and reduces the incidence of symptomatic cerebral hemorrhage after rt PA, mainly by promoting transforming growth factor (TGF)-β1 secretion, inhibiting the secretion of MMP-2 and MMP-9 to achieve active therapeutic effects; After the initial reperfusion of rt- PA, continuous follow up with HSD was given, and the results of treatment one week after stroke also improved [36]. From the above, it is not difficult to see the great potential of HSD in stroke treatment, and some literature has mentioned that its acute oral toxicity test LD50 in traditional Chinese medicine formulas is greater than 2000 mg/kg, and animal experiments have also confirmed that HSD has good biological safety [84]. It has been pointed out that TGF-β1, SIRT1, ERK1/2 and RAGE, as well as

ferroptosis, may be affected by many flavonoids, especially the activation of ERK1/2 signaling pathway is related to the pathological process of cerebral vasospasm vascular wall proliferation, because cell proliferation in the vascular wall is the key factor of CVS development in SAH, and TLR4 downstream of ERK1/2 can promote the secretion of inflammatory factors through c-Fos phosphorylation, which can aggravate the inflammatory reaction [85] Table 1.

3.2. Neurodegenerative diseases

Neurodegenerative diseases are a group of diseases that affect the central and peripheral nervous systems. Their clinical and pathological manifestations are varied, which are caused by loss of neurons in different regions [86]. These include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and so on. AD is mainly characterized by extracellular aggregation of β-amyloid plaques in the cerebral cortex and marginal zone and intracellular nerve fiber tangles composed of hyperphosphorylated τ-protein, characterized by memory loss and progressive neurocognitive impairment [87]; PD is the second largest neurodegenerative disease after AD, characterized by neural inclusions in the form of Lewis bodies and Lewis neurites, as well as cell loss in the substantia nigra and other brain regions [88]; HD is caused by the abnormal expansion of CAG repeat sequence near the N-terminal of Huntington protein gene (HTT), which leads to the production of HTT gene [89]. The causes of these diseases are not only genetic and environmental factors, but also brain aging, strong oxidative stress, mitochondrial DNA mutation, inflammatory response, apoptosis regulation defects and other factors [90]. Nones et al. enhanced the neuronal population by treating neural progenitor cells with HSD, increase the number of β-tubulin III cells by 80 %, regulate the survival of neuronal precursors, and regulate neuronal cell death by activating MAPK and PI3K pathways, providing the possibility for the use of flavonoids in the treatment of neurodegenerative diseases [37]. And now more and more animal studies have shown that HSD has a protective effect on neurodegenerative diseases [38–41]. In a recent model of Parkinson's disease like Drosophila induced by iron exposure, HSD was used to study motor and non-motor changes. The results showed that HSD improved dopaminergic function, reduced iron levels in the head, and suppressed the development of non-motor changes such as memory deficits and anxiety like behaviors [42]. It is worth noting that HSD may also have iron chelating activity, which will promote the further exploration of the medicinal value of HSD Table 1.

3.3. Depression

Depression is a recurrent mood disorder, characterized by persistent depression and cognitive impairment, with high prevalence, high recurrence rate, high suicide rate, high disability rate and so on [91]. Depression affects about 840 million people around the world, and women are twice as affected as men, which is the second leading cause of disability in China and has become an important public health problem [92]. Theories about depression mainly focus on monoamine neurotransmitter depletion hypothesis, neuroplasticity hypothesis and hypothalamus-pituitary-adrenal axis (HPA) hypothesis, but these all have some limitations, such as inability to explain the delayed effects of antidepressants and lack of attention to cells other than neurons in the central nervous system [93]. Recent studies have described depression as a microglia-related disease (microglia disease), and demonstrated that microglia-mediated neuroinflammation interacts with the above three related theories [93]. Neuroinflammation and HPA axis are considered to be synergistic, and their disorders may mediate the occurrence of depression [94]. Oxidative stress and inflammation, known as "aging twins", may also be related to the pathogenesis of depression and the response to antidepressant treatment [94]. Animal experiments have shown that HSD can improve the depression-like behavior of SPS-induced post-traumatic stress disorder model by inhibiting the decrease of 5-hydroxytryptamine in hippocampus [43]. Studies have found that administering HSD after modeling mild traumatic brain injury (MTBI) significantly alleviates the depressive symptoms induced. In addition, it also decreased the levels of IL-1 β, TNF- α and MDA in hippocampus, and increased the level of brain-derived neurotrophic factor BDNF in hippocampus [44]. HSD was also used in the treatment of chronic unpredictable mild stress (CUMS) model and found that HSD could significantly reduce the depressive behavior of CUMS rats, reduce the expression of IL-1β, IL-6, TNF-a, NLRP3, Caspase-1 and ASC in prefrontal cortex and microglia, and inhibit the activation of microglia [45]. As mentioned above, we may find that the antidepressant effect of HSD is the result of the interaction of multiple mechanisms, not a single mechanism can be explained clearly Table 1.

4. Discussion

From the above point of view, HSD has a certain medical value, no matter from its biological activity or its role in central nervous system diseases. However, it is not difficult to find that most of the research results are based on animal experiments and lack of clinical trial results, which undoubtedly limits the application of HSD. In fact, some inconsistent effects of HSD in human studies are partly due to individual differences in its bioavailability, which in turn highly depends on α-rhamnosidase activity and the composition of intestinal microflora [95]. In the human body, oral HSD is hydrolyzed into hesperitin by intestinal microbial rhamnosidase in the colon. Hesperidin appears in plasma in the form of glucaronides (87 %) and sulphaglucooronides (13 %) 3 h after ingestion, reaches the maximum at 5–7 h, and then undergoes cyclic fission and catabolism to produce phenolic acids and their respective metabolites [96]. However, the water solubility of HSD is extremely poor and its bioavailability is limited, so measures need to be taken to improve its bioavailability. Some studies have shown that when flavonoids are used in combination with various chemotherapeutic drugs, even at relatively low doses, they seem to increase the therapeutic effect and reduce the toxicity at the cellular level, such as HSD combined with the anticancer drug doxorubicin, which helps to improve the efficacy of anticancer drugs, reduce the side effects of cell migration induced by doxorubicin and prevent cancer recurrence [97,98]. In order to overcome the problem that flavonoids are insufficient to achieve their respective goals, preparations based on nanotechnology can be used to improve the bioavailability and solubility of

flavonoids, and to help achieve targeted drug delivery, controlled release mode and enhance efficacy [98]. For example, hesperidin conjugated gold nanoparticles (HSP-AuNPs) are synthesized by chemical reduction method, which has significant antioxidant activity through HSP- AuNPs, with the levels of SOD, CAT and GSH are increased, and the level of MDA is decreased [99]. It can prevent the cognitive dysfunction of diabetic rats. Phospholipids and cyclodextrins are two commonly used amphiphilic compounds. They can form complexes with polyphenols/flavonoids to improve bioavailability [100]. For example, after the complexation of HSD and soybean phosphatidylcholine, the plasma concentration of phospholipid and cyclodextrin increased in vivo, which may be due to the increased synergism of drugs at the active site to enhance the therapeutic activity of HSD [101]. Unlike its aglycone, HSD has poor membrane permeability and is mainly absorbed through the paracellular pathway, which means that the tight junction of intestinal cells may limit its absorption [102]. It is worth noting that HSD can pass through the blood-brain barrier, which is the source of its neuroprotective effect. However, there are exceptions to everything. Not all flavonoids have positive therapeutic effects. For example, rotenone will aggravate mitochondrial damage and neuronal ferroptosis, which will lead to the aggravation of intracerebral hemorrhage [103].

Throughout this paper, we can see that most of the research evidence of hesperidin comes from pre-clinic, which hinders the clinical popularization of hesperidin. In addition to the aforementioned bioavailability problems, there are also studies showing that it may be due to the difference in pharmacokinetics of citrus flavonoids. Methylation, glucuronidation and sulfation of metabolites were observed in rats (and dogs), but only glucuronidation and sulfation occurred in humans. The therapeutic effect of hesperidin on non-human species is not completely suitable for human treatment [104]. In addition, it has been reported that hesperidin has drug interactions, which may reduce the absorption of celiprolol and diltiazem, increase the absorption of verapamil, slow down blood coagulation and lead to excessive sleepiness [105]. In short, the purpose of this paper is to describe the biological activity of HSD, one of the most important active components of citrus, and its role in central nervous system diseases, and to provide ideas for the clinical application of HSD. There is currently limited research on the clinical application of HSD, such as bioavailability, appropriate dosage, tolerance, and the efficacy of HSD and its metabolites in central nervous system diseases. In addition, due to the fact that some studies on the clinical efficacy of HSD mostly focus on healthy individuals, and the effectiveness of HSD treatment in animal experimental models, there is a question of whether HSD is used as a therapeutic drug or a supplement, which is a question that needs to be highly valued in future research. Because citrus fruits not only contain hesperidin, but also contain many other beneficial compounds, such as vitamin C, which can increase the bioavailability and antioxidant effect of hesperidin. Although supplements may be hesperidin specially designed to provide the necessary therapeutic dose for treating certain diseases, they lack the broader nutritional benefits in natural foods. Although the natural sources of hesperidin and its supplements are safe, their use must take into account such factors as the required therapeutic effect, potential side effects, diet balance and personal health. Generally speaking, natural sources are safer to improve overall health, and supplements should be used with caution and under medical supervision, especially for therapeutic purposes [54].

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CRediT authorship contribution statement

Rui Ma: Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Hong You:** Writing – review & editing, Supervision, Resources, Project administration. **Hong Liu:** Supervision, Methodology, Data curation. **Juan Bao:** Supervision, Methodology, Conceptualization. **Min Zhang:** Writing – review & editing, Validation, Supervision, Resources, Project administration.

Declaration of competing interest

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