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Letter to the editor:

RECENT INSIGHTS INTO THE BIOLOGICAL FUNCTIONS OF HESPERIDIN

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Hesperidin (3,5,7-trihydroxyflavanone 7-rhamnoglucoside) is a β-7-rutinoside of hesperetin (4′-methoxy-3′,5,7-trihydroxyflavanone) (Sharma et al., 2021). It is a flavonoid and, thus, one of the much extended flavanones, which are among the most abundantly existing phenol compounds in plants (Hajialyani et al., 2019; Rahmani et al., 2023). Hesperidin and its aglycone derivatives are major compounds in citrus fruits of the Rutaceae family: orange (*Citrus sinensis*), grapefruit (*Citrus paradise*), tangerine (*Citrus reticulata*), lime (*Citrus aurantifolia*) and lemon (*Citrus limon*) (Lee and Han, 2013; Phucharoenrak et al., 2022; Rodrigues and Pintado, 2024; Wu et al., 2007; Xu et al., 2024). Their abundance in citrus fruit depends on the plant variety, fruit tissue type, climate and the stage of fruit ripening (Gattuso et al., 2007; Pyrzynska, 2022).

Hesperidin possesses biological and pharmacological activities, such as antioxidant, anti-inflammatory, antibacterial, antiviral, anti-allergic, anticancer, cardiovascular protective, and neuroprotective properties (El-Shiekh et al., 2025; Kowalczyk, 2024; Ma et al., 2024).

Both pre-clinical and clinical studies have demonstrated the beneficial effects of hesperidin on various diseases, such as bone, cardiovascular, neurological, respiratory, digestive and urinary tract diseases (Hosawi, 2023; Ji et al., 2024). Previously, the chemical composition and major skin application areas for hesperidin were described as follows: (i) anti-ageing and skin barrier protection, (ii) UV radiation damage, (iii) hyperpigmentation and depigmentation conditions, (iv) wound healing, and (v) skin cancer and other cutaneous diseases (Rodrigues and Pintado, 2024). The novelty of this work is based on the exploitation of the encouraging skincare and elasticity applications of hesperidin, which represents a sustainable ingredient in the circular economy. Here, we discuss important recent studies that have been conducted to assess the health-promoting and pharmacological properties of hesperidin (Table 1).

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Table 1: Recent studies on the biological and pharmacological activities of hesperidin

Key findings	Reference
Hesperidin (HSD) attenuated PANoptosis, which was induced by mtROS overproduction through inhibition of ROS/P53/PGC-1α mediated mitochondrial injury, thus ameliorating deoxynivalenol-induced liver injury.	Wang et al., 2025
Protective effects were observed for HSD and HSNPs (nanoparticles) against APAP (N-acetyl-para-aminophenol)-induced hepatotoxicity in male Wistar rats. HSD-NPs were more efficacious. These protective effects may be attributed to the modulation of APAP biotransformation, oxidative stress, inflammation, and apoptosis.	Shaban et al., 2025
HSD hydrogel is superior to biodentine in maintaining VEGF release and could be considered a next generation biomaterial for direct pulp capping. Its angiogenic properties and long-term pulp vitality-generating capacity illustrate the promise in revolutionising the field of regenerative endodontics.	Geervani et al., 2025
HSD is a potential drug-like stabiliser of c-Myc G4 (silencer), providing a targeted approach for treating breast cancer. Through the direct suppression of c-Myc, hesperidin could be applicable for clinical use as a novel selective anticancer agent.	Choudhury et al., 2025
HSD induced autophagy by increasing EI24 (Etoposide-induced protein 2.4) expression, which was beneficial for pulmonary fibrosis in vitro and in vivo.	Zhang et al., 2025
HSD decreased the contents of MPO, 5-NTD, and ROS and the contents of MDA and NF-κB in the cerebral cortex and significantly increased the contents of global antioxidants and anti-inflammatory factors, which protected the cerebral cortex against palmitic acid toxicity.	Ahmed et al., 2025
TTO (Tea Tree Oil)-loaded HSD-NLCs (nanostructured lipid carriers) are promising candidates with excellent wound healing activities, and they can be considered as an effective medicinal product for the treatment of cutaneous wounds.	Arneth et al., 2025
HSD might attenuate inflammation by inhibiting the NF-κB signalling pathways in monocrotaline-induced rat PAH (pulmonary arterial hypertension).	He and Liao, 2025
Glucosyl-HSD supplementation prevented tubulointerstitial fibrosis and inflammation in a mouse diabetic nephropathy model without a hypoglycaemic effect.	Hashimoto et al., 2025
HSD effectively ameliorated renal injury, decreased the renal inflammatory response, and blocked renal immune complex deposition, which might be associated with the inhibition of the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway.	Tang et al., 2025
HSD hesperidin has great potential as a feed additive for broilers, enhancing their growth performance by increasing gastric acid secretion and promoting nutrient utilisation via proton pump activation. Hesperidin supplementation (150mg/Kg) in the basal diet was effective.	Li et al., 2025
Compared to the placebo, HSD significantly reduced serum CRP (c-reactive protein), suggesting an anti-inflammatory effect without significant clinical improvement.	Shirodkar et al., 2024
HSD exerted a protective effect in malathion-mediated ovarian toxicity through the regulation of cytokines levels, apoptosis, inflammation and miRNA expression..	Talebi et al., 2024
Both HSD and diosmin have emerged as candidates for development as co-treatments with cisplatin for HCC (Hepatocellular carcinoma) and may be useful in ameliorating senescence in normal kidney cells.	Artanti et al., 2024

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HSD had strong antioxidant and antifibrotic effects on TAA-induced hepatic fibrosis through TGF-β (transforming growth factor-beta)/α-SMA (alpha-smooth muscle actin) pathways.	Megahed et al., 2024
HSD suppressed the migratory and EMT (epithelial to mesenchymal transition) capacity of RPE (retinal pigment epithelial) cells relevant to the formation of PVR (proliferative vitreoretinopathy), thus showing promise as a future therapeutic drug for PVR.	Çınar et al., 2025
HSD decreased the ROS content, thus inhibiting valproic acid-induced arrest of the cell cycle and apoptotic activities in the hippocampus and prefrontal cortex cells.	Kaewngam et al., 2024
Both HSD and FMT (fecal microbiota transplantation) influenced body weight and decreased and alleviated HFD (high-fat diet)-induced disorders in HFD-fed mice, potentially by regulating the composition of gut microbiota.	Liu et al., 2024
HSD with binding affinity to a plasma protein model exhibited strong activity against colorectal cancer cells.	Deng et al., 2024
Since it has antioxidant, anti-inflammatory, anti-apoptotic and hormone-regulating effects, HSD is an attractive candidate as an adjuvant therapy in female cancer patients treated with radiotherapy protocols.	Mohamed et al., 2024
HSD also has potential in managing various CVDRFs (cardiovascular disease risk factors) for humans, including blood lipid levels, blood glucose and inflammatory marker regulation.	Huang et al., 2024a
HSD was relatively more efficacious in reducing most of the serum and urine parameters studied, indicating their role as potential alternatives for managing urolithiasis, but a detailed safety and dose-finding study in humans is necessary.	Kale et al., 2024
HSD (γ-HSD) is a possible natural modulator of metabolism and not only has therapeutic effects for IDD but may enhance the benefits of oestrogen therapy for improving spinal health without increasing the risk for cancer. This study proposes a novel clinical scheme for IDD therapy and provides a novel theoretical basis for new drug development as well as further experimental study.	Zhang et al., 2024
HSD has potential roles in affecting AD (Alzheimer's disease) through oxidative stress and inflammation. Therefore, HSD may exert underlying protective roles for pathogenesis of Aβ, α-synuclein aggregation, tau pathology and cognitive performance during the pathophysiology of AD.	Kuşi et al., 2025
HSD suppressed ER (endoplasmic reticulum) stress and alleviated ferroptosis of terbuthylazine (TBA) by preserving MAM (mitochondria-associated endoplasmic reticulum membrane) integrity, offering a new idea for protecting against TBA toxicity.	Guo et al., 2024
HSD attenuated ERMCS (endoplasmic reticulum mitochondria contact sites) disorder and resisted mitochondria dysfunction, thereby reducing ROS (reactive oxygen species) generation and relieving intestinal barrier damage in piglets under oxidative stress.	Gou et al., 2024
HSD-supplementation attenuated insulin resistance and oxidative stress in HFSS (high fat, high salt, high sugar) diet-fed mice, suggesting the dose-dependent therapeutic effects of HSD on MetS (Metabolic syndrome).	Jamal et al., 2024
Pre-mating, HSD exposure provides additional strategies for protection against primary brain cancer in the next generation. Reducing HSD can be effective in augmenting antioxidant defence and reducing developmental neurotoxicity and the toxicity of DNA-alkylating agents.	Khezri et al., 2024

Key findings	Reference
HSD might attenuate MAM-induced mitochondrial calcium accumulation, improving the mitochondrial function and relieving oxidative stress and gut injury in DON (deoxynivalenol)-stimulated piglets.	Li et al., 2024
HSD was effective in mediating cisplatin-induced ototoxicity through the antioxidant Nrf2/NQO1 pathway in sensory hair cells, reducing ROS accumulation, inhibiting hair cell apoptosis and decelerating hearing loss.	Lou et al., 2024
HSD protected bMECs (bovine mammary epithelial cell) against oxidative stress injury by activating the Nrf2 signalling pathway, indicating that hesperidin, as a natural antioxidant, may have potential as a feed additive or plant drug to promote bovine mammary health.	Huang et al., 2024b
HSD efficiently ameliorated plasma antioxidant, LDL (Low-density lipoprotein) oxidation and serum inflammatory cytokine levels in hyperlipidaemia-stressed rat models. HSD may protect the liver from oxidative stress by enhancing hepatic function.	Kumar et al., 2024
HSD reduced I/R (ischemia-reperfusion)-associated injury in the gastric tissue by suppressing lipid peroxidation and protein oxidation, the duration of antioxidant reactivity and free radical scavengers. Thus, HSD may present a promising therapeutic option in clinical practice to attenuate the ischaemia reperfusion injury of stomach tissue.	Ozyigit et al., 2024
Pretreatment with HSD on X-ray-induced intestinal barrier dysfunction by regulating TJ (tight junctions)-related proteins, suggesting that hesperidin prevents and treats X-ray-induced intestinal barrier dysfunction.	Park and Yu, 2024
The cytotoxic activity against human oral cancer cells (KB cells) and the anti-inflammatory potential of HSD suggest that it merits additional investigations and may contribute to the development of oral carcinoma therapy. These results revealed that several molecular pathways were involved with hesperidin, as a potential anti-oral tumour agent.	Jayaraman et al., 2024
HSD demonstrated a strong protective effect against alcohol-induced mitochondrial toxicity in the FAS (fetal alcohol syndrome) system. Furthermore, these results suggest that hesperidin is a potential compound for preventing alcohol-induced foetal developmental defects during pregnancy.	Jamali et al., 2024
HSD is an antihypertensive drug whose mechanisms of action are related to its diuretic and hypotensive effects and its ability to decrease proteinuria in AVP-(arginine vasopressin) -induced pre-eclamptic rats.	Reddy et al., 2024
Hesperidin attenuated lithium-induced mitochondrial dysfunction through its antioxidant influence on the mitochondria of cardiomyocytes and may have advantageous effects on the prevention and/or treatment of lithium toxicities, as a medication to treat BD (bipolar disorders), and/or as an environmental pollutant.	Shabani et al., 2024
The inhibition of HSD alleviated the detrimental effect of MAL (malathion) on ovarian tissue by upregulating the protein expression of PCNA (proliferating cell nuclear antigen) and FSHR (follicle-stimulating hormone receptor) and activating antioxidant defence.	Zarein et al., 2023
HSD enhanced osteoblast-induced bone formation and inhibited pro-inflammatory cytokines, suppressing oxidative stress related to osteoporosis.	Hu et al., 2023
The protective effect of HSD against PbAc-induced testicular damage was shown through the inhibition of OS (oxidative stress) and alteration of reproductive hormones, demonstrating the potential of HSD as an adjunct therapy for recovery.	Abu-Khudir et al., 2023
HSD mitigated the adverse impacts of aggressive sildenafil citrate therapy towards liver and testicular health, reduced oxidative stress and re-adjusted the haematological parameters. Thus, hesperidin might be a protective agent against oxidative destruction related to long-term sildenafil citrate administration.	Laila et al., 2023
HSD may serve as a potential candidate inhibitor of sarcopenia in the elderly by regulating immune homeostasis.	Oh et al., 2023

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HSD has a protective effect on the epithelial barrier function, along with the suppressing effect of ROS production and inflammation which is characteristic of periodontal diseases.	Maquera-Huacho et al., 2023
HSD has remarkable potential to act as an anti-depressive neuroprotectant and may affect MDD (major depressive disorder) by modulating NLRP3 (NOD-like receptor thermal protein domain associated protein 3)-mediated pyroptosis	Cao et al., 2023
The dosage and application mode of HSD may provide a new therapeutic approach for burn healing and management.	Durgun et al., 2023
HSD positively contributed to the significant improvement of liver morphology, liver structure, inflammation, fibrosis and oxidative stress of BDL (bile duct ligation)-induced cholestatic liver injury rats.	Nasehi et al., 2023
HSD preconditioning ameliorated biochemical and histopathological changes in the kidney and lung tissue of ischemia reperfusion rats. This study indicates the protective effects of HSD on the rat's renal and lung tissues following ischaemia reperfusion injury.	Karacaer et al., 2023
HSD has anti-hyperthyroidism, immune-inflammatory regulatory and antioxidant properties, inhibiting inflammation and rectifying the damaged oxidative stress through the amelioration of the physio-architectural structure of thyroid glands. Such an effect may be mechanised through immunomodulatory, anti-inflammatory, anti-apoptotic and/or antioxidant pathways.	Ashry et al., 2023
HSD suppressed BPH (benign prostatic hyperplasia) by inhibiting prostate cell proliferation, inflammation and EMT (epithelial-mesenchymal transition) via the TGF-β1 (transforming growth factor-beta 1)/Smad signalling pathway. Therefore, our findings may provide a novel therapeutic target for BPH treatment.	Kim et al., 2023
HSD may have a potential role in IPF (idiopathic pulmonary fibrosis) therapy due to its capacity to prevent lung fibroblast senescence.	Han et al., 2023

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Conflict of interest

The authors declare no conflict of interest.

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