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Research Article

HESPERIDIN AND DIOSMIN - A NOVEL DRUGS

JAYDEEP ROY[1], MOHAMMAD AZAMTHULLA[1*], DHRUBOJYOTHI MUKKERJEE[2]

[1]Department of Pharmacology, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, India -560054

[2]Department of Pharmaceutics, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, India -560054

*Author for Correspondence

Dr. Mohammad Azamthulla

Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Science, MSR Nagar, MSRIT Post, Bangalore-560054, INDIA

Phone: +91-080-23608942

E-mail: mohammadazamthulla@gmail.com

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ABSTRACT:

Hesperidin, famously known as Vitamin P and Diosmin are the popular, abundant and inexpensive products obtained from citrus agronomy. With no signs of toxicity, these flavonoids are largely consumed as a dietary supplement and have a long history of medication. In various studies, conducted on Hesperidin & Diosmin have reported a number of protective potentials such as neuroprotective, cardio protective, hepato protective, anti-inflammatory, antioxidant, lipid lowering, and insulin-sensitizing properties. Despite their enormous remedial potential, the poor aqueous solubility and minimal bioavailability are some major curbs that restrict the utilization of Hesperidin and Diosmin in medical perception. Though, future of medicine belongs to synthesis and usage of nano-dimensioned materials by means of nanotechnology which has been revolutionising the delivery of different constituents with much more precision oriented delivery to the target.

This review highlights the *in vivo* and clinical studies to elucidate the therapeutic and pharmacological properties of Hesperidin & Diosmin that have been reported since 2015, also displays the gaps in our knowledge about both the compounds and the growing influence of nanotechnology to overcome the characteristic limitations which deserves more exploration.

KEYWORDS: Flavonoids, Diosmin, Hesperidin, Nano formulation

INTRODUCTION

Since ancient times, mankind have been exploiting the natural resources for numerous medicinal purposes. With the track of time, the inquisitiveness nature of men to explore the medicinal benefits of natural resources is being increased and now becoming a prime focus of scientific research (1). Flavonoids are amongst the class of naturally occurring phyto constituents which are found in most of the citrus plants, berries, green tea, black tea, red wine, cocoa, etc. Diosmin and Hesperidin are the two citric fruit derived flavonoids marketed as dietary supplements also as a combination famously known as micronized purified flavonoid fraction (Daflon) which act on venous tone, lymphatic vessels, micro-circulation and treats hemorrhoids. Numerous studies on Diosmin and Hesperidin have reported various pharmacological activities. New findings have revealed that Dios has anti-parkinsonism property and hesperidin has shown anti-atherogenic and anti-inflammatory activity. Despite of continuous research transformations and efforts aiming to vanquish the challenges of Hesperidin and Diosmin, the application of nanoparticle formulations may act as a "panacea" which logically incorporated an exemplary model for treating a varied range of chronic disorders with the application of Nano-hesperidin/Diosmin through effective drug delivery process. Numerous *in vivo* studies have addressed about the development of specific-site delivery of Hesperidin & Diosmin with better permeability, and increased bio-distribution with significant efficient responses. Information's were collected via electronic search by using Science Direct, PubMed, Nature and other internet sources.

Hesperidin and Diosmin

Diosmin and Hesperidin are flavanone glycosides majorly found in citrus fruits (Family *Rutaceae*). Hesperidin (Hesperitin 7-rhamnoglucoside, Hesperitin-7-rutinoside), $C_{28}H_{34}O_{15}$ is a yellow to brown powder with a molecular weight of 610.56. It is insoluble in water, shows solubility in pyridine, DMC, NaOH. Have a melting point from 250-255°C show a characteristic absorption spectrum at 285nm (Fig.1). Diosmin is a bioflavonoid,

semi-synthetic drug, (3,5,7-trihydroxy-4 methoxyflavone-7-rutinoside), $C_{28}H_{32}O_{15}$ is yellow-brown to brown powder with a molecular weight of 608.54. Insolubility in water, solubility in DMSO, NaOH like organic solvents, melting point 274°C shows maximum absorption at 268nm.

Diosmin can be found in the plants *Teucrium gnaphalodes,* citrus, vetches, hyssop (2). It is been reported for numerous activities but is popularly known to have neuroprotective activity (3). Hesperidin is a flavanone glycoside, obtained in a large amount from the Rutaceae family, citrus plants like grapefruit, lemon, orange, tangerine, etc. even from various other plant species such peppermint and welsh onion (4,5). Hesperidin has been reported for numerous activities such as antioxidant, anti-inflammatory, anti-viral, anti-carcinogenic and has been reported to protect against DNA damage, lipid peroxidation. In combination with other bioflavonoids like Diosmin, it is marketed as Daflon-500mg (Servier) tablets which contain micronized flavonoids-hesperidin (50mg) and Diosmin (450mg) to treat lymphedema and are majorly used to treat blood vessel disorders such as varicose veins, venous stasis, and hemorrhoids. In a study using animal models, the combination was evaluated by for safety and toxicity studies showing good GIT acceptability of the micronized formulation with no genotoxicity, no drug incompatibility or interaction (6). However, Maher and Sabir has investigated the effect of the Diosmin and Hesperidin combination on hypercholesterolemia and hyperglycemia in patients with type 2 diabetes mellitus. Reporting reduction in glucose levels and cholesterol levels with no adverse events, therefore, reducing the cardiovascular risk factor in diabetic patients (7).

Dietary intake of flavonoids; HES, DIOS

Being the secondary plant metabolites, flavonoids are not synthesized in the human body. Therefore they are consumed through the dietary sources including fruits (citrus fruits, grapes, pomegranates, berries, and apples), vegetables (broccoli, celery, onions, and leafy greens), soy products, legumes and beverages (red wine, tea) (8). The intake of the flavonoids varies greatly depending on the availability of quality food and dietary habits of the consumer with different preferences. On global comparison the intake of flavonoids in Asians is more than westerns; Europeans and Americans. Diosmin and Hesperidin, are not been widely reported for any interactions with drug or food substances. Dietary supplements of both the compounds are present in the market for treatment and prevention of vascular system-related disorders and improvement of cardiovascular health. Few studies have shown anti-microbial, anti-inflammatory like activities but the mechanism of action for these activities are not been revealed. Some studies (Table 1 & 2) have also reported the compounds may have a neuroprotective & cardioprotective activity which can help to prevent neuro-degeneration & cardiac-related problems if these flavonoids are included into daily supplementary consumption from childhood to the old ones (3).

Table 1: Products of Diosmin and Hesperidin, available respectively alone in the market

S No	Labeller	Brand Name	Dosage	Activity/ Purpose
1	*Dulac* Farmaceutici	Diosmin Expert-Omniven legs	Gel cream	Heavy legs; varicose veins
2	*Dulac* Farmaceutici	Diosmin Exper- procto complex	Gel cream	Treatment of piles
3	Dr Max	Diosmina	Capsules	Vascular system
4	Swanson	Hesperidin dietary supplement	Capsules	Cardiovascular health
5	Thorne Research	HMC hesperidin 250mg	Capsules	Vascular system
6	Piping Rock	Hesperidin 500mg	Capsules	Vascular system

Table 2: Products of Diosmin and Hesperidin combination available in the market

S No	Labeller	Brand Name	Dosage	Activity/Purpose
1	Servier	Daflon/ Venixxa	Tablets	Varicose veins, Hemorrhoids
2	*Dulac* Farmaceutici	Diosmin Expert-Omnivon 500	Tablets	Microcirculation of hemorrhoid plexus
3	Swanson	Diosvein	Capsules	Cardiovascular health
4	Purity products	Hesperidin and Diosmin complex	Capsules	Vascular system

LITERATURE STUDY

Flavonoids have gained popularity due to their broad range of benefits, now different works had been done on these two compounds specifically to evaluate their activity alone and with nanoparticles. A list of tables below had been put to summarize the important works done (Table 3 and 4).

Table 3: Various biological activities reported for Diosmin

S. No.	Reported by	Research focus	Results concluded by the authors	Activities concluded
1.	Ahmed *et al.*, 2016	Evaluation of diosmin in causing downregulation of oxidative markers in alloxan-induced diabetic nephropathy along with controlling the NF- kB signal transduction pathway	Oral administration of diosmin shows normalization of the level of NF- kB, showing role in maintaining renal function, and elevation of malondialdehyde with a declination of glutathione, nitric oxide and, catalase and superoxide dismutase. Concluding anti-hyperglycemia-mediated oxidative stress	Anti-oxidant, anti-inflammatory, anti-diabetic activity (9).
2.	Ali *et al.*, 2018	Hepatoprotective activity diosmin and sildenafil against cholestatic liver cirrhosis and role of Keap-1/Nrf-2 and P_{38}-MAPK/NF-κB/iNOS signaling pathway	The study evaluated the hepatoprotective activity of diosmin alone and with sildenafil and found combination therapy is more effective. Combination alleviates liver cirrhosis with upregulation of Nrf-2, GSH, SOD, eNOS, and cytoglobin and downregulation of Keap-1, NF-κB, P38-MAPK, MDA, and iNOS.	Hepatoprotective activity (10).
3.	Ali, Fanaei and Keikhaei, 2017	neuroprotective and cognitive improving action in traumatic brain injury (TBI) rat model	Pretreatment with Diosmin has revealed protective effects against memory impairment due to (TBI). The protective action may be due to a decrease in the TNF-α concentration in the hippocampus region	Neuroprotective activity (11).
4.	Arab *et al.*, 2015	Anti-ulcer activity against ethanol-induced gastric injury	Suppression of gastric inflammation by decreasing myeloperoxidase, NF-κB, and TNF-α levels. Along with augmentation of IL-10 levels. Including suppression of oxidative stress and apoptosis by anti-oxidant and cytoprotective action	Anti-Ulcer activity (12).
5.	Carballo-Villalobos *et al.*, 2018	Hyperalgesic effect centrally and peripherally in neuropathic pain	The study provided evidence that diosmin produce anti-hyperalgesic effects by acting centrally on opioid and D2 dopaminergic receptors, and reduction in cytokines levels shows peripheral action	Anti-hyperalgesic (13).
6.	Queenthy, Mainzen and Babu, 2017	Cardioprotection against isoprenaline-induced heart mitochondrial oxidative stress	Anti-oxidant property of diosmin inhibiting cardiac mitochondrial oxidative stress/damage in myocardial infarcted rats	Cardioprotective activity (14).
7.	Sawmill	Reduction of	The study showed a significant	Anti-Alzheimer's (15).

	er *et al.*, 2016	cerebral Aβ levels, tau hyperphosphorylation, neuroinflammation, and cognitive impairment in Alzheimer diseased mice	reduction of Alzheimer pathology and cognitive impairment in Alzheimer induced and inhibited Aβ generation and microglial activation along also inhibited APP γ-secretase and GSK-3β	
8.	Shalkami, Hassan and Bakr, 2017	Diosmin against acetic acid-induced ulcerative colitis	The study revealed the significant elevation in markers of inflammation (TNF-α, COX-II & MPO) and oxidative stress represents the increase in colon caspase-3 expression. After treatment with Diosmin, decreased colon damage index when compared with acetic acid caused damage index, and declination in inflammatory and oxidative stress markers were observed therefore reducing the expression of caspase-3	Anti-inflammatory, anti-apoptotic, anti-oxidant (16).
9.	Christine *et al.*, 2018	Evaluation of anti-inflammatory and antiradical effects 2% diosmin cream on human skin culture as a model	Under the UV-B irradiation model, diosmin cream has shown declination in cyclobutane pyrimidine formation and hydrogen peroxide production showing the anti-radical effect and decreased IL-8 release shows anti-inflammatory effect.	Anti-inflammatory, anti-radical (17).
10.	Shabani, 2018	Neuroprotective activity in scopolamine-induced cognitive degradation/ impairment	Scopolamine-induced cognitive impairment and disruption of synaptic plasticity prevention by diosmin. The decline in TNF-α concentration as a proinflammatory cytokine in the hippocampus	Neuroprotective activity (18).

AST - Alanine aminotransferase, ALT - Aspartate aminotransferase, GSH - Glutathione, CAT - Catalase, GPx - Glutathione peroxidase, SOD - Superoxide dismutase, MDA - Malondialdehyde, TAC - Total antioxidant capacity, IL6- Interleukin 6, TNF-α - Tumor necrosis factor α, MPO - Myeloperoxidase, NF-κB - Nuclear factor-kappa light chain enhancer of activated B cells, MAPK – Mitogen Activated Protein Kinases and iNOS - *Inducible nitric oxide synthase*

Table 4: Various biological activities reported for Hesperidin

S No.	Reported by	Research focus	Results concluded by the authors	Activities concluded
1.	Ansar *et al.*, 2018	The study evaluated anti-effect by hesperidin against oxidative stress induced by nano zinc oxide particles	Hesperidin mitigated the biomarker levels such as AST, ALT, and MDA, 88GSH, GPx, CAT, SOD which are opposite in nano zinc oxide induced hepatotoxicity.	Hepatoprotective (19).
2.	Bhargava *et al.*, 2019	Study the agonistic action peroxisome proliferator-activated receptor	Compared to the enalapril-Hesperidin combination, Hesperidin and enalapril alone treatment exhibited similar effects,	Cardioprotective activity (20).

		gamma (PPAR- γ), which is responsible for inhibiting of cardiac hypertrophy signaling pathways	attenuating pathological changes, suppressing oxidative stress along with increasing PPAR-γ expression	
3.	Homayouni *et al.*, 2018	Examined the hesperidin supplement effect on inflammatory markers and blood pressure in type 2 diabetes patients in a double-blind controlled clinical trial	Patients were observed with a significant difference in diastolic, mean arterial blood pressure, along with a decrease in TAC serum and anti-inflammatory markers suggesting anti-hypertensive and anti-inflammatory action	Anti-hypertensive, anti-inflammatory (21).
4.	Hong and An, 2018	Neuroprotective effect of hesperidin in learning and memory deficit mice	Hesperidin significantly reversed the decreased phosphorylation of GSK-3β, Akt, lessened Nrf2 and increased expression of HO-1, phosphorylation of IκBα along with caused inhibition of RAGE expression and NF κB/p65	Neuroprotective activity (22).
5.	Kosari-Nasab *et al.*, 2018	Influence of hesperidin in attenuating depression-related symptoms in mice with mild traumatic brain injury	Depressive-like behaviors cause increases inflammatory cytokines and oxidative markers and reduce BNDF levels in the hippocampus region. Hesperidin reversed these levels	Anti-depressant activity (23).
6.	Li *et al.*, 2018	The wound healing ability of hesperidin against streptozotocin-induced diabetic rats	Significant upregulation of mRNA expressions in wound tissues such as VEGF-c, Ang-1, Tie-2, TGF-β and Smad 2/3, also increased SOD, GSH levels by hesperidin, which are downregulated by streptozotocin	Wound healing activity (24).
7.	Li *et al.*, 2019	Evaluated hesperidin's activity against imiquimod-induced psoriasis in mice model and human keratinocytes cells	Improvement in skin lesions of imiquimod-induced mice and hesperidin also inhibited lipopolysaccharide-induced human keratinocytes cell proliferation. In addition, it also decreased and normalized insulin and glucose levels, further found to modulate the levels of leptin, adiponectin, and resistin. Inhibiting the initiation of the IRS-1/ERK1/2 signaling pathway	Anti-dermatitis (25).
8.	Liu *et al.*, 2018	The study investigated the capability of hesperidin to prevent high glucose-induced retinal pigment epithelial cell damage	Hesperidin effectively inhibited ROS production due to high glucose and also showed scavenging activity by normalizing various biomarkers along with opposite effect on high glucose-induced cell apoptosis pathway via caspase-9/3 upregulation, cytochrome c release into cytosols.	Glucose reducing activity; prevention against diabetic retinopathy causing visual impairment (26).

9.	Meng *et al.*, 2018	Investigated hesperidin's ability to modulate inflammatory responses, acute myocardial infarction, and anti-oxidant activity	Significantly decreased levels of TNF-α, IL-1β, CAT, SOD along with suppressed expression of Bcl-2/Bax and elevated PPAR- γ in mice model	Cardioprotective activity (27).
10.	Poetini *et al.*, 2018	Attenuating action against Iron-induced oxidative stress and dopamine reduction in Drosophila Melanogaster as Parkinson's disease model	It significantly decreased the iron levels in the brain responsible for Parkinson disease, along with scavenging of reactive species, improving motor function, and cholinergic activity in the flies	Anti-parkinsonis (28)

AST - Alanine aminotransferase, ALT- Aspartate aminotransferase, GSH - Glutathione, CAT - Catalase, GPx - Glutathione peroxidase, SOD - Superoxide dismutase, MDA - Malondialdehyde, TAC - Total antioxidant capacity, IL6 - Interleukin 6, TNF-α - Tumor necrosis factor α, VEGF-c - Vascular Endothelial Growth Factor C, Ang-1 - Angiopoietin 1, TGF-β - Transforming growth factor beta, GSK-3β - Glycogen synthase kinase 3 beta, Akt - also known as Protein kinase B, Nrf2 - Nuclear factor erythroid 2, IκBα - Inhibitor of kappa B protein alpha

Other than animal studies, clinical studies are also been done to evaluate their effects. In table 5 and 6 Hesperidin and Diasmin clinical studies are reported (Table 5 and 6).

Table 5: Status of recent and on-going clinical trials reported for Hesperidin for various diseases

S No	Study	Sponsor	Status	Phase	Conditions
1.	Effect of hesperidin on insulin sensitivity	University of Maryland	Withdrawn	2	Insulin Resistance
2.	Effect of hesperidin on Bone metabolism and Bone mineral density of postmenopausal women	Nestlé	Completed	3	Osteoporosis
3.	vascular effect of hesperidin on metabolic syndrome	University of Rome Tor Vergata	Completed	4	Incompetent accessory saphenous veins

Table 6: Status of recent and on-going clinical trials reported for Diosmin for various diseases

S. No.	Study	Sponsor	Status	Phase	Conditions
1.	Effect of Detralex (Daflon) for anti-inflammatory activity	University Hospital Dubrava	Completed	4	Chronic Venous Insufficiency
2.	Effect of Diosmin for infertilites prevention	-NA-	Completed	2, 3	Infertility
3.	Effect of Diosmin 600mg and Diosmin+Hesperidin for chronic venous insufficiency	Fundação Educacional Serra dos Órgãos	Completed	4	Incompetent accessory saphenous veins
4.	The efficiency of Diosmin 600mg for chronic venous disease of lower limbs	Laboratoire Innotech International	Completed	3	Chronic Venous disease of Lower Limb

Nano-approach for Hesperidin & Diosmin to enhance bioavailability for various activities:

As both the compounds endow various kinds of properties such as anti-microbial, anti-viral, anti-inflammatory, anti-oxidant and anti-tumour effects as summarized in above tables. Hesperidin and Diosmin face GIT absorption problem due to low solubility in water, they are only soluble in few organic solvents and this results in low bioavailability of the compounds in the body. Numerous research groups are focusing on how to improve the bioavailability and provide efficient targeted delivery with transport stimulation. New approaches to providing direct delivery into the cells include nano formulation like entrapment in diamond-like nanoparticles, phospholipid complex, cyclodextrin complex, etc. Various biological activities reported for Diosmin and Hesperidin and application of nanoparticles and showed in table 7.

Table 7: Various biological activities reported for Diosmin and Hesperidin and application of nanoparticles

S. No.	Reported by	Research focus	Results concluded by the authors	Activities concluded
1.	Corciova *et al.*, 2015	Evaluation of antibacterial and antioxidant activity of Hesperidin:β-cyclodextrin complexes	agar diffusion method was used to culture *Staphylococcus aureus* ATCC 25923, *Escherichia coli*ATCC 25922 and *Candida albicans* ATC C 10231, the complex showed antibacterial activity. Inhibition of lipoxygenase activity, DPPH radical scavenging activity showed antioxidant activity	Antioxidant, anti-bacterial (29).
2.	Sahu *et al.*, 2016	Synthesizing Ag nanoparticles for flavonoids: hesperidin, diosmin, and naringin to evaluate antibacterial and cytotoxicity effect	using human promyelocytic leukemia (HL-60) cells investigated cytotoxicity and bacterial effect concluding Ag nanoparticles from flavonoids showed good stability, better antibacterial, and cytotoxic activity	Antibacterial, cytotoxicity (30)
3.	(Thomas *et al.*, 2019)	Mechanism of interaction of Diosmin and gold nanoparticles with calf thymus DNA	The complex formation of Diosmin-AuNps with ctDNA, through MTT assay, revealed toxicity and anti-proliferative effect on normal human cell lines and MCF-7	Anti-cancer activity (31)

(Mary *et al.*, 2017) formulated a chitosan-based nanoformulation for hesperidin to overcome its water insolubility, aimed to passively target cancer cells (32). Chitosan-based hesperidin nano-formulation enhances hesperidin induced apoptosis of HCT15 cells exposing it be a likely candidate to treat colorectal cancer. Another β-Cyclodextrin based nanocomplexes of hesperidin was formulated by (Corciova *et al.*, 2015), demonstrated the enhancement in the solubility, anti-bacterial and antioxidant activities of hesperidin (29).

Conclusion and future perspective

Diosmin and Hesperidin are among the class of flavonoids gaining popularity globally because of their potential health benefits in minimizing neurodegenerative signs, blood vessels inflammation, microbial, improving cardiovascular health and effective antioxidant, and influencing immunomodulation activities. Either alone or in combination, they are able to modulate the activities of various targets which play a pivotal role to produce a biological and therapeutic action, where they are also depended on their physiochemical and structural properties.

Both the compounds show poor solubility, absorption, and distribution which are the major setbacks to produce any therapeutic activity and Nanotechnology plays a vital role here. The reasons for these could be their molecular weight, solubility, structure, pH sensitivity etc. at present scenario the micronization of their combination (Daflon 500mg) have helped in improving its solubility and GIT absorption. Interestingly, recent studies have proposed the application of nanotechnology can improve the solubility, bioavailability, pharmacokinetics, targeted treatment, and their therapeutic action. Nanotechnology has already achieved many milestones in the bio and medical field and helping to explore more new and better ways to treat and prevent modern day diseases. Nanotechnology application is modifying the way of delivering active compounds in less amount but more efficiently, prolonging circulation & bioavailability, drug exposure to the specific target, and minimizing multidrug resistance. The nano formulations of these compounds can be administered intraperitoneally, intranasal, or intravenous therefore, improving the way of treatment and prevention of CVD, neurodegenerative disorders, bacterial, viral and several other diseases. Therefore, this review suggests more studies on both the compounds with nano-approach to explore its new findings.

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