Plant metabolite diosmin as the therapeutic agent in human diseases

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A B S T R A C T

Plants of the family Rutaceae are known for their diverse medicinal uses due to the presence of a variety of plant compounds called flavonoids, among which diosmin stands out. Diosmin, a flavone glycoside derived from the plants of the genus Citrus, is known to possess a wide range of biological activities. This review aims to highlight the therapeutic properties and potential applications of diosmin in human diseases.

1. Introduction

Diosmin (diosmetin 7-O-rutinoside) is a natural flavone glycoside possessing a molecular weight of 608.549 g/mol. IUPAC named it 5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(25,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[(2R,3R,4R,5R,6S)-3,4,5,6,7-pentahydroxy-2-yl]oxy-5-methoxy-2-yl]oxychromen-4-one. Apart from IUPAC name, it is also called as venosmin (Teucrium gnaphalodes) (Barberin et al., 1985). It is commonly occurs in citrus plants belonging to the rutaceae family such as tangerine (Citrus reticulata) (Drahansky et al., 2016) and is obtained by oxidation of hesperidin, a corresponding flavanone glycoside. Diosmin has a double bond between two carbon atoms in the C-ring, which makes it readily absorbed and distributed throughout the body. Approximately, 96% ethanol is used to obtain crystalline precipitate of diosmin after 48 h (Ivashev et al., 1995). Diosmin is poorly soluble in water which limits its absorption through the gastro-intestinal tract when administered orally. Formation of inclusion complexes of diosmin with cyclodextrins viz. β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HPβ-CD) enhances its solubility (Ai et al., 2014).

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1.1. Anti-oxidant property

Oxidative stress has been reported as a conducive factor in the development of various ailments including myocardial ischemia, cerebral ischemia-reperfusion injury, neuronal cell injury, hypoxia, diabetes, and cancer (Maheshwari et al., 2006). Diosmin possess several therapeucic properties due to its anti-oxidant activity. Treatment of diabetic rats, induced by streptozotocin nicotinamide (STZ-NA) with diosmin shows ameliorative effects. Diabetic rats show decline in the activities of anti-oxidant enzymes; glutathione-S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) and levels of low molecular weight antioxidants viz. vitamin C, vitamin E and reduced glutathione (GSH) were found to be low whereas the markers of lipid peroxidation (LPO) were found to be elevated in the liver and kidney tissues, compared to normal control rats. Oral administration of diosmin (100 mg/kg/day) for 45 days exhibited improvement in the glycemic and anti-oxidant status of diabetic rats. Lipid peroxidation was also found to be reduced upon treatment with diosmin (Sriniwasan and Puri, 2012). It also presents anti-hypertensive property in deoxycorticosterone acetate (DOCA)-salt induced rats. The levels of non-enzymatic and enzymatic antioxidants were found to be decreased whereas the lipid peroxidation products (thiobarbituric acid reactive substances, lipid hydroperoxides and conjugated dienes) were found to be substantially increased in blood plasma and tissues such as liver, kidney, heart and aorta with DOCA which was restored on diosmin treatment. A dose of 50 mg/kg/body weight was found to be most effective. These observations were further confirmed by histopathological studies of kidney and heart (Silambarasan and Raja, 2012). Diosmin also exhibits hepatoprotective effect against ferrous sulfate-induced liver injury in adult male albino rats. Excess iron induces oxidative stress, lipid peroxidation, inflammation, and tissue necrosis. Elevation in ALT, AST, ALP, GGT, LDH activity and bilirubin levels indicates hepatocyte membrane damage. Diosmin treatment significantly normalized these parameters. Diosmin serves as a good hepatoprotective agent as it preserves membrane integrity, relieves oxidative stress and corrects dyslipidemia. The hepato protective potential of diosmin is prominently exerted by its antioxidant and anti-inflammatory activity (Abdel-reheim et al., 2017). Pre-treatment with diosmin reduces oxidative stress in rat heart after ischemia/reperfusion. Reperfusion of ischemic tissues generates oxidative stress which in turn leads to cellular damage (ischemia–reperfusion injury). The hearts of control rats (no diosmin pre-treatment) showed decrease in the activities of enzymatic antioxidants (viz. SOD, CAT and GPx) and GSH levels when subjected to ischemia/reperfusion whereas the levels of lipid peroxidation products were found to be elevated. Oral administration of diosmin (50 and 100 mg/kg) for 7 days was found to normalize these parameters i.e. the activities of enzymatic antioxidants and GSH levels were found to be elevated and a reduction in levels of lipid peroxidation products was observed (Senthamizhvelan et al., 2014). Ischemia-reperfusion injury also leads to retinal edema and tissue damage resulting in loss of vision. In male Wistar rats, diosmin was observed to impede the retinal edema by protecting the blood-retinal membrane integrity, relieves oxidative stress and corrects dyslipidemia. The free-radical scavenging effect of diosmin also confers protection against myocardial infarction (Queneth and John, 2013).

1.2. Anti-inflammatory property

Many diseases including arthritis, allergy, asthma, autoimmune diseases, atherosclerosis, diabetes, and cancer are the result of inflammation. Inflammation can be characterized by the increased levels of selective biomarkers known as inflammatory markers. Most common inflammatory markers include:

- Cells of the immune system: neutrophils, basophils, eosinophils, platelets, macrophages etc.
- Cell surface receptors and adhesion molecules: selectins (L-selectin, P-selectin and E-selectin) and integrins.
- Soluble mediators: cytokines (IL-1, IL-2, IL-6, TNF-α, TGF-β and IFN-γ), chemokines, NF-kB and acute phase proteins (complement factors, C-reactive protein and the coagulation factor fibrinogen) (Roggen et al., 2014).

Diosmin has been found to alleviate these markers in many studies owing to its anti-inflammatory property. In lung injury induced by lipopolysaccharide (LPS) treatment, pro-inflammatory cytokines (IL-2, IL-6, IL-17 and TNF-α) and NF-κB were found to be elevated. Pre-treatment with diosmin (50 and 100 mg/kg) in male adult Balb/c mice for 7 days showed a significant reduction in the levels of these markers in LPS induced lung injury (Ismam et al., 2015). Similar mitigous observations were reported by Islam et al. on Swiss albino mice. They highlighted that pre-treatment with diosmin (100 and 200 mg/kg body weight) for 14 days exerted protective effect against benzo(a)pyrene mediated oxidative stress and lung damage owing to its anti-oxidant and anti-inflammatory properties (Islam et al., 2020). In trinitro benzene sulfonic acid (TNBS) induced rat colitis, diosmin was found to inhibit LTβ4 (eicosanoid) and colonic MDA production (Crespo et al., 1999). Studies show that diosmin administered orally at doses 10 and 20 mg/kg b.wt for 9 weeks reduces the levels of COX-2 and iNOS (inflammatory markers) in chemically induced (diethylnitrosamine (DEN) and promoted by 2-acetylaminofluorene (2-AAF) hepatocarcinogenesis in female Wistar rats (Tahir et al., 2013). In addition to this, Orally administered diosmin (25 and 50 mg/kg), was found to modulate the levels of tumour necrosis factor-α (TNF-α) and cyclooxygenase-2 (COX-II) in acetic acid induced (rectal administration of 1 ml acetic acid (4% v/v) ulcerative colitis in male Swiss albino rats. Animals showed significant dose dependent reduction in TNF-α and COX-II levels upon diosmin treatment (Shalkami et al., 2017).

1.3. Anti-cancer property

Recent studies have shown that diosmin exerts dose dependent pro-apoptotic effects on various animal cancers including breast, prostate, colon, oral and urinary bladder. Diosmin has been shown to promote cytosstatic autophagy and premature senescence in MCF-7 cells at 5 and 10μM concentrations and induces apoptosis at 20 μM by inducing cytoxic autophagy along with nitosative stress. Effects of diosmin were also observed on other breast cancer cell lines, MDA-MB-231 and SKBR-3 cells, but MCF-7 was found to be the most responsive. At lower doses, diosmin induced G2/M cell cycle arrest, enhanced levels of p53, p21 and p27, elevated SA-β-gal activity, oxidative stress and DNA damage in MCF-7 cells, all of which are associated with senescence. Apoptosis may be caused by increase in the levels on nitric oxide, ROS, total superoxide and protein carbonylation (Lewinska et al., 2017). Studies on androgen independent prostate cancer cell line, DU145, have confirmed pro-apoptotic activity of diosmin. Geno and cytotoxicity of three flavonoid glycosides (diosmin, naringin and hesperidin) were investigated in DU145 prostate cancer cell line. Maximum genotoxicity was induced by diosmin. These flavonoids were able to induce intracellular redox imbalance or oxidative stress in DU145 cells by impairing the mitochondrial membrane potential resulting in apoptotic cell death. Diosmin caused significant increase in total ROS production. Moreover, treatment
with diosmin increased the levels of double stranded nicks in DNA and formation of micronuclei (genotoxicity) (Lewinska et al., 2015). Kuntz et al. observed anti-proliferative potential of diosmin in human colon cancer cell lines (EC50 value: 76.5 ± 6.5 μM for HT-29 cells and 112.2 ± 6.9 μM for Caco-2 cells) (Kuntz et al., 1999). Diosmin has also been found to inhibit P-glycoprotein mediated efflux of drugs in Caco-2 cells (Hye et al., 2007). Tanaka et al., observed chemopreventive effect of diosmin on azoxymethane induced colon carcinogenesis in male F344 rats. Oral administration of diosmin significantly decreased colon carcinogenesis which might be due to inhibition of ornithine decarboxylase (ODC), a rate determining enzyme in polyamine biosynthesis (Tanaka et al., 1997a). Inhibition of ODC causes cell apoptosis induced by DNA damage (Pendeville et al., 2001). ODC levels have been found to increase in various tissues upon exposure to carcinogens. The colonic mucosa of azoxymethane treated rats show increased ODC activity (Tanaka et al., 1997). Diosmin is found to be more effective than diosmetin (aglycone form diosmin), in inhibiting oral carcinogenesis in male F344 rats. The chemotherapeutic potential of diosmin on azoxymethane induced colon carcinoma in male rats is characterized by abnormal carbohydrate, protein and fat metabolism and complications related to it. Diabetes mellitus is a chronic disease characterized by abnormal carbohydrate, protein and fat metabolism and is caused by lack and/or reduced insulin activity. Diosmin has potential anti-hyperglycemic activity as shown by many studies. Pari et al. administered diosmin (25, 50, 100 mg/kg b.w) for 45 days in streptozotocin-nicotinamide (STZ-NA) induced diabetes in male albino wistar rats. They observed improvement in glycemic condition. Diosmin was found to lower the plasma glucose levels in a dose dependent manner. Moreover, oral uptake of diosmin (100 mg/kg b.w) significantly decreased glycosylated haemoglobin and increased haemoglobin and plasma insulin. It also upregulates the key hepatic enzymes, namely, hexokinase and glucose-6-phosphate dehydrogenase and down regulates the glucose-6-phosphatase and fructose-1,6-bisphosphatase in diabetic rats. An increase in body weight of diabetic rats was also reported (Pari and Srinivasan, 2010).

### 1.4. Anti-diabetic property

Diosmin has been known to exhibit therapeutic effects on diabetes and complications related to it. Diabetes mellitus is a chronic disease characterized by abnormal carbohydrate, protein and fat metabolism and is caused by lack and/or reduced insulin activity. Diosmin has potential anti-hyperglycemic activity as shown by many studies. Pari et al. administered diosmin (25, 50, 100 mg/kg b.w) for 45 days in streptozotocin-nicotinamide (STZ-NA) induced diabetes in male albino wistar rats. They observed improvement in glycemic condition. Diosmin was found to lower the plasma glucose levels in a dose dependent manner. Moreover, oral uptake of diosmin (100 mg/kg b.w) significantly decreased glycosylated haemoglobin and increased haemoglobin and plasma insulin. It also upregulates the key hepatic enzymes, namely, hexokinase and glucose-6-phosphate dehydrogenase and down regulates the glucose-6-phosphatase and fructose-1,6-bisphosphatase in diabetic rats. An increase in body weight of diabetic rats was also reported (Pari and Srinivasan, 2010).

Diosmin was also found to ameliorate abnormalities in lipid metabolism associated with diabetes. Hypercholesterolemia, accumulation of lipids in hepatic tissues, altered plasma lipid and lipoprotein profile are hallmarks of metabolic dyslipidemia associated with type 2 diabetes (Farmer, 2008; Shepherd, 2005). Diosmin treatment effectively normalized the altered levels of plasma lipids, tissue lipids (cholesterol, TGs, FFAs and PLs) and plasma lipoproteins (LDL, VLDL) (Srinivasan and Pari, 2013). Diosmin also reverses the changes in glycoprotein profile associated with type 2 diabetes. In STZ-NA induced diabetic rats the level of plasma glycoproteins were found to increase significantly. In liver and kidney of diabetic rats, the level of hexose, hexosamine and fucose were significantly increased whereas the level of sialic acid was significantly
decreased. Diosmin was found to reverse these changes in glycoprotein profile upon oral administration (Leelavinothan Pari Subramani Srinivasan Mohammed Saddiq, 2010). Diosmin nanoparticles have shown more efficacy against diabetes and associated atherosclerosis as it improves water solubility of polymeric matrix and therefore its bioavailability (Om et al., 2020).Neuropathy is one of the most common complications associated with diabetes mellitus affecting more than half of patients. It occurs due to prolonged untreated and uncontrolled hyperglycemia and is characterized by pain, tingling and numbness in the peripheries and slow nerve conduction. Hyperglycemia induced oxidative stress leads to the accumulation of polyols and advanced glycation end products, as well as impairment of (Na+/K+)–ATPase activity and endothelial function. Neurons undergo apoptosis due to oxidative damage. Type 2 diabetes induced in male Sprague-Dawley rats by streptozotocin and high fat diet, on diosmin treatment (50 and 100 mg/kg, p.o.) for 4 weeks showed restriction in development of early diabetic neuropathy. It restored the altered levels of GSH, NO and SOD activity, thereby relieving oxidative stress (Jo et al., 2014). Significant normalization of NF-kB, which plays a pivotal role in the pathogenesis of diabetic neuropathy and other inflammatory diseases were observed on diosmin treatment in alloxan-induced diabetic Wistar rats (Ahmed et al., 2016). In male swiss mice, diosmin was found to relieve neuropathic pain induced by chronic constriction injury (CCI). Intrapitoneal administration of diosmin (1 or 10 mg/kg) was found to relieve CCI-induced mechanical as well as thermal hyperalgesia. Diosmin exposure also suppress spinal cord cytokines (IL-1β and IL-33/Slf2) and glial cells activation (Bortozzi et al., 2017).Beside this diosmin also act as protective agent in renal stone formation by reducing the pH of urine thus preventing urolithiasis (Vinoth Prabhu et al., 2016).

### 1.5. Anti-microbial property

Any substance that is capable of destroying bacteria or inhibiting their growth or their ability to reproduce is considered as an anti-bacterial agent. Bacteria have developed resistance against most of the antibiotics. In order to identify new and effective anti-bacterial agents, plant products are being explored. Plant based bioactive components known as phytochemicals are effective against various organisms including fungi, yeasts, bacteria, insects and nematodes. They are able to attenuate peptidoglycan synthesis, damage microbial membrane structures, impairs bacterial membrane surface hydrophobicity and also modulate quorum-sensing (QS) (Monte et al., 2014). Sahu et al. prepared silver nanoparticles (AgNPs) of diosmin to investigate its anti-bacterial property by disc diffusion method against Escherichia coli, Pseudomonas putidaa and Staphylococcus aureus. Hexagonal AgNPs of about 5–40 nm in size were found to be mildly anti-bacterial. The size of zone of inhibition produced by diosmin against E. coli, P. putida and S. aureus were 6, 6 and 7 mm respectively. The possible mechanisms of anti-bacterial action were reported to be formation of pits on bacterial cell wall, disruption of cell membrane permeability, inhibition of transduction, inhibition of respiratory enzymes due to free radical formation, and inactivation of various enzymes having thiol group (Sahu et al., 2016). Combination of diosmin with amoxicillin-clavulanic acid (AMC) shows mycobactericidal activity against Mycobacterium marinum. In-vitro validation came from the fact that the survival of M. marinum infected Drosophila melanogaster fly model increased by ~60% upon treatment with a combination of AMC and diosmin. Further, its antimicrobial activity was confirmed against Mtb H37Ra and MDR clinical isolate. The AMC-diosmin combination was found to target L, D-transpeptidase (Ldt) enzymes involved in Mtb cell wall biosynthesis and induced cellular leakage in M. marinum cells (Pushkaran et al., 2019). Hysopus officinalis, a source of diosmin, possesses anti-leishmanial activity particularly against Leishmania major species. Diosmin is present in the leaves, stems, sepals and roots of this plant (Hikal and Ahl, 2017). Role of diosmin from H. officinalis can be investigated in future for the cure of infectious diseases like malaria, dengue, Chikungunya, SARS-CoV-2 and Leishmaniasis.

### 1.6. Combinational therapy

Diosmin (phlebotropic agent) is a veno-active drug administered orally for the treatment of chronic venous insufficiency (CVI) (Russo et al., 2018; Ramelet et al., 2005). In CVI, veins have trouble sending blood from limbs back to the heart as a result of which blood gets pooled in the veins of legs. Reflux of the venous valves is the most common cause of decreased venous return. Diosmin, known to decrease venous stasis, is able to stimulate venous blood flow through its effect on venous valves and venous wall smooth muscle. Diosmin has been found to increase venous blood flow and venous outflow resistance at the site of varicose veins (Dietl et al., 2013). This effect is due to its action on venous smooth muscle, leading to a decrease in venous return and a decrease in venous stasis (de Mulder et al., 1986). In addition, diosmin has been found to reduce venous capillary hyperpermeability and to decrease venous dilation and venous outflow resistance at the site of varicose veins (Dietl et al., 2013). This effect is due to its action on venous capillary endothelial cells, leading to a decrease in venous permeability and a decrease in venous stasis (de Mulder et al., 1986). Table 1 lists the properties of diosmin from a variety of sources and highlights its potential as a therapeutic agent for the treatment of chronic venous insufficiency.
Table 2

**Targeted proteins:** In the papers discussed so far, diosmin has been found to target following proteins.

| Therapeutic property | Proteins targeted by diosmin | Effect | References |
|----------------------|-----------------------------|--------|------------|
| **Antioxidant property** | Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (Gpx) and glutathione-S-transferase (GST) | Upregulated | (Srinivasan and Pari, 2012), (Senthamizhvelan et al., 2014), (Tong et al., 2012) |
| | InOS | Downregulated | Abdel-Reheim et al. (2017) |
| | VEGF | Down | Tong et al. (2013) |
| | PEDF | Up | Liu et al. (2014) |
| **Anti-inflammatory property** | Cytokines (IL-2, IL-6, IL-17 and TNF-α) and NF-κB | Down | Imam et al. (2015) |
| | COX-2 and iNOS | Down | Shalkami et al. (2017) |
| | TNF-α and COX-2 | Down | Shalkami et al. (2017) |
| **Chemotherapeutic properties** | p53, p21, p27 and Senescence-associated beta-galactosidase (SA-β-gal) | Up | Lewinska et al. (2017) |
| | Ornithine decarboxylase (ODC) | Inhibit | Tanaka et al. (1997a) |
| | p53, caspase 3, caspase 9 | Up | Rajamanickam and Shanmugam (2017) |
| | Bel-2, matrix metalloproteinase 2 and metalloproteinase 9 | Down | Shalkami et al. (2017) |
| | Ornithine decarboxylase (ODC) and dihydrofolate reductase (DHFR) | Inhibit | Tanaka et al. (1997b) |
| | Phosphoinositide 3-kinase (PI3K), murine double minute 2 homolog (PIMK-Akt-MDM2 signaling pathway) and p53 | Inhibit | Dung et al. (2011) |
| **Anti-diabetic property** | hexokinase and glucose-6-phosphate dehydrogenase | Inhibit | Pari and Srinivasan (2010) |
| | Superoxide dismutase (SOD) | Up | Jo et al. (2014) |
| | NF-κB | Down | Ahmed et al. (2016) |
| | Cyclic guanosine monophosphate (cGMP), protein kinase G (NO/cGMP/PKG/KATP signaling pathway) | Activate | Bertuzzi et al. (2017) |
| **Anti-bacterial property** | B-16 and B-22/St2 Respiratory enzymes having thioid group | Inhibit | Sahu et al. (2016) |
| | L, D-transpeptidase (Lde) enzymes | Inhibit | Pushkaran et al. (2019) |

![Fig. 2. Administrative routes of diosmin.](image-url)

**of CVI** (Christopoulos et al., 1988). Diosmin in combination with hesperidin (MPFF) has been found more effective in relieving venous symptoms than diosmin alone (Ramelet et al., 2005) but a recent study has showed similar efficacies of both preparations (Steinbruch et al., 2020). The most common symptoms of CVI include leg ache, sensation of heaviness or tension, nocturnal cramps, sensation of swelling, restless legs, and itching (Katsenis, 2005). Daflon treatment for 2 months improves sensation of burning, heaviness, weakness and functional discomfort. It also improves blood velocity in the skin microcirculation. Since daflon does not address the initiating factor of CVI, it is not considered as a cure, rather it is considered to improve symptoms associated with the disease (Frick, 2000). In patients suffering from CVI, diosmin as Micronized Purified Flavanoid Fraction (MPFF) have been found to act on venous tone, lymphatic drainage and microcirculation. It improves venous tone by impeding the breakdown of noradrenalin (norepinephrine) by COMT (catechol-O-methyltransferase) thereby prolonging the noradrenergic activity. It decreases the diameter of lymphatic vessels and intra-lymphatic pressure whereas increase the number of functional lymphatics, lymphatic flow, capillary haematocrit and red cell velocity. It also protects microvascular permeability by inhibiting adhesion of leukocytes, their intra-tissue migration and the release of leukocyte (L-selectin) and endothelial (ICAM-1, VCAM-1) adhesion molecules. The anti-inflammatory mediators (Ramelet, 1016). Daflon treatment for four weeks (four tablets per day, in two divided doses) also shows improvement in the symptoms associated with haemorrhoids (pain, heaviness, bleeding, pruritus and anal discharge) (Meshikhes, 2004). Daflon has also been reported to exhibit anti-oxidative property (Cypriani et al., 1993). Combination of diosmin with amoxicillin-clavulanic acid (AMC) has been found to possess mycrobacterical activity against *Mycobacterium marinum* (Pushkaran et al., 2019).

Finally, we summarize our review work where diosmin actively plays critical roles in controlling well-known signaling components and pathways. Table 2 shows a number of proteins which are known to interact with diosmin. These proteins play important role in inflammatory processes, cancer pathways, antidiabetic, antioxidant, and antibacterial targets.
1.7. Administrative routes

In the papers discussed so far, diosmin has been administered through following routes, Oral, intra gastric and intra-peritonal as described in Table 1 and Fig. 2.

Future prospective: Diosmin, a phytocompound with anti-oxidant, anti-inflammatory and anti-microbial activities holds promising therapeutic potential but like other plant based secondary metabolite there are several challanges in using it as a therapeutic drug candidate including its solubility, stability, and bio-availability. Russo et al., tested and compared the bioavailability of two diosmin formulations by oral administration to healthy volunteers (62). The study indicated that methods, that favor the bioconversion of diosmin to its aglycone form, raised its plasma concentration and thus increase clinical efficacy. Artificial intelligence tools like QSAR, ADMET, molecular-simulations, molecular-docking, pharmacokinetics, and pharmacodynamics studies in future would further strengthen information on this secondary metabolite as a novel therapeutic drug candidate.

Changes in lifestyle have increased incidences of metabolic disorders that include insulin resistance, type 2 diabetes, cardiovascular complications etc. Oxidative stress along with chronic inflammation accelerates these disorders, diosmin being an antioxidant and anti-inflammatory agent; might prove beneficial with respect to current marketed treatment regimen. Alternatively, it could also be used in the treatment of SARS-CoV-2, as it possibly may decrease the viral load by lowering oxidative stress but further experiments with animal models and clinical trials are required to establish diosmin as strong therapeutic molecule in COVID-19 treatment.

2. Conclusion

Diosmin, an active flavone glycoside obtained from citrus plants, possesses anti-oxidant, anti-cancer, anti-diabetic and mild anti-bacterial properties. It serves as an excellent therapeutic agent for a number of diseases by the virtue of its biological properties. It relieves oxidative stress by modulating the activities of specific protein markers and induces apoptotic cell death in several cancer cell lines by targeting the key signalling cascade. It also reduces the levels of several inflammation markers which accounts for its anti-inflammatory activities. It also ameliorates the complications associated with diabetes viz. neuropathy and dyslipidemia. Diosmin has been observed to exert most of these effects via interacting with different molecules, both directly and indirectly. Fig. 3 shows some of the direct targets of diosmin based on previous works and FunCoup 2.0 network database. This network was drawn using cytoscape (AlexeyenkoE., 2009; Okawa et al., 2015; Mustafa et al., 2021). shows probable interaction of diosmin with key signalling molecules such as caspase3, NF-kB, Beclin, VEGF, PEDF, JAK2, STAT3, PI3K, iNOS, MMP2, Akt, LTβ, p27, IL-17, COX2, IL-6 etc. Combination of diosmin with other flavonoids, particularly hesperidin, have found to be very effective in the treatment of chronic venous insufficiency and haemorrhoids, thus setting a good example of drug synergism. Thus diosmin treatment looks promising in the treatment of different kinds of cancers, diabetes and diseases associated with oxidative stress and inflammation. Besides serving as an anti-hyperglycemic agent, diosmin also ameliorates complications associated with it. Its ability to regulate VEGF/PEDF ratio can be explored to elucidate its role as a pro-angiogenic or anti-angiogenic factor. Its combination with other flavonoids or phytochemicals need to be explored in future.

CRediT authorship contribution statement

Saad Mustafa: Conceptualization, Writing - original draft, Methodology, Data curation, Software, Writing - review & editing, Investigation, Visualization.
Mahmood Akbar: Writing - review & editing, Writing - original draft, Data curation, Investigation.
Mohammad Aasif Khan: Writing - review & editing, Kumari Sunita: Data curation, Software.
Jogendra Singh Pawar: Writing - review & editing, Sheersh Massey: Data curation, Software. Nupur Rani Agarwal: Visualization, Writing - review & editing.
Syed Akhtar Husain: Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 3. Protein-protein Interactions appears in diosmin network analysis.
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