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Review Article

Targeting Diabetic Neuropathic Pain with Flavonoids: Mechanistic Insights and Pharmaceutical Perspectives

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ABSTRACT

Diabetic neuropathy is a prevalent and painful condition impacting the nervous system and a common clinical consequence of Diabetes Mellitus (DM). Effective management of various forms of Diabetic Neuropathy (DN), such as peripheral neuropathy, autonomic neuropathy, proximal neuropathy and mononeuropathy, remains challenging. Management of blood glucose levels in diabetic patients may delay the onset of diabetic neuropathic conditions. Recently, considerable research on natural products, including isolating bioactive phytochemicals from plants and investigating their potential impact on DN, is underway. Flavonoids are abundant secondary metabolites in plants and this review primarily focuses on the possible applications of key flavonoids (such as quercetin, rutin, catechin, diosmin, kaempferol and naringin) for preventing and treating DN. In recent times, herbal medicine, especially flavonoids for treating pain, inflammation, DM and other conditions, has been investigated thoroughly to develop them as promising candidates for DN. This paper discusses the probable mechanism of action of flavonoids against DN. Clinical and pharmaceutical challenges for the management of DN and developing flavonoids as drug molecules targeting DN are also highlighted.

Keywords: Diabetes mellitus, Neuropathy, Pain, Phytochemicals, Flavonoids.

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INTRODUCTION

International Diabetes Federation projected that nearly 425 million adult individuals are living with Diabetes Mellitus (DM). Diabetic Neuropathy (DN) is a predominant complication of DM. Usually, symptoms appear after 14.5 years in people with type 1 DM if blood glucose is not managed correctly and as early as 8.1 years in individuals suggesting from type 2 DM. It was estimated that half of diabetic people suffer due to DN and 15-30% of such cases are painful. About 30% of hospitalized diabetic patients and 25% of those in the community experience Diabetic Neuropathic Pain (DNP), a prevalent, costly and incapacitating consequence of DM.[1] The incidence of painful Diabetic Peripheral Neuropathy (DPN) varies, ranging from 10-20% in people with DM and 40-50% in those with DN. This condition occurs more in people with type 2 DM (20%) than in individuals with type 1 DM (5%). Pathogenesis of DNP includes somatosensory nervous system injury or illness. It is primarily conveyed by unwanted responses known as dysesthesia or pain brought on by stimuli characteristically painless, known as allodynia. Pain in extremities, predominantly in the hands and feet, can significantly alter the quality of life.[2]

Hyperglycaemia, inflammation, constriction of nerve and vascular injury are underlying causes of DNP.[3] Individuals with hypercholestemia and hypertension are at high risk of experiencing DNP. Moreover, smoking and alcohol consumption can exacerbate DNP symptoms.[4] A study stated that skin nerve fiber density, mainly in feet, is decreased due to pain, which may be connected with dysfunctional growth factors and the generation of other inflammatory cytokines.[5] Figure 1 elaborates on possible pathogenesis involved in DNP. Although people with DPN experience difficulties and painful conditions, appropriate care and following precautions can help such individuals to lead healthy and fulfilling lives. Allopathic medicines like tricyclic antidepressants, anticonvulsants and opioids are frequently prescribed in the management of DNP.[6] Medical techniques such as nerve blocks and electrical nerve stimulation were beneficial in lessening pain in some DNP cases. Moreover, lifestyle management, such as exercise and weight loss, may have some benefits in reducing pain in such individuals. In addition to its clinical manifestations, DPN can impact individuals psychologically and socially and might worsen their quality of life.[7]

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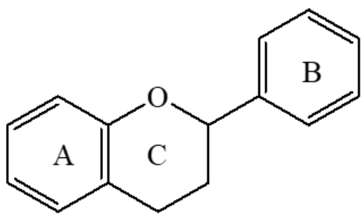
FLAVONOIDS AND DNP

Flavonoids are polyphenolic compounds found in fruits, flowers, peels, grains, vegetables, roots, tea, stems, etc. Chemically, flavonoids are 15-carbon frameworks consisting of two benzene rings connected by a heterocyclic pyran ring. Flavonoids can be divided into different subgroups according to the C-ring carbon to which the B-ring is attached, as well as the degree of oxidation and unsaturation of the C-ring.[8]



Basic Structure of Flavonoids

Flavonoids are the most ubiquitous polyphenolic compounds found across natural sources, mainly in different plant parts. Flavonoids have been investigated for anti-inflammatory, antioxidant, antidiabetic, antimicrobial, antiallergic, antitumor, anticancer, anti-hypertensive, anti-ulcer, spasmolytic, antidepressant and neuroprotective activities. Flavonoids established as functional foods that can play a role in promoting health and prevention of diseases act through diverse mechanism.[9,10]

QUERCETIN

Quercetin (a flavonol) is found in many fruits, cereals, vegetables and leaves and has been investigated for different therapeutic efficacy. The possible therapeutic effect of quercetin in DNP explains its anti-inflammatory, analgesic and antioxidant effects.

Anti-inflammatory effect

Inflammation plays a critical role in the pathogenesis of DN. Quercetin is a potent anti-inflammatory substance that acts by reducing the level of inflammatory cytokines like Tumour Necrosis Factor-alpha (TNF-α), interleukin (IL)-1β and IL-6 and different signalling pathways related to the aetiology of diabetic neuropathy and related discomfort.[11]

Antioxidant effect

Potent Reactive Oxygen Species (ROS) scavenging mechanism of quercetin helps to avert oxidative stress and can protect neurons against oxidative stress-induced damage. Quercetin was found to upregulate paranodes at paranodal junctions, downregulate amyloid precursor protein and ionized calcium-binding adaptor molecule 1 in experimentally induced DNP rats.[12]

Effect on neurotrophic factor

The neuroprotective effect of quercetin is likely to contribute to its benefits on DN. The expression of neurotrophic factors is reduced during DN, resulting in nerve damage and discomfort. Quercetin has been demonstrated to boost neurotrophic factor expression, which can contribute to neuron regeneration and pain relief following nerve injury.[13]

RUTIN

Rutin is available in various plants, such as buckwheat, asparagus, citrus fruits and tea. It offers several health benefits, including antioxidant, anti-inflammatory, anticancer, anti-vascular, neuroprotective and cardioprotective properties. The mechanisms by which rutin exerts its beneficial effects on DNP still need to be fully understood. However, several pathways have been proposed, including:

Antioxidant activity

Rutin protects neurons by scavenging ROS that potentially damage neurons by inducing oxidative stress. Rutin may help prevent cell deterioration, preserve nerve fibers from harm and enhance nerve function by lowering oxidative stress.[14]

Anti-inflammatory activity

Rutin inhibits the production of proinflammatory cytokines like ILβ and TNF-α while promoting the production of anti-inflammatory cytokine interleukin-10.[15]

Regulation of ion channels

Rutin can influence the activity of ion channels such as TRPV1 and CaV3.2 T-type calcium channels involved in pain perception and neuronal function.[16]

Modulation of glucose metabolism

Rutin can enhance glucose uptake and utilization, which may improve nerve function by reducing hyperglycemia-induced damage to nerve fibres.[17]

CATECHIN

Catechin is a flavan-3-ol that often belongs to the polyphenol subclass commonly found in plants and fruits such as blueberries, gooseberries, apples, kiwi, grape seeds etc. Catechin may alleviate diabetic neuropathic pain by preventing the production of Advanced Glycation End products (AGES), activating the AMP-activated Protein Kinase (AMPK) pathway and enhancing the metabolism of glucose and insulin sensitivity and response.[18,19] Some of the possible pathways of catechins about their therapeutic effect against DNP include:

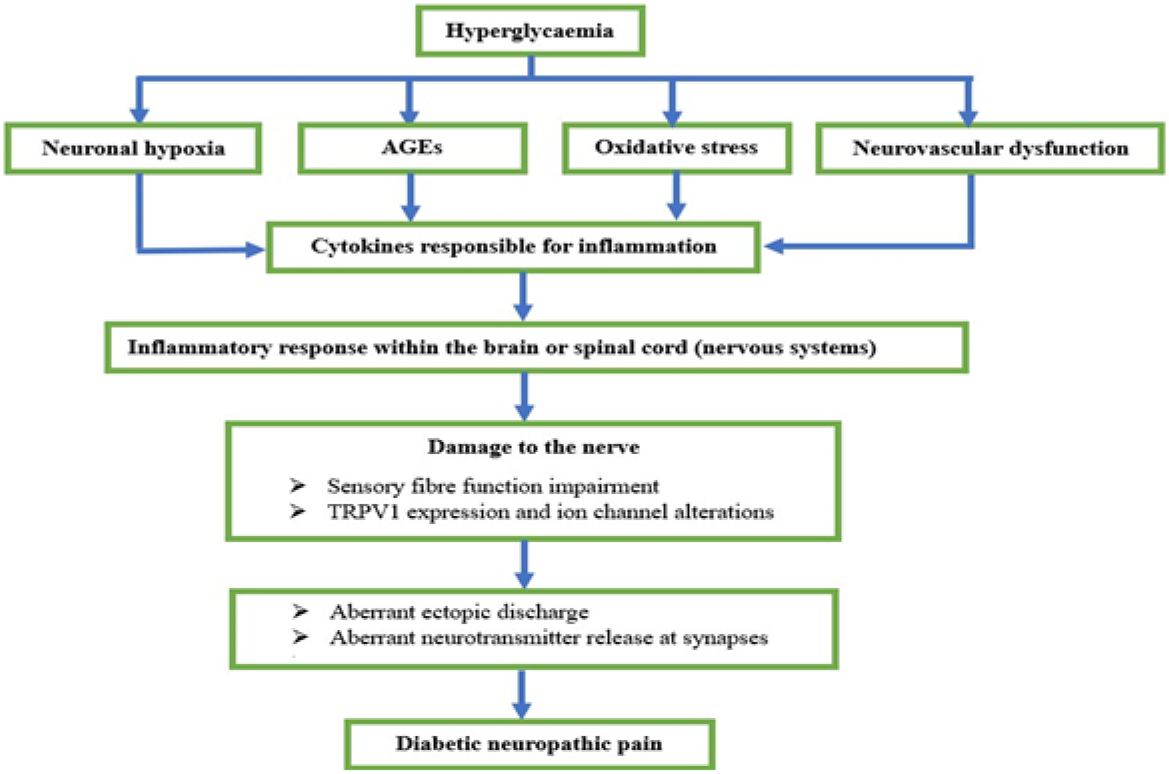


Figure 1: Pathogenesis of Diabetic neuropathic pain.

Modulation of oxidative stress

DNP is associated with nerve damage and dysfunction caused by oxidative stress. Catechins reduce ROS and boost antioxidant enzyme activity, such as Superoxide Dismutase (SOD) and Catalase (CAT), resulting in reduced inflammation and oxidative stress.[20]

Modulation of inflammatory pathways

There is evidence that inflammation contributes to nerve damage and dysfunction in DNP. Catechins reduce inflammation by inhibiting proinflammatory pathways such as NF-κB and Mitogen-Activated Protein Kinase (MAPK). Catechins can inhibit the activation of nuclear Factor-kappaB (NF-κB) by blocking the phosphorylation and degradation of its inhibitor, IκBα. This inhibition can decrease the expression of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6. In addition, catechins block Extracellular signal-Regulated Kinase (ERK), Jun N-terminal Kinase (JNK) and p38 phosphorylation, which inhibits MAPK activation, that in turn, decreases proinflammatory cytokines and chemokines, such as IL-8, Monocyte Chemoattractant Protein-1 (MCP-1) and Regulated on Activation, Normal T Expressed and Secreted (RANTES) protein.[21]

Modulation of neuronal pathways: Catechin was found to alter N-Methyl-D-Aspartate (NMDA) receptor pathways, which are involved in the perception and transmission of pain. NMDA receptor is a key neuropathic pain mediator and activating it can increase the sensitivity of spinal cord cells. Thus, catechin inhibits neuronal excitability and pain by blocking NMDA receptor activation.[22]

Improvement of vascular function

Nerve dysfunction and damage are common symptoms of DNP due to impaired vascular function. The ability of catechin to increase Nitric Oxide (NO) production and decrease Endothelin-1 (ET-1) levels improves vascular function. In addition to making blood flow more efficient, NO is a potent vasodilator, which can reduce nerve damage and pain associated with neurovascular tissue. In addition to its potent vasoconstrictive properties, ET-1 can also be beneficial for reducing oxidative stress and pain by improving blood flow to neurovascular tissue.[23]

DIOSMIN

Diosmin (diosmetin 7-O-rutinoside) is a natural flavonoid from the *Citrus sinensis* plant, commonly known as sweet orange. Diosmin may exhibit therapeutic benefits through several mechanisms, including antioxidants, anti-inflammatories and neuroprotectants.

Antioxidative mechanism

Diosmin and its metabolites contain significant antioxidant activity, which helps prevent nerve damage caused by oxidative stress. Diosmin was found to reduce oxidative stress markers such as Malondialdehyde (MDA) and NO while enhancing SOD and glutathione levels in rats with DN.[24]

Anti-Inflammatory mechanism

Evidence suggests that diosmin can slow down DN development by lowering nerve inflammation. In diabetic rats, it decreased proinflammatory cytokines such as TNF-α and IL-6 levels. Additionally, it decreased the activation of NF-κB and IκBα, two critical inflammatory mediators. Further, diosmin was found to regulate neuropathic pain through modulation of the Keap1/Nrf2/NF-κB signalling pathway.[25,26]

Neuroprotective mechanism

Diosmin may have a neuroprotective effect on nerves by reducing oxidative stress and inflammation, promoting nerve regeneration and improving nerve function. In animal studies, diosmin improved nerve conduction velocity and reduced nerve damage in diabetic rats.[27]

KAEMPFEROL

Kaempferol is a flavonol found in many plants and foods, including apples, grapes, tomatoes, potatoes, onions, squash, cucumber, lettuce, green beans, berries, legumes, tea, spinach and broccoli. Kaempferol shows its beneficial effects on DNP by numerous mechanisms such as:

Antioxidative mechanism

Kaempferol benefits DNP through its antioxidant properties, which modulate nerve oxidative stress. Kaempferol supplementation reduced MDA and Protein Carbonyl (PCO) in the sciatic nerve of diabetic rats, resulting in an improvement in nerve conduction velocity and a reduction in hyperalgesia (increased sensitivity to painful stimuli).[28]

Anti-inflammatory effect

The capacity of kaempferol to suppress the synthesis of proinflammatory cytokines and chemokines, which encourage the formation and maintenance of inflammation in nerve cells, is the basis of its anti-inflammatory action in treating DPN.[29] It has been found that kaempferol prevents NF-κB, a transcription factor that controls the expression of genes associated with inflammation, from being activated. The generation of cytokines, including TNF-α, IL-1 and IL-6, which may be important in the aetiology of DPN, is inhibited by kaempferol.[19,30] In addition, kaempferol also reduced the expression of the Cyclooxygenase (COX)-2 enzyme, reducing the generation of prostaglandins responsible for pain and inflammation. Kaempferol can also modulate the expression and activity of several other inflammatory mediators, such as inducible Nitric Oxide Synthase (iNOS), matrix Metalloproteinases (MMPs) and adhesion molecules, which play an important role in the pathogenesis of diabetic neuropathy.[31]

Modulation of pain pathways

Kaempferol has been found to alter the expression of genes implicated in pain signalling pathways, such as Transient Receptor Potential Vanilloid 1 (TRPV1) and Calcitonin Gene-Related Peptide (CGRP).[32] TRPV1 is a pain receptor whose expression is elevated in DN. Kaempferol has been shown to lower TRPV1 expression, which lessens pain sensitivity.[33]

NARINGIN

Naringin is a flavonoid glycoside that is abundant in the peel of grapefruit and orange. Naringin is a promising lead for the treatment of DNP because of its numerous therapeutic beneficial effects, which include its anti-inflammatory, neuroprotective, antioxidant and glycemic control characteristics. Naringin reported may exhibit its effects on DNP by the following mechanisms:

Neuroprotective mechanism

Naringin demonstrates its neuroprotective properties through the inhibition of free radicals and cytokines, such as TNF-α.[34]

Reduction of inflammation

Naringin reduced inflammation associated with chronic constriction injury-induced neuropathic pain in rats by downregulating TNF-α and IL-6. Narginin treatment in rats reduced MPO, NO and cell apoptosis and enhanced the nociceptive threshold, Na-K-ATPase and motor nerve conduction velocity. This suggests that naringin may alleviate DPN by reducing inflammation.[35-37]

Antioxidant defense mechanism

Naringin improves the antioxidant defense system in response to oxidative stress by suppressing Superoxide Dismutases (SOD), Glutathione (GSH) and catalase activity.[37]

FUTURE PROSPECTIVE

DN became prevalent and the treatment of DN became a major challenge for physicians and the pharmaceutical industry. Recent researchers have shown that flavonoids can be a choice of drug for treating diverse pathological conditions and preventing different ailments. Flavonoids are naturally occurring secondary metabolic products that have gained significant interest in the pharmaceutical industry as potential candidates for developing drugs to treat DN. Flavonoids decreased oxidative stress, glycogenolysis, AGEs, increased glucose utilization and suppressed the α-glycosidase enzyme.[9,10,38] Flavonoids are believed to counteract the oxidative stress and chronic inflammation that contribute to nerve damage in DN. Flavonoids such as quercetin, rutin, catechin, diosmin, kaempferol and naringin have emerged as intriguing candidates for treating DM, holding significant potential in the pharmaceutical industry.[39] However, the bioavailability of flavonoids is usually low and can differ highly among different types of flavonoids; for example, relative urinary excretion rates of daidzin and anthocyanins were found to be 43% and 0.3%. Complex structures and high molecular weights were also found to reduce bioavailability. This difference highlights the significant variability in the bioavailability of flavonoids.[40] Principal challenges for the pharmaceutical industry to develop flavonoids as drug molecules include poor aqueous solubility, limited systemic absorption and extensive metabolism. Presently, the pharmaceutical investigation focuses on novel delivery systems so that the bioavailability and bioactivity issues of flavonoids can be adequately addressed to enhance the clinical application of flavonoids.[41]

Harnessing the therapeutic potential of these flavonoids may lead to developing novel pharmaceutical formulations or supplements for DN, offering hope for improved management and relief for individuals affected by this debilitating condition. As pharmaceutical research continues to explore the therapeutic potential of flavonoids, they may emerge as valuable drug candidates in the ongoing quest to develop more effective treatments for DN, addressing an unmet medical need for millions of individuals worldwide.

CONCLUSION

Flavonoids have features that make them a good target for diabetic neuropathy treatment. It is apparent that, due to their antioxidant properties, naturally occurring polyphenols, including flavonoids, can connect with several cellular signaling pathways and have many potential advantages crucial in functioning cells in everyday life. Flavonoid-flavonoid interaction Pathologies of cell signaling have a variety of beneficial outcomes, including enhanced brain activity, reduced oxidative stress, apoptosis, endothelial barrier damage, cognitive activity enhancement, and neurodegeneration. However, there is a need for additional scientific attention to *in vivo* circumstances evaluating flavonoids' particular dose and bioavailability, which target several survival signaling systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DM: Diabetes Mellitus; **DN:** Diabetic Neuropathy; **DNP:** Diabetic Neuropathic Pain; **DPN:** Diabetic Peripheral Neuropathy; **TNF-α:** Tumour Necrosis Factor-alpha; **IL-1β:** Interleukin -1 beta; **IL-6:** Interleukin 6; **ROS:** Reactive Oxygen Species; **TRPV1:** Transient receptor potential vanilloid 1; **AGEs:** Advanced Glycation End products; **AMPK:** AMP-activated Protein Kinase; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **NF-κB:** Nuclear factor-kappa B; **MAPK:** Mitogen-Activated Protein Kinase; **IκBα:** Inhibitor of nuclear factor kappa B; **ERK:** Extracellular signal-regulated Kinase; **JNK:** Jun N-terminal Kinase; **IL-8:** Interleukin 8; **MCP-1:** Monocyte Chemoattractant Protein-1; **RANTES:** Regulated on Activation, Normal T Expressed and Secreted; **NMDA:** N-Methyl-D-Aspartate; **NO:** Nitric Oxide; **ET-1:** Endothelin-1; **MDA:** Malondialdehyde; **Keap1:** Kelch-like ECH-associated protein 1; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **PCO:** Protein Carbonyl; **COX:** Cyclooxygenase; **iNOS:** Inducible Nitric Oxide Synthase; **MMPs:** Matrix Metalloproteinases; **CGRP:** Calcitonin Gene-Related Peptide; **MPO:** Myeloperoxidase; **Na-K-ATPase:** Sodium–potassium adenosine triphosphatase; **GSH:** Glutathione.

REFERENCES

1. Yang XD, Fang PF, Xiang DX, Yang YY. Topical treatments for diabetic neuropathic pain [review]. Exp Ther Med. 2019;17(3):1963-76. doi: 10.3892/etm.2019.7173, PMID 30783472.
2. Abdissa D. Prevalence and associated factors of painful diabetic peripheral neuropathy among diabetic patients on follow up at Jimma University Medical Center. J Diabetes Metab Disord. 2020;19(2):1407-13. doi: 10.1007/s40200-020-00661-7, PMID 33520843.
3. Tesfaye S, Boulton AJ, Dickenson AH, Freeman R, Horowitz M. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. Diabetes Care. 2013;36(9):2456-65. doi: 10.2337/dc12-1964, PMID 23970715.
4. Callaghan BC, Cheng HT, Stables CL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2015;14:956-68.
5. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, *et al.* Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136-54. doi: 10.2337/dc16-2042, PMID 27999003.
6. Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev. 2012; 28; Suppl 1: 8-14. doi: 10.1002/dmrr.2239, PMID 22271716.
7. Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of diabetic neuropathy. Curr Neurol Neurosci Rep. 2014;14:1-10.
8. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47. doi: 10.1017/jns.2016.41, PMID 28620474.
9. Hasnat H, Shompa SA, Islam MM, Alam S, Richi FT, Emon NU, *et al.* Flavonoids: A treasure house of prospective pharmacological potentials. Heliyon. 2024;10(6):e27533. doi: 1 0.1016/j.heliyon.2024.e27533, PMID 38496846.
10. Rana AC, Gulliya B. Chemistry and pharmacology of flavonoids-A review. Indian J Pharm Educ Res. 2019;53(1):8-20. doi: 10.5530/ijper.53.1.3.
11. Zhao B, Zhang Q, Liang X, Xie J, Sun Q. Quercetin reduces inflammation in a rat model of diabetic peripheral neuropathy by regulating the TLR4/MyD88/NF-κB signalling pathway. Eur J Pharmacol. 2021;912:174607. doi: 10.1016/j.ejphar.2021.174607, PMID 34743981.
12. Xie J, Song W, Liang X, Zhang Q, Shi Y, Liu W, *et al.* Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level. Biomed Pharmacother. 2020;127:110147. doi: 10.1016/j.biopha.2020.110147, PMID 32559841.
13. Ferreira PE, Lopes CR, Alves AM, Alves ÉP, Linden DR, Zanoni JN, *et al.* Diabetic neuropathy: an evaluation of the use of quercetin in the cecum of rats. World J Gastroenterol. 2013;19(38):6416-26. doi: 10.3748/wjg.v19.i38.6416, PMID 24151360.
14. Tian R, Yang W, Xue Q, Gao L, Huo J, Ren D, *et al.* Rutin ameliorates diabetic neuropathy by lowering plasm glucose and decreasing oxidative stress via Nrf2 signaling pathway in rats. Eur J Pharmacol. 2016;771:84-92. doi: 10.1016/j.ejphar.2015.12.021.
15. Al-Enazi MM. Ameliorative potential of rutin on streptozotocin-induced neuropathic pain in rat. Afr J Pharm Pharmacol. 2013;7(41):2743-54. doi: 10.5897/AJPP2012.1534.
16. Basu P, Basu A. *In vitro* and *in vivo* Effects of Flavonoids on Peripheral Neuropathic Pain. Molecules. 2020;25(5):1171. doi: 10.3390/molecules25051171, PMID 32150953.
17. Sood A, Kumar B, Singh SK, Prashar P, Gautam A, Gulati M, *et al.* Flavonoids as potential therapeutic agents for the management of diabetic neuropathy. Curr Pharm Des. 2020;26(42):5468-87. doi: 10.2174/1381612826666200826164322, PMID 32851955.
18. Julius AN, Hopper WA. Inhibition of advanced glycation end-product formation by quercetin and catechin: an alternative therapy for treating diabetic complications. Asian J Pharm Clin Res. 2017;10(11):173-6. doi: 10.22159/ajpcr.2017.v10i11.19412.

19. Kabir MT, Tabassum N, Uddin MS, Aziz F, Behl T, Mathew B, *et al.* Therapeutic potential of polyphenols in the management of diabetic neuropathy. Evid Based Complement Alternat Med. 2021; 2021:9940169. doi: 10.1155/2021/9940169, PMID 34093722.
20. Samarghandian S, Azimi-Nezhad M, Farkhondeh T. Catechin treatment ameliorates diabetes and its complications in streptozotocin-induced diabetic rats. Dose-Response. 2017;15(1):1559325817691158. doi: 10.1177/1559325817691158, PMID 28228702.
21. Kim JM, Heo HJ. The roles of catechins in regulation of systemic inflammation. Food Sci Biotechnol. 2022;31(8):957-70. doi: 10.1007/s10068-022-01069-0, PMID 35345441.
22. Xifró X, Vidal-Sancho L, Boadas-Vaello P, Turrado C, Alberch J, Puig T, *et al.* Novel epigallocatechin-3-gallate (EGCG) derivative as a new therapeutic strategy for reducing neuropathic pain after chronic constriction nerve injury in mice. PLOS ONE. 2015;10(4):e0123122. doi: 10.1371/journal.pone.0123122, PMID 25855977.
23. Dash JR, Pattnaik G, Ghosh G, Rath G, Kar B. Protective effect of epicatechin in diabetic-induced peripheral neuropathy: a review. J App Pharm Sc. 2023;13(1):56-63. doi: 10.7324/JAPS.2023.130105-1.
24. Jain D, Bansal MK, Dalvi R, Upganlawar A, Somani R. Protective effect of diosmin against diabetic neuropathy in experimental rats. J Integr Med. 2014;12(1):35-41. doi: 10.1016/S2095-4964(14)60001-7, PMID 24461593.
25. Carballo-Villalobos AI, González-Trujano ME, Pellicer F, Alvarado-Vásquez N, López-Muñoz FJ. Central and peripheral anti-hyperalgesic effects of diosmin in a neuropathic pain model in rats. Biomed Pharmacother. 2018;97:310-20. doi: 10.1016/j.biopha.2017.10.077, PMID 29091880.
26. Zhao L, Tao X, Wang Q, Yu X, Dong D. Diosmetin alleviates neuropathic pain by regulating the Keap1/Nrf2/NF-κB signaling pathway. Biomed Pharmacother. 2024;170:116067. doi: 10.1016/j.biopha.2023.116067, PMID 38150877.
27. Sivakumar PM, Prabhakar PK, Cetinel S, R N, Prabhawathi V. Molecular insights on the therapeutic effect of selected flavonoids on diabetic neuropathy. Mini Rev Med Chem. 2022;22(14):1828-46. doi: 10.2174/1389557522666220309140855, PMID 35264089.
28. Kishore L, Kaur N, Singh R. Effect of kaempferol isolated from seeds of *Eruca sativa* on changes of pain sensitivity in streptozotocin-induced diabetic neuropathy. Inflammopharmacology. 2018;26(4):993-1003. doi: 10.1007/s10787-017-0416-2, PMID 29159712.
29. Kong M, Xie K, Lv M, Li J, Yao J, Yan K, *et al.* Anti-inflammatory phytochemicals for the treatment of diabetes and its complications: lessons learned and future promise. Biomed Pharmacother. 2021;133:110975. doi: 10.1016/j.biopha.2020.110975, PMID 33212375.
30. Chang S, Li X, Zheng Y, Shi H, Zhang D, Jing B, *et al.* Kaempferol exerts a neuroprotective effect to reduce neuropathic pain through TLR4/NF-κB signaling pathway. Phytother Res. 2022;36(4):1678-91. doi: 10.1002/ptr.7396, PMID 35234314.
31. Abo-Salem OM. Kaempferol attenuates the development of diabetic neuropathic pain in mice: possible anti-inflammatory and anti-oxidant mechanisms. Open Access Maced J Med Sci. 2014;2(3):424-30. doi: 10.3889/oamjms.2014.073.
32. Singh H, Bhushan S, Arora R, Singh Buttar HS, Arora S, Singh B. Alternative treatment strategies for neuropathic pain: role of Indian medicinal plants and compounds of plant origin-A review. Biomed Pharmacother. 2017;92:634-50. doi: 10.1016/j.biopha.2017.05.079, PMID 28578258.
33. Zarei MM, Abdolmaleki Z, Shahidi S. Bioflavonoid exerts analgesic and anti-inflammatory effects via transient receptor potential 1 channel in a rat model. Arq Neuro Psiquiatr. 2022;80(9):900-7. doi: 10.1055/s-0042-1755321, PMID 36351417.
34. Quintans JS, Antoniolli AR, Almeida JR, Santana-Filho VJ, Quintans-Júnior LJ. Natural products evaluated in neuropathic pain models-a systematic review. Basic Clin Pharmacol Toxicol. 2014;114(6):442-50. doi: 10.1111/bcpt.12178, PMID 24252102.
35. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Neuroprotective effect of naringin by modulation of endogenous biomarkers in streptozotocin induced painful diabetic neuropathy. Fitoterapia. 2012;83(4):650-9. doi: 10.1016/j.fitote.2012.01.010, PMID 22343014.
36. Ahmad MF, Naseem N, Rahman I, Imam N, Younus H, Pandey SK, *et al.* Naringin attenuates the diabetic neuropathy in STZ-induced type 2 diabetic Wistar rats. Life (Basel). 2022;12(12):2111. doi: 10.3390/life12122111, PMID 36556476.
37. Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. J Diabetes Complications. 2012;26(6):483-90. doi: 10.1016/j.jdiacomp.2012.06.001, PMID 22809898.
38. Sood A, Kumar B, Singh SK, Prashar P, Gautam A, Gulati M, *et al.* Flavonoids as potential therapeutic agents for the management of diabetic neuropathy. Curr Pharm Des. 2020;26(42):5468-87. doi: 10.2174/1381612826666200826164322, PMID 32851955.
39. Rath D, Bhukta P, Sethy K, Sahu BB, Patro CS, Pattanik G, *et al.* Promising flavonoids against neuropathic pain: their mechanism and therapeutic opportunities. J Pharm Negat Results. 2022;13(8):3530-36.
40. Thilakarathna SH, Rupasinghe HP. Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients. 2013;5(9):3367-87. doi: 10.3390/nu5093367, PMID 23989753.
41. Yuan D, Guo Y, Pu F, Yang C, Xiao X, Du H, *et al.* Opportunities and challenges in enhancing the bioavailability and bioactivity of dietary flavonoids: A novel delivery system perspective. Food Chem. 2024;430:137115. doi: 10.1016/j.foodchem.2023.137115, PMID 37566979.

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