Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

Network Pharmacology of Pareesha (Thespesia Populnea. L) and Shirisha (Albezia Lebbeck. L) in the Management of Diabetic Wound. an In-Silico Approach towards Concept of Pratinidhi Dravya

Dr. R. S. Hiremath[1], Dr.Rashmi*

Professor and HoD, Department of Rasashastra and Bhaishajya Kalpana, Shri.B.MKankanawadi ayurvedic college Belagavi[1]

Final year PG Scholar Department of Rasashastra and Bhaishajya Kalpana, Shri.B.MKankanawadi ayurvedic college Belagavi*

(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May2025)

KEYWORDS

Network pharmacology, *Pratinidhi*, Compounds, Pathway, *Pareesha*, *Shireesha*

ABSTRACT:

Introduction: The concept of *Pratinidhi Dravya* mentioned in classics, an alternative drug that can be used as the substitute of another when the original is not available Geographically or no longer in use or is difficult to obtain. *Shirisha* is considered as *Pratinidhi Dravya* for *Pareesha,* where both drugs possess wound healing activity. *Ayurveda* maintains its comprehensive approach to healing while adapting to altering resource availability by using this concept.

Objectives: To compare *Pareesha* and *shirisha*, through network pharmacology and prove its relevance as *pratinidhi* Dravya in today's era.

Methods: *Pareesha* and *Shirisha* phytochemicals were sourced from Dr. Dukes, IMPPAT databases, previous studies. Using Lipinski's criteria, the drug-likeness of phytochemicals associated with PubChem CID was examined using Swiss ADME. Target was predicted by Binding DB and Swiss target database Uniprot used to acquire Gene ID. KEGG pathways were analysed using the String database, networks framed using Cytoscape 3.7.2.

Results: It discovered from bioinformatics the key phytochemicals identified include Kaempferol, Quercetin, Gossypol found in *Pareesha,* Acacetin, Okanin, and Echinocystic acid in *Shirisha* have been shown to interact significantly with proteins like MAPK3, PRKCA, PRKCG, of *Pareesha* and PTP1B, CA2, and FABP3 of *Shirisha* regulating sphingolipid signalling pathway, serotonergic synapses, inflammatory mediator control of TRP channels, and EGFR tyrosine kinase inhibitor resistance that are involved in diabetic wound.

Conclusions: The in-silico method is a useful technique for finding multi-compound treatment plans, improving drug discovery, and providing scientific validation to classical writings by proving that the concept of *Pratinidhi dravy*a remains valid even today.

1. Introduction

Diabetes involves several harmful metabolic effects that exacerbate pathophysiological issues like foot ulcers.[1] Diabetic foot ulcers (DFUs) can develop in approximately 12–25% of people with diabetes.[2] Due to decreased blood flow and damaged nerves, patients with uncontrolled diabetes are more likely to sustain wounds that do not heal or become infectious.

Ayurvedic medicinal preparations are the combination of different medicinal herbs, due to their lack of availability in the geographic area, a few herbs are challenging to obtain.

The demand for herbal goods skyrocketed in the 20th and 21st centuries because of the negative effects of synthetic medications. Because of improper collection methods in wild areas, industrialization, it causes the extinction of

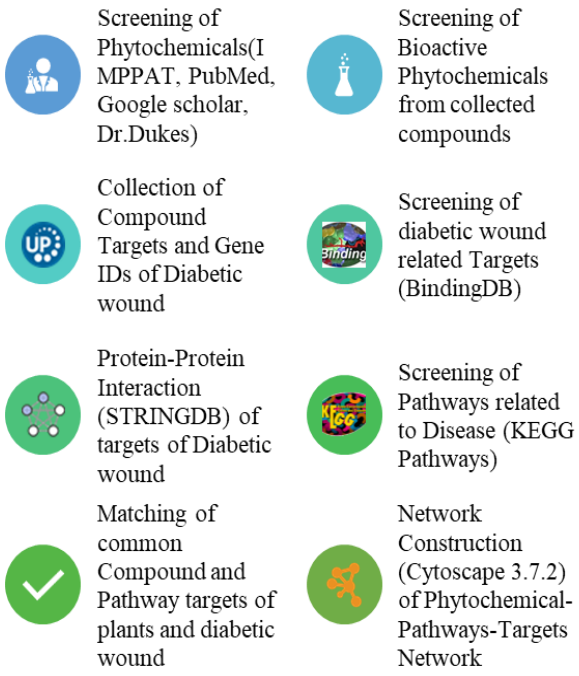
Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

significant medicinal plants. In Ayurvedic literature *Pratinidhi Dravya* concept describes use of alternative that have comparable therapeutic qualities to the original herb. Establishing *Pratinidhi Dravya's* effectiveness and ensuring its rational application in conventional and integrative medicine require an understanding of the molecular mechanisms behind it. In literature, *Shirisha* (*Albezia lebbeck.L*), is taken as *Pratinidhi Dravya to Pareesha* (*Thespesia populnea.L*). Both these drugs are known for its wound healing activity. [4,5]. A strong framework for investigating the relationships between bioactive substances, target proteins, and disease pathways is offered by network pharmacology. The discovery of important molecular targets and pathways impacted by *Pratinidhi Dravya* is made possible by network pharmacology, which provide scientific evidence that ancient statements are still relevant today.

2. Objectives

To compare *Pareesha* and *shirisha*, by employing network pharmacology with similar pathways and prove its relevance as *Pratinidhi Dravya* in today's era.

3. Methods



Bioactive phytochemical screening:

Databases such as IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics), Dr. Duke's Phytochemical and Ethnobotanical Databases, and research publications from PubMed and Google Scholar were searched for the phytochemicals of *Thespesia populnea* and *Albezia lebbeck*. The phytochemistry, canonical smiles, and toxicity of these phytochemicals were all verified using the PubChem Database. To prevent phytochemical repetition, duplicate phytoconstituents were eliminated.

Predicting the drug likeness of Thespesia populnea and Albezia lebbeck compounds.

Using the Swiss ADME database, each phytochemical linked to PubChem CID was examined for drug-likeness using Lipinski's "rule of five." Molecular weight less than 500, less than ten hydrogen bond acceptors, fewer than five hydrogen bond donors, and a MolLogP value less than five are all factors that determine a molecule's bioavailability, and oral absorption Lipinksi's rule violation.

Identification of the target:

For the identification of the targets two database were used, namely Binding DB database and swisstarget database. Each phytochemical's target proteins were found using the Binding DB database, which had a similarity index of 0.85. Then, duplicate entries were eliminated. The UniProt database was used to extract the names of protein genes that describe their interactions with humans.

Collection of diabetic wound genes:

Gene IDs of diabetic wounds were obtained using the Genecard database, and Venny 2.0 was employed to analyse overlapping genes. And data was used for further analysis of protein-protein interaction and pathway.

Analysis of KEGG pathway:

To determine the pathways linked to each gene, a subset of gene names was carefully examined in the STRING pathway enrichment database. These pathways were then examined in more detail to ascertain whether they would influence the pathophysiology of diabetic wound.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

Network construction:

Network design was done using Cytoscape 3.7.2 to show the relationships between target protein molecules, phytochemicals, and specific pathway targets. Using the Network Analyzer program, several networks were combined and examined. Colour, node size, and shape were among the features used to improve the network's presentation. The phytochemical with the greatest influence on a certain disease pathway was found using degree.

4. Results

Bioactive phytochemical screening.

Phytochemicals from *Thespesia populnea* and *Albezia lebbeck* were compiled from a variety of IMPPAT and dukes and scholarly literature publications. Data for compounds were obtained after screening PubChem Compound Identifiers (CIDs). Drug likeness was anticipated using the Swiss ADME database of these phytochemicals. Active compounds satisfy Lipinski's Rule for positive drug likeness are noted.

Table no 1: Drugs with total number of Phytochemicals.

Drug name	Total phytochemicals	After screening from pubchemCID(compound identifiers)	Compounds satisfying Lipinski's Rule
Thespesia populnea	121	81	47
Albezia lebbeck	130	85	59

Predicting the drug likeness of *Thespesia populnea* and *Albezia lebbeck* compounds.

After screening for phytochemicals with high absorption and a bioavailability of 0.55 and passing Lipinkis violation, 37 final phytochemicals from Pareesha and 27 from Shirisha were found.

Identification of the target:

The binding and Swiss target databases generated a total of 432 Pareesha targets and 363 Shirisha targets. The Uniprot database was used to identify the gene ID of these targets.

Collection of diabetic wound genes:

A total of 5928 diabetic wound genes were produced using the Genecard database. Venny software was used to obtain overlapping genes using the gene ID and target gene that were acquired from Uniprot.

Analysis of KEGG pathway:

A total of 148 genes of *Thespesia populnea* and 117 of *Albezia lebbeck* were acquired and overlapping genes were added to the STRING database to check protein-protein interaction and KEGG pathway analysis. The relevant data was obtained after 10 pathways were created using the KEGG pathway tool. The involvement of these pathways in the pathophysiology of diabetic wound was then studied. Figure 1 and Figure 2 shows protein-protein interaction of *Pareesha* and *Shirisha* with the targets. Figure 3 and Figure 4 lists 10 pathways of *Pareesha* and *Shirisha* associated with diabetic wounds respectively.

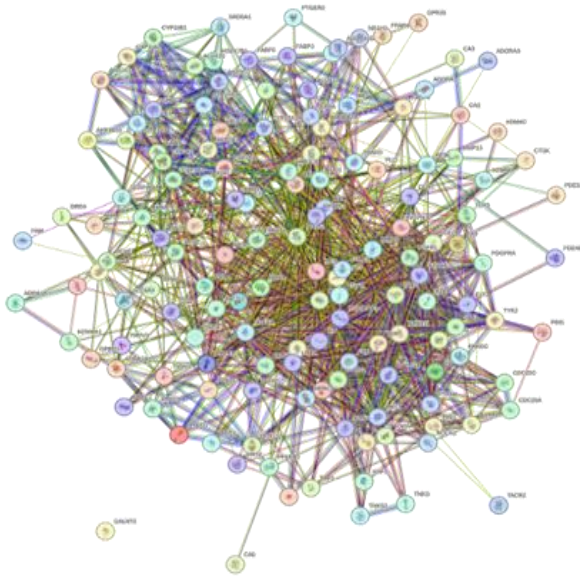


Fig:1 Protein-Protein interaction of *Pareesha*

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

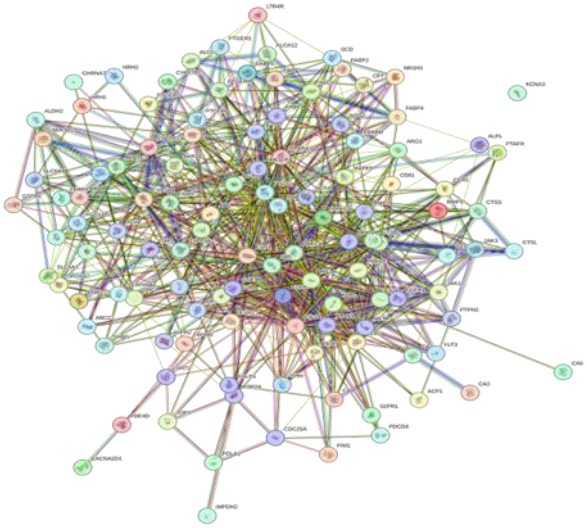


Fig:2 Protein-Protein interactionof *Shirisha*

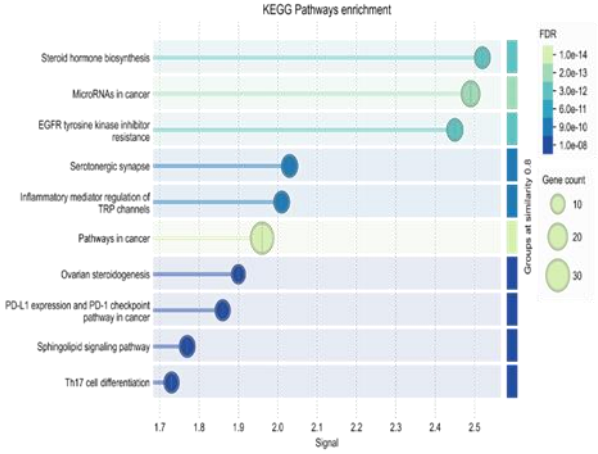


Fig 3: KEGG pathway of *Pareesha*

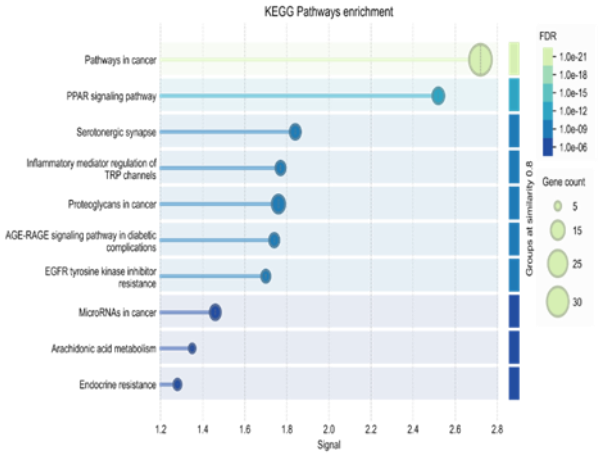


Fig 4: KEGG pathway of *Shirisha*

Network construction:

Out of the 32 phytochemicals examined in the network linking phytochemicals, targets, and pathways associated with diabetic wound, all were found to be implicated, the network constructed includes 100 nodes and 155 edges representing 10 pathways and. Network interaction is shown in Fig. 5

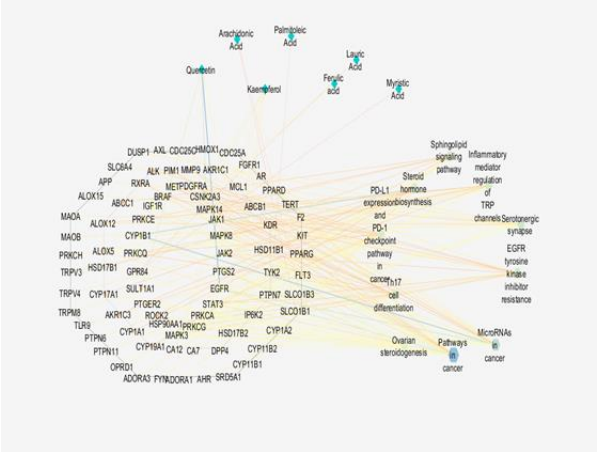


Fig. 5. Network between phytochemicals of Pareesha with protein targets and pathways related to Diabetic wound.

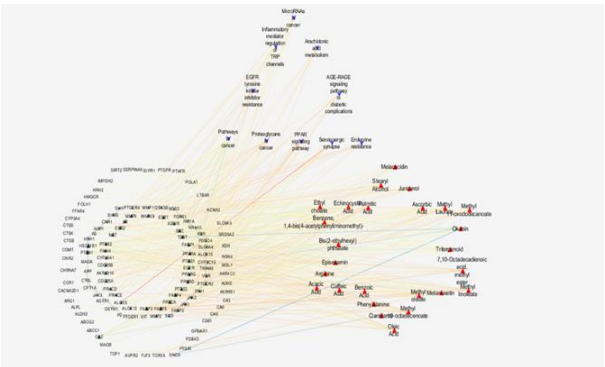


Fig. 6. Network between phytochemicals of *Shirisha* with protein targets and pathways related to Diabetic wound.

5. Discussion:

This principle is rooted in the idea that botanicals with similar pharmacological profiles can serve as effective substitutes without compromising therapeutic efficacy. *Shirish (Albezia lebbeck.L)* is the substituted drug to *Pareesha (Thespesia populnea.L)* as mentioned in the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

classics. In this study, we explored potential interactions between phytochemicals found in *Pareesha* and *Shirisha* are compared with pathways for diabetic wound. The key phytochemicals identified include kaempferol, quercetin, Okanin. Where compounds target proteins identified such as MAPK3, PRKCA, HSD11B1, PTPN1 which are involved in regulating various pathways related to diabetic wound pathogenesis, including Inflammatory mediator regulation of TRP channels, AGE-RAGE signalling pathway in diabetic complications, Serotonergic synapse. These results provide support to the *Ayurvedic* concept of *Pratinidhi Dravyas* are scientifically sound substitutes with complementary therapeutic effects.

Kaempferol: In various stages of wound healing, bioactive plant-based components have been demonstrated to enhance wound contraction and epithelization.[9] Plants synthesize flavonoids, which are phenolic compounds with several pharmacological actions, such as antibacterial, neuroprotective, cardioprotective, antidiabetic, and antioxidant properties.[10]

Quercetin: Quercetin's antihyperglycemic activity has been associated with several mechanisms, including enhanced insulin resistance, improved sensitivity to insulin, and increased glycogen production.[11] IL-6 and TNF-a, two proinflammatory factors, were statistically reduced, higher expression levels of the anti-inflammatory factor IL-10. the expression levels of angiogenesis-related factors, CD31 and VEGF-a, were noticeably higher in group treated with quercetin. Together, these results imply that quercetin can increase the expression of angiogenesis-related factors and inhibit the production of proinflammatory factors in diabetic wound areas.[12]

Gossypol: Gossypol, a polyphenolic molecule that has drawn attention due to its biological properties.[13] It has been reported that Gossypol is more potent antibacterial agent against gram positive bacteria when compared to gram negative. Gram-positive bacteria do not have the outer membrane that Gram-negative species possess, and their cell walls contain more peptidoglycan. This may have an impact on how gossypol is transported to its intended target.[14]

Acacetin: A flavonoid, acacetin present in many plants has demonstrated effectiveness in a range of biological processes. A study was conducted to investigate interaction of acacetin with glycolytic enzymes, and its potential action in the management of diabetes, which revealed acacetin interacts effectively with glycolytic enzymes by inhibiting their activity.[15]

Okanin: By controlling oxidative stress and inflammatory pathways, Okanin, a bioactive chalcone, has demonstrated promise in reducing diabetic peripheral neuropathy symptoms. Okanin helps mitigate oxidative stress and inflammation by regulating the AGEs/NF-κB/Nrf-2 pathway, which plays a crucial role in diabetic complications Its capacity to reduce inflammation and oxidative stress indicates that it may have therapeutic utility in wound healing in diabetic wound.[16]

MAPK3: In diabetic wound healing, MAPK3 (Mitogen-Activated Protein Kinase 3) is essential because it controls cellular responses, tissue remodelling, and inflammation. Mitogen-Activated Protein Kinase 3 (MAPK3) affects cellular signalling pathways involved in inflammation, angiogenesis, and tissue regeneration, which is important for diabetic wound healing. Due to oxidative stress, decreased endothelial function, and chronic inflammation, diabetes frequently results in dysregulated MAPK activation, which impairs wound healing.[17] Targeting MAPK3 and associated pathways may provide therapeutic approaches to enhance tissue repair and reduce inflammation in diabetic wounds.

PRKCA: PRKCA (Protein Kinase C Alpha) affects oxidative stress responses and intracellular calcium signalling, which contributes to diabetic wound healing. Ca2+ concentration rises in diabetes circumstances, triggering PRKCA activation, which phosphorylates NRF2 at Ser-40. PRKCA malfunction in diabetes results in decreased VEGF production, which hinders oxygen supply to wound sites and microvascular healing.[18]

PTP1B: PTP1B, or protein tyrosine phosphatase 1B, is a negative regulator of key metabolic processes and is expressed in most tissues. Under diabetes circumstances, tissues overexpress PTP1B. Inhibiting PTP1B has recently been shown to improve wound healing. Diabetic wound healing is facilitated by PTP1B suppression, which reduces inflammation and bacterial infection at the wound site while encouraging angiogenesis and tissue regeneration.[19]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

EGFR tyrosine kinase inhibitor resistance: EGFR inhibition has also been reported as a potential antidiabetic mechanism in type 2 diabetes. Administration of an EGFR inhibitor (RD153035) was linked to a reduction in M1 proinflammatory macrophage infiltration in adipose tissue, as well as an initial decrease in TNFα and IL6 production, according to studies conducted in diabetic mice administered a high-fat diet.[17]

Sphingolipid signalling pathway: SphK1 Sphingosine Kinase plays a crucial role in sphingolipid metabolism, is also important maintaining the blood vessel integrity.[18] SphK activation has been shown to prevent vascular diseases associated with diabetes and to increase β-cell survival and insulin production.[19] Future clinical studies and in vivo testing are necessary to confirm the functions of the two SphK isoforms and the several S1P receptor subtypes in the pathophysiology of diabetes.

Inflammatory mediator regulation of TRP Channels: TRP channels are crucial transduction molecules that react to a range of chemical and physical stimuli in the intracellular and extracellular environment, including changes in temperature, osmolarity, pH, reactive chemicals, and shear stress. A key mechanism in the regulation of inflammatory and immune cell activities is changes in intracellular calcium concentrations [Ca2 +] Given that TRP channels are cation channels that Favor Ca2 + permeability, it is possible that they could support inflammatory and immunological responses when they interact with other important molecular pathways.[20]

Conclusion:

The study emphasizes how crucial it is to include Ayurvedic concepts like Pratinidhi Dravya—the idea of therapeutic substitutes—into current biomedical research. Through network pharmacology, this study demonstrates the potential of *Albizia lebbeck* and *Thespesia populnea* in the treatment of diabetic wounds. Through the identification of important bioactive phytochemicals and their interactions with certain proteins, it delivers insight on how these compounds regulate biological processes related to wound healing. Kaempferol, Quercetin, Gossypol found in *Pareesha,* Acacetin, Okanin, and Echinocystic acid have been shown to interact significantly with proteins like MAPK3, PRKCA, PRKCG, of *Pareesha* and PTP1B, CA2, and FABP3, of *Shirisha* indicating their involvement in important pathways such as serotonergic synapse modulation, inflammatory mediator regulation of TRP channels, and EGFR tyrosine kinase inhibitor resistance.

The in-silico method is a useful technique for finding multi-compound treatment plans, improving drug discovery, and providing scientific validation to classical writings by proving that the concept of *Pratinidhi dravy*a remains valid even today. Validating these interactions and transforming them into efficient diabetic wound healing management will require further experimental validation and clinical research.

References

1) Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. Int J Mol Sci. 2020 Mar 6;21(5):1835. doi: 10.3390/ijms21051835. PMID: 32155866; PMCID: PMC7084712.

2) Katherine McDermott, Michael Fang, Andrew J.M. Boulton, Elizabeth Selvin, Caitlin W. Hicks; Etiology, Epidemiology, and Disparities in the Burden of Diabetic Foot Ulcers. *Diabetes Care* 2 January 2023; 46 (1): 209–221. https://doi.org/10.2337/dci22-0043

3) Ganga Rao, Battu & Konda, Jeevitha & Devarakonda, Ramadevi & Battu, Heera. (2018). REVIEW OF LITERATURE: PHYTO PHARMACOLOGICAL STUDIES ON THESPESIA POPULNEA. 4787-4792.

4) Sheetal S Samant, Vijay A Jagtap, Prajakt Kalangutkar, Raghunath Morye, Akshaya Gadekar, Riddhi Rane, Samidha Desai. Phytochemistry and therapeutic uses of Albizia lebbeck. Int J Herb Med 2023;11(5):22-26. DOI: 10.22271/flora.2023.v11.i5a.884

5) Dr. Gujar Rakeshkumar, Prabhu Pavan, Masalekar Srinivas. Conceptual Study on Prameha Pidakas w.s.r. to Skin Lesions In Diabetes. J Ayurveda Integr Med Sci [Internet]. 2017Aug.31 [cited 2025May20];2(04):236-42. Available from: https://jaims.in/jaims/article/view/272

6) Al-Ghanayem, Abdullah & Alhussaini, Mohammed & Mohammed, Asad & Joseph,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1808-1814 | ISSN:2251-6727

Babu. (2024). Kaempferol promotes wound-healing in diabetic rats through antibacterial and antioxidant effects, devoid of proliferative action. Bioscience Journal. 40. 10.14393/BJ-v40n0a2024-68974.

7) Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016 Dec 29;5:e47. doi: 10.1017/jns.2016.41. Erratum in: J Nutr Sci. 2025 Jan 29;14:e11. doi: 10.1017/jns.2024.73. PMID: 28620474; PMCID: PMC5465813.

8) Salehi B, Machin L, Monzote L, Sharifi-Rad J, Ezzat SM, Salem MA, Merghany RM, El Mahdy NM, Kılıç CS, Sytar O, Sharifi-Rad M, Sharopov F, Martins N, Martorell M, Cho WC. Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health. ACS Omega. 2020 May 14;5(20):11849-11872. doi: 10.1021/acsomega.0c01818. PMID: 32478277; PMCID: PMC7254783.

9) Jia Fu, Jingjuan Huang, Man Lin, Tingting Xie, Tianhui You, Quercetin Promotes Diabetic Wound Healing via Switching Macrophages From M1 to M2 Polarization, Journal of Surgical Research,Volume 246, 2020, Pages 213-223, ISSN 0022-4804, https://doi.org/10.1016/j.jss.2019.09.011.

10) Mohammad Rafiq Ganie, Nadeem Khan, Manish Shukla, Shreya Sood, Sushma Devi, Poonam Arora, Manish Kumar, Imtiyaz Ahmed Najar, Jianlei Tang,Okanin alleviates symptoms of nociceptive-like responses in diabetic peripheral neuropathy in type 1 diabetic Wistar rats by regulating the AGEs/NF-κB/Nrf-2 pathway,Journal of Pharmacological Sciences,Volume 157, Issue 1,2025,Pages 12-24,ISSN 1347-8613,https://doi.org/10.1016/j.jphs.2024.11.003.

11) Hegazi S, Aly R, Mesilhy R, Aljohary H. Diabetic Foot Ulcer Wound Healing and Tissue Regeneration: Signaling Pathways and Mechanisms [Internet]. Diabetic Foot Ulcers - Pathogenesis, Innovative Treatments and AI Applications. IntechOpen; 2024. Available from: http://dx.doi.org/10.5772/intechopen.1004267

12) Gavasker A. Sivaskandarajah, Marie Jeansson, Yoshiro Maezawa, Vera Eremina, Hans J. Baelde, Susan E. Quaggin; Vegfa Protects the Glomerular Microvasculature in Diabetes. *Diabetes* 1 November 2012; 61 (11):29582966. https://doi.org/10.2337/DB11-1655

13) Keshmiri-Neghab, H., & Goliaei, B. (2013). Therapeutic potential of gossypol: An overview. *Pharmaceutical Biology*, *52*(1), 124–128. https://doi.org/10.3109/13880209.2013.832776

14) Vadehra DV, Kalla NR, Saxena M, et al. (1985). Antimicrobial activity of gossypol acetic acid. IRCS Med Sci 13:10–11

15) Nagar KK. Acacetin Interacts with Glycolytic Enzymes and Inhibits Diabetes.

16) Ana Figueiredo, Ermelindo C. Leal, Eugénia Carvalho,Protein tyrosine phosphatase 1B inhibition as a potential therapeutic target for chronic wounds In diabetes,Pharmacological Research,Volume 159,2020,104977,ISSN 1043-6618,https://doi.org/10.1016/j.phrs.2020.104977.

17) Prada P.O., et. al.: EGFR tyrosine kinase inhibitor (PD153035) improves glucose tolerance and insulin action in high-fat diet-fed mice. Diabetes 2009; 58: pp. 2910-2919.

18) Bonder CS, Sun WY, Matthews T, Cassano C, Li X, Ramshaw HS, Pitson SM, Lopez AF, Coates PT, Proia RL, et al: Sphingosine kinase regulates the rate of endothelial progenitor cell differentiation. Blood. 113:2108–2117. 2009.

19) Parham KA, Zebol JR, Tooley KL, Sun WY, Moldenhauer LM, Cockshell MP, Gliddon BL, Moretti PA, Tigyi G, Pitson SM and Bonder CS: Sphingosine 1-phosphate is a ligand for peroxisome proliferator-activated receptor-γ that regulates neoangiogenesis. FASEB J. 29:3638–3653. 2015.

20) Parenti A, De Logu F, Geppetti P, Benemei S. What is the evidence for the role of TRP channels in inflammatory and immune cells? Br J Pharmacol. 2016 Mar;173(6):953-69. doi: 10.1111/bph.13392. Epub 2016 Feb 18. PMID: 26603538; PMCID: PMC5341240.