STM JOURNALS

Research & Reviews: A Journal of
Pharmaceutical Science

ISSN: 2229-7006
Volume 16, Issue 1, 2025
January–April
DOI (Journal): 10.37591/RRJoPS

https://journals.stmjournals.com/rrjops

Review RRJoPS

Screening of Newer Phytoconstituents on Novel Enzymes for Their Biological Activity

Mukund D. W.[1,*], Natarajan K.[2], Vineeth Chandy[3]

Abstract

Background: *Hyperlipidemia and gout are prevalent metabolic disorders significantly impacting global health. The xanthine oxidase and HMG-CoA reductase pathways play pivotal roles in the pathophysiology of these conditions. This study explores the potential of natural phytoconstituents – daidzein, resveratrol, and genistein – as dual inhibitors for these enzymatic targets, offering insights into innovative therapeutic strategies.* ***Aim:*** *To evaluate the potential of natural phytoconstituents – daidzein, resveratrol, and genistein – as dual inhibitors of xanthine oxidase and HMG-CoA reductase through molecular docking studies and to assess their drug-likeness and pharmacokinetic properties using ADME analysis via SwissADME.* ***Methodology:*** *The ligands genistein, resveratrol, and daidzein were directed against the enzymes HMG CoA reductase (PDB ID 416A) and xanthine oxidase (PDB ID 1FO4). Version 1.5.6 of the AUTODOCK VINA tool and BIOVIA Discovery Studio were used for docking simulations. Analysis was done on all the protein sequences' amino acid residues and hydrogen bonding interactions. Following the docking method, the phytochemicals were further evaluated utilizing the SwissADME ONLINE program for insilico ADME analysis and drug-like prediction. TSPA (topological polar surface area) and miLogP (molinspiration log P) values were used to test for drug-likeness characteristics. Result: Xanthine oxidase produced the best docking simulations with Daidzein (–8.7 kcal/mol), Genistein (–8.4 kcal/mol), and Resveratrol (–7.4 kcal/mol). Similarly, when HMG CoA reductase was the target, Genistein (–8.4 kcal/mol), Daidzein (–7.8 kcal/mol), and Resveratrol (–7.7 kcal/mol) had the best docking scores. Certain phytoconstituents adhere to the drug likeness Log P values and ADME limitations.* ***Conclusion:*** *The molecular docking studies revealed that daidzein, resveratrol, and genistein exhibit strong binding affinities towards xanthine oxidase and HMG-CoA reductase, suggesting their potential as dual inhibitors for managing hyperlipidemia and gout. ADME analysis further confirmed their favorable drug-likeness and pharmacokinetic profiles, highlighting their viability as promising candidates for therapeutic development.*

Keywords: Phytoconstituents, Xanthine Oxidase, HMG CoA Reductase, docking

***Author for Correspondence**
Mukund D. W.
E-mail: mdwankhede2003@gmail.com

[1]Research Scholar, Department of Pharmaceutical Biotechnology, T. John College of Pharmacy, Bangalore, Karnataka, India.
[2]Associate Professor, Department of Pharmaceutical Biotechnology, T. John College of Pharmacy, Bangalore, Karnataka, India.
[3]Principal, T. John College of Pharmacy, Bangalore, Karnataka, India.

Received Date: February 04, 2025
Accepted Date: March 03, 2025
Published Date: March 12, 2025

Citation: Mukund D. W., Natarajan K., Vineeth Chandy. Screening of Newer Phytoconstituents on Novel Enzymes for Their Biological Activity. Research & Reviews: A Journal of Pharmaceutical Science. 2025; 16(1): 81–86p.

INTRODUCTION

Hyperlipidemia and gout are major global health concerns, often interconnected due to shared metabolic pathways and is defined by elevated lipid levels in the bloodstream, significantly increases the risk of cardiovascular diseases and is considered a cornerstone of metabolic syndrome [1]. Gout, on the other hand, results from the crystallization of monosodium urate in tissues, a consequence of hyperuricemia caused by excess uric acid production or impaired excretion [2].

Xanthine oxidase (XO), a key enzyme in purine metabolism, is responsible for catalyzing the production of uric acid and XO inhibitors, such as allopurinol, are commonly used in the management of gout by reducing serum uric acid levels [3].

© STM Journals 2025. All Rights Reserved

Meanwhile, HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, serves as a primary target for lipid-lowering therapies, like statins, which are pivotal in managing hyperlipidemia and preventing cardiovascular events [4].

Recent studies have emphasized the potential of phytochemicals, such as resveratrol, daidzein, and genistein as dual modulators of these pathways. Resveratrol, a natural polyphenol, exhibits potent antioxidant and anti-inflammatory effects, contributing to its cardioprotective properties [5]. Similarly, genistein and daidzein, both isoflavones, have been shown to modulate lipid metabolism and exhibit uric acid-lowering effects, making them promising candidates for managing hyperlipidemia and gout [6].

The current study aims to target HMG CoA Reductase and xanthine oxidase in inhibiting the synthesis of cholesterol and uric acid crystal respectively an already proven as anti-hyperlipidemic and anti-hyperuricemic agents (Table 1). This study utilizes molecular docking to investigate the binding interactions of resveratrol, daidzein, and genistein with xanthine oxidase and HMG-CoA reductase. Furthermore, ADME analysis is performed to evaluate the pharmacokinetic profiles of these compounds, providing insights into their potential as dual therapeutic agents.

Table 1. Role and MOA of the selected phytoconstituents in gout and hyperlipidemia.

S. N.	Compound	Role in Gout	Role in Hyperlipidemia	Mechanism of Action
1	Daidzein	Reduces uric acid levels, inhibits urate crystal formation, and modulates inflammation [7].	Modulates lipid metabolism, reduces cholesterol levels, and has antioxidative effects [7].	Inhibits inflammation via NF-κB and COX-2; metabolic conversion by gut bacteria to active forms [8].
2	Resveratrol	Anti-inflammatory, decreases oxidative stress, and reduces uric acid synthesis.	Reduces LDL cholesterol, enhances HDL cholesterol, and exerts antioxidative properties.	Modulates lipid profiles via SIRT1 activation; reduces inflammation via NF-κB inhibition.
3	Genistein	Reduces inflammation, uric acid levels, and oxidative stress [7].	Improves lipid profiles, reduces total cholesterol, and triglycerides [8].	Inhibits inflammatory markers; modulates lipid metabolism by regulating AMPK and SIRT1 [8].

MATERIALS AND METHOD

Protein and Phytoconstituent Selection

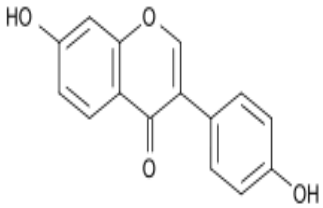
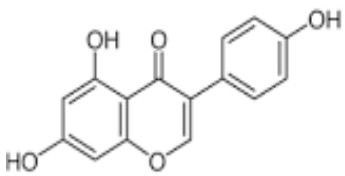
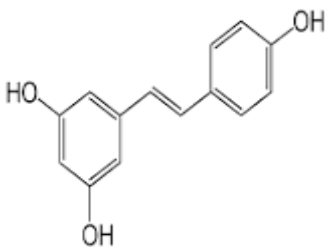
Table 2. List of selected enzymes for docking simulation.

S. N.	Enzyme	EC Classification	PDB ID	Structure
01	Xanthine oxidase	1.17.3.2	1F04	

© STM Journals 2025. All Rights Reserved

02	HMG CoA reductase	1.1.1.34	416A	

Table 3. List of ligands chosen for molecular docking simulation.

S. N.	Ligand	Structure	Description
1.	Diadzein		Daidzein is a member of the class of 7-hydroxyisoflavones. It has a role as an antineoplastic agent, a phytoestrogen, a plant metabolite, an EC 3.2.1.20 (alpha-glucosidase) inhibitor and an EC 2.7.7.7 (DNA-directed DNA polymerase) inhibitor.
2.	Genistein		Genistein is a 7-hydroxyisoflavone with additional hydroxy groups at positions 5 and 4'. It is a phytoestrogenic isoflavone with antioxidant properties. It has a role as an antineoplastic agent, a tyrosine kinase inhibitor, an EC 5.99.1.3 [DNA topoisomerase (ATP-hydrolyzing) inhibitor, a phytoestrogen, a plant metabolite, a Gero protector and a human urinary metabolite.
3.	Resveratrol		Resveratrol is a stilbenol, that is stilbene in which the phenyl groups are substituted at positions 3, 5, and 4' by hydroxy groups. It has a role as a phytoalexin, an antioxidant, a glioma-associated oncogene inhibitor and a Gero protector. It is a stilbenol, a polyphenol and a member of resorcinol's.

RESULTS AND DISCUSSION

The results of the docking simulations between Glutamate dehydrogenase and Glutaminase with Genistein, Daidzein, and Resveratrol offer promising insights into the search for effective treatment of gout and hyperlipidemia. Xanthine oxidase and HMG CoA reductase are the rate limiting enzymes for the uric acid crystals synthesis and cholesterol synthesis.

© STM Journals 2025. All Rights Reserved

Genistein and daidzein exhibited the highest binding affinity when targeted against HMG CoA Reductase and xanthine oxidase respectively. The docking score was –8.4 kcal and –8.7 kcal respectively. This indicates a strong interaction between Genistein and HMG CoA reductase, daidzein and xanthine oxidase. Genistein and daidzein likely forms favorable interactions with the active site residues of HMG CoA reductase and xanthine oxidase, such as hydrogen bonds, van der Waals interactions, and possibly hydrophobic interactions, leading to a stable complex formation.

These results suggest that daidzein and genistein may be promising candidates for further investigation as potential inhibitors or modulators of both HMG CoA reductase and xanthine oxidase with implications for therapeutic interventions targeting pathways involved in the synthesis and cholesterol and uric acid crystals (Tables 4–5).

Table 4. List of selected protein and their interaction with the newer targets.

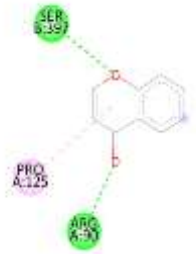
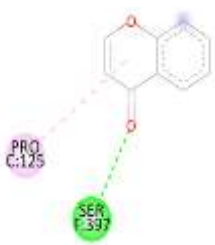
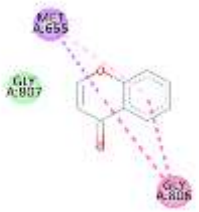
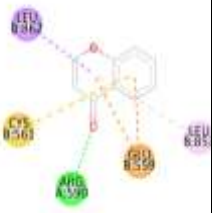
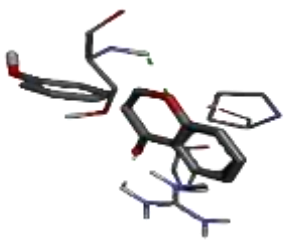
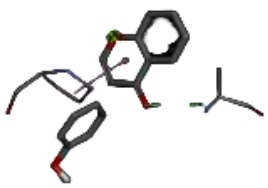
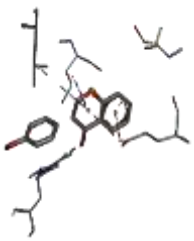
S. N.	Enzyme Structure and PDB ID	Daidzein	Genistein	Resveratrol
1.	Xanthine oxidase			
2.	HMG CoA reductase			

Table 5. 3D analysis of docking results.

S. N.	Enzyme Structure And PDB ID	Daidzein	Genistein	Resveratrol
1	Xanthine oxidase			

© STM Journals 2025. All Rights Reserved

2	HMG CoA reductase			

ADME Analysis

The selected phytoconstituents based on the already proven characteristics daidzein, genistein, and resveratrol had the best docking scores. The phytochemicals after the docking process were screened further for the *insilico* ADME analysis and drug like prediction using the swiss ADME ONLINE tool. The drug-likeness properties were screened based on miLogP (molinspiration Log P) values and TSPA (topological polar surface area). All the phytoconstituents obey the ADME limitations and drug likeness Log P values (Table 6).

Table 6. Molinspiration property values of selected phytoconstituents.

Compound	miLogP	TSPA	Natoms	MW	nON	nNOHN	Nrotb	Nviolations
Daidzein	1.08	70.67	19	254.24	4	2	1	0
Genistein	1.61	170.05	31	432.38	10	6	4	1
Resveratrol	1.08	60.69	17	228.24	3	3	2	0
Note: "miLogp" – partition coefficient for octanol/water (–2 to 6.5), TSPA – Total molecular polar surface area, "Natom" – Number of atoms in the compound, MW – Molecular weight (between 160 and 500), "noN" – No of H atom acceptor (not be more than 10), nNOHNH – Estimated no. of H donor (not be more than 5), "nrotb"– Number of rotatable bonds.								

CONCLUSIONS

The molecular docking and ADME analysis of daidzein, resveratrol, and genistein against xanthine oxidase and HMG-CoA reductase reveal their potential as therapeutic agents for managing gout and hyperlipidemia. These polyphenolic compounds demonstrated significant binding affinities toward the target enzymes, suggesting their inhibitory potential. Moreover, their pharmacokinetic profiles, assessed through ADME analysis, highlighted their drug-like properties, reinforcing their suitability for further drug development.

Daidzein, with its ability to modulate inflammatory pathways, and genistein, with its lipid-modulating properties, stand out as promising candidates for hyperlipidemia. Resveratrol's dual role in reducing oxidative stress and improving lipid profiles positions it as an effective agent for cardiovascular complications associated with hyperlipidemia and gout. These findings emphasize the therapeutic potential of natural bioactive compounds in addressing chronic metabolic and inflammatory diseases.

To convert these discoveries into practical applications, more research is necessary, including in vivo validation and clinical trials. This research underscores the role of computational tools in exploring novel bioactive agents and supports the integration of natural compounds into modern therapeutics for gout and hyperlipidemia management.

© STM Journals 2025. All Rights Reserved

REFERENCES

1. Lender D, Sysko SK. The metabolic syndrome and cardiometabolic risk: scope of the problem and current standard of care. Pharmacotherapy. 2006 May;26(5 Pt. 2):3S–12S. doi: 10.1592/phco.26.5part2.3S.
2. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016 Oct 22;388(10055):2039–2052. doi: 10.1016/S0140-6736(16)00346-9.
3. Maiuolo J, et al. Oxidative stress in hyperuricemia and associated disease. Front Biosci. 2016;8:665–675.
4. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986 Apr 4;232(4746):34–47. doi: 10.1126/science.3513311.
5. Guo J, Suma T, Richardson JJ, Ejima H. Modular assembly of biomaterials using polyphenols as building blocks. ACS Biomater Sci Eng. 2019 Apr 30;5(11):5578–5596.
6. Yamada ALYdS, Merenda MEZ, Pereira LC, Bonneti NMd, Martins IdO, Komarcheuski AS, et al. Effects of isoflavone intake on energy requirement, satiety, and body composition of neutered adult cats. Animals. 2024;14:3574. doi: 10.3390/ani14243574.
7. Kassab RB, Elhenawy AA, AbdulrahmanTheyab H, Hawsawi YM, Al-Amer OM, Oyouni AAA, et al. Modulation of inflammatory, oxidative, and apoptotic stresses mediates the renoprotective effect of daidzein against glycerol-induced acute kidney injury in rats. Environ Sci Pollut Res Int. 2023 Dec;30(56):119016–119033. doi: 10.1007/s11356-023-30461-4.
8. Yang L, Zhao M, Liu M, Zhang W, Zhi S, Qu L, et al. Effects of genistein on lipid metabolism, antioxidant activity, and immunity of common carp (Cyprinus carpio L.) fed with high-carbohydrate and high-fat diets. Aquac Nutr. 2023 Mar 31;2023:9555855. doi: 10.1155/2023/9555855.
9. Tshibangu JN, Chifundera K, Kaminsky R, Wright AD, König GM. Screening of African medicinal plants for antimicrobial and enzyme inhibitory activity. J Ethnopharmacol. 2002 Apr 1;80(1):25–35. doi: 10.1016/S0378-8741(01)00409-3.
10. Khan A, Unnisa A, Sohel M, Date M, Panpaliya N, Saboo SG, et al. Investigation of phytoconstituents of Enicostemma littorale as potential glucokinase activators through molecular docking for the treatment of type 2 diabetes mellitus. In Silico Pharmacol. 2021 Dec 2;10(1):1. doi: 10.1007/s40203-021-00116-8.

© STM Journals 2025. All Rights Reserved