Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
Impact Factor (RJIF): 6.35
www.phytojournal.com
JPP 2025; 14(5): 83-86
Received: 04-06-2025
Accepted: 06-07-2025

Chaitra S Shriyan
The Institute of Science, Dr. Homi Bhabha State University, Mumbai, Maharashtra, India

Iravati J Chengalur
St. Xavier's College (Empowered Autonomous Institute), Mumbai, Maharashtra, India

Vishal Banewar
The Institute of Science, Dr. Homi Bhabha State University, Mumbai, Maharashtra, India

Corresponding Author:
Vishal Banewar
The Institute of Science, Dr. Homi Bhabha State University, Mumbai, Maharashtra, India

Advances in semi-synthetic derivatives of quercetin: Enhanced methodologies and pharmacological potential

Chaitra S Shriyan, Iravati J Chengalur and Vishal Banewar

DOI: https://doi.org/10.22271/phyto.2025.v14.i5b.15554

Abstract
Quercetin, a naturally occurring common dietary flavonoid, is mainly found in vegetables, fruits and other plants. It can regulate cellular signaling pathways related to disease progression. Quercetin is known to have a plethora of activities, ranging from anti-oxidant, anti-inflammatory, antibacterial, among others. But its medicinal potential is hindered because of it low bioavailability and limited selectivity due to poor water solubility and permeability. This study aims at synthesizing semi-synthetic derivatives of quercetin with a view to improve its bioavailability.

Keywords: Quercetin, chemical derivatization, semi-synthetic derivatives, methodology, natural product derivatization, improved efficacy

Introduction
In recent times, a lot of focus is laid on the use of natural products and bioactives for disease mitigation and cure due to their varied pharmacological activities, lower toxicity and side effects. There is renewed interest in natural products for disrupting protein-protein interactions and for phenotypic screening. Nearly 50% of anticancer medications introduced between the 1940s and 2014 were discovered to be based on, or inspired by, natural products or semisynthetic structures [1, 2]. From 1981 to 2002, most natural product medications approved by the FDA were for the treatment of infectious disorders, notably antiviral, antibiotic, and antifungal agents. Natural products have also been a valuable source of antibiotics and antibacterial compounds, with penicillin, tetracycline, and erythromycin being popular examples. These medications have proven critical in the treatment of bacterial infections, which continue to be a serious public health concern due to antibiotic resistance [3].
Quercetin (3,3′,4′,5,7-pentahydroxyflavanone), a naturally occurring bioactive, is a prominent flavonoid. It is widely distributed in various plants and is recognized for its diverse health benefits [4, 5]. Its common presence in fruits, vegetables, and medicinal herbs, alongside its known pharmacological activity such as antioxidant, anti-inflammatory, antiviral, and anticancer characteristics, highlights its significance in both nutritional and medical fields [6, 7]. Quercetin has a significant antioxidant activity due to the double bonds and phenolic hydroxyl group present in it. The prevention and treatment of cancer and cardiovascular illnesses are directly related to its antioxidant and anti-inflammatory effects [8., 9]. Despite its vast therapeutic potential, quercetin suffers constraints due to its intrinsic physicochemical features, including limited water solubility and poor bioavailability, which restrict its systemic administration and efficiency [10, 11].
In order to overcome these restrictions, chemical derivatization has become a viable approach with the goal of improving its pharmacokinetic profile and expanding its therapeutic uses. can be used to improve their therapeutic value [3, 12]. Chemical derivatization refers to the modification of the chemical structure of a naturally occurring compound, while keeping the core intact, to improve its efficacy, selectivity, solubility and metabolic stability. These modifications essentially help in improving the drug-like properties and thereby achieving the desired pharmacological properties. This can help unlock the entire therapeutic potential of quercetin by utilising its natural bioactivity and altering its structure to enhance solubility, stability, and target-specific delivery [4, 13].
The current paper offers an overview and methodology for the synthesis of semi-synthetic derivatives of quercetin, in order to examine the alterations and their effects.

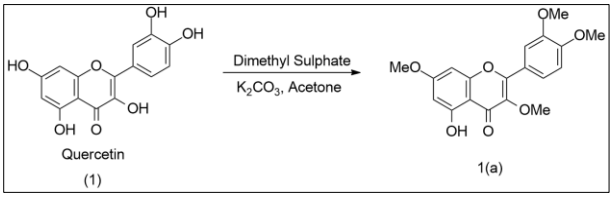
Materials and Methods

All reagents and solvents were commercially procured. Evaporation was performed using rotary evaporators, and purification by flash chromatography. TLC was run with acetone:hexane (1:1). NMR (400 MHz, CDCl3) and mass spectrometry were used for analytical confirmation.

Experimental Section

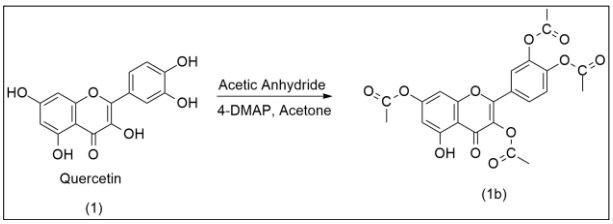
General Experimental Conditions: All the starting materials and solvents were commercially available. Standard rotavapor instruments were used to remove solvent. The synthesized products were purified using flash chromatography.

Scheme 1: Methylation of Quercetin [2, 12, 14]



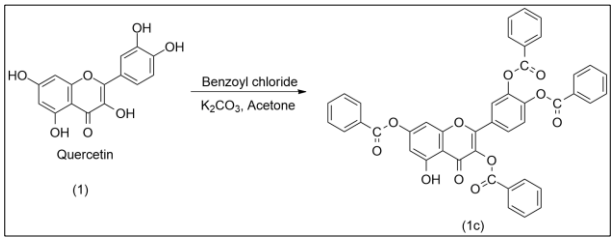
To a solution of quercetin (0.739 mmol, 250 mg) in acetone (30 cm^3), K_2CO_3 (14.781 mmol, 2.042 g) and dimethyl sulphate (14.781 mmol, 1.368 cm^3) were added. The resulting solution was stirred at room temperature overnight. TLC of the solution was recorded using acetone:hexane (1:1). The solution was dried to remove excess solvent. The residue obtained was purified by flash column chromatography using acetone as an eluent to afford product 1a as a dark yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.64 (s, 1H), 7.75 - 6.36 (m, 5H) 3.97 - 3.86 (m, 12H), m/z: 359.11

Scheme 2: Acylation of Quercetin [12, 15]



To a solution of quercetin (0.333, 100 mg) in acetone (20 cm^3), 4-DMAP (6.66 mmol, 813.66 mg) and acetic anhydride (6.66 mmol, 0.6 cm^3) were added. The resulting solution wasstirred at room temperature overnight. TLC of the solution was recorded using acetone:hexane (1:1). The solution was dried to remove excess solvent. The residue obtained was purified by flash column chromatography using acetone as the eluent to afford product 1b, which was crystallized as a yellow solid using methanol. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.30 (s, 1H), 8.2 - 6.5 (m, 5H), 3.0 (s, 9H), 2.0 (s, 3H), m/z: 471.09.

Scheme 3: Benzoylation of Quercetin [2, 12]



To a solution of quercetin (0.296 mmol, 100 mg) in acetone (20 cm^3), K_2CO_3 (2.96 mmol, 409.08 mg) and benzoyl chloride (2.96 mmol, 0.3 cm^3) were added. The resulting solution was stirred at room temperature overnight. TLC of the solution was recorded using acetone:hexane (1:1). The solution was dried to remove excess solvent. The residue obtained was purified by flash column chromatography using acetone as an eluent to afford product **1c** as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.24 (s, 1H), 8.25 - 8.00 (m, 8H), 7.62 - 7.19 (m, 17H), m/z: 719.16

Results and Discussion

Yield and Purity

Each semi-synthetic derivative was obtained in pure form following chromatographic separation. NMR and mass profiling substantiated structural modifications, with distinctive signals correlating to methyl, acetyl, and benzoyl groups.

Spectral Analysis

UV-Vis spectra revealed shifts in absorption maxima, attributed to replacement of hydroxyl groups in quercetin by electron donating/withdrawing moieties. These modifications impacted chromophoric properties and likely altered bioavailability. IR analysis confirmed the introduction of acyl and benzoyl functionalities by observation of strong carbonyl stretching and reduced phenolic O-H signals.

Comparative Spectral Studies

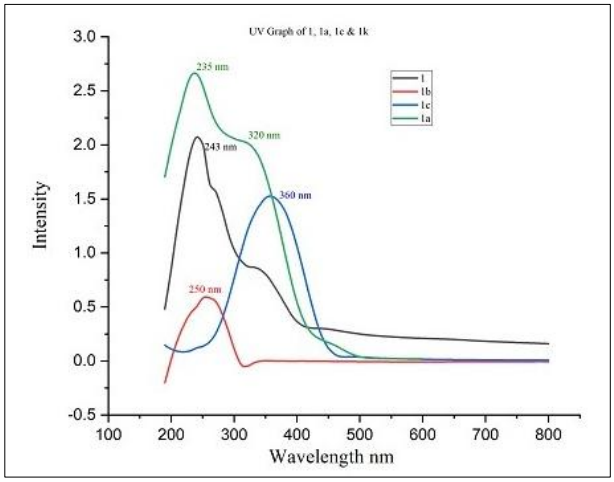


Fig 1: Comparative UV plot of 1, 1a, 1b andn1c

UV-Visible Spectroscopy

The UV comparison (Fig 1) revealed notable changes in the maximum absorbance (λmax) among the parent quercetin and its derivatives. These shifts are a result of introduced electron-donating and electron-withdrawing groups altering the chromophore environment.

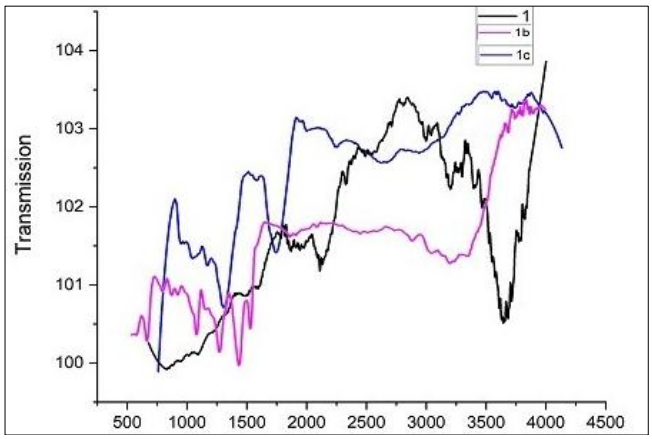


Fig 2: Comparative IR plot of 1, 1a, 1b andn1c

Such changes can enhance the compound's behavior in biological systems, particularly in antioxidant mechanisms that depend on light absorption and energy transfer.

Infrared (IR) Spectroscopy

IR spectra (Fig 2) supported the presence of acyl and benzoyl functionalities in the derivatives.

The disappearance or shift of phenolic -OH stretching frequencies, indicating successful substitution in quercetin.

A strong carbonyl (C=O) stretches characteristic of acetyl and benzoyl groups indicated by IR spectrum.

Enhanced Solubility and Bioavailability

Chemical modifications fostered significant increases in hydrophobicity and metabolic stability of quercetin derivatives. Methylation and acylation, in particular, improved membrane permeability and protected hydroxyl groups from metabolic conjugation. Benzoylated quercetin exhibited optimal stability for sustained therapeutic activity.

Pharmacological Implications

Semi-synthetic derivatives demonstrated comparable or superior antioxidant activity, with altered redox dynamics favoring prolonged cellular protection. *In vitro* studies from other researchers show enhanced anti-tumor efficacy for select derivatives, especially in colon carcinoma models. Moreover, improved pharmacokinetic profiles suggest substantial promise for drug development targeting infectious, inflammatory, and oncological diseases.

Improved Physicochemical Properties

Chemical modification increased the lipophilicity and metabolic resilience of quercetin derivatives. Methylation reduced the number of reactive -OH groups, decreasing susceptibility to rapid phase II metabolism (e.g., glucuronidation and sulfation), which often impairs bioavailability for natural quercetin.

Acylation and benzoylation further enhance membrane permeability and stability, promoting potential improvements in drug-like properties such as retention time and distribution in biological systems.

Therapeutic Implications

The altered spectral fingerprints reflect structural changes that potentially translate to superior pharmacokinetic profiles. Literature shows such derivatives may display greater activity against cancer cell lines and less cytotoxicity to normal cells, attributed to selective uptake and retention. An enhanced antioxidant capacity, demonstrated by spectral shifts, supports their role in reducing oxidative stress and inflammation. The derivatives, by improved pharmacodynamic and pharmacokinetic performance, can be considered as promising candidates for developing treatments against cancer, cardiovascular diseases, and infections.

Conclusion

Semi-synthetic derivatization of quercetin constitutes a promising route for achieving superior physicochemical and biological profiles. The methodologies described herein serve as a blueprint for scalable synthesis with robust therapeutic indices. These advancements underscore the relevance of natural product modification in modern pharmacology, with quercetin derivatives poised for translation into clinical candidates pending further bioactivity and toxicology evaluation.

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

All authors have given their consent for publication of this manuscript.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgements

The authors express gratitude to The Director, Institute of Science for providing necessary facilities and support for this research. The authors would also like to acknowledge Department of Science and Technology (DST) and Sophisticated Analytical Instrumentation Facility (SAIF), Punjab University, Chandigarh prompt NMR and HRMS services.

References

1. Erlund I. Review of the flavonoids quercetin, hesperetin, and naringenin: dietary sources, bioactivities, bioavailability, and epidemiology. Nutrition Research. 2004;24(10):851-874. DOI:10.1016/j.nutres.2004.07.005
2. Mukherjee A, Mishra S, Kotla NK, Manna K, Roy S, Kundu B, Bhattacharya D, Das Saha K, Talukdar A. Semisynthetic quercetin derivatives with potent antitumor activity in colon carcinoma. ACS Omega. 2019;4(4):7285-7298. DOI:10.1021/acsomega.9b00143
3. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nature Reviews Drug Discovery. 2005;4(3):206-220. DOI:10.1038/nrd1657
4. Aghababaei F, Hadidi M. Recent advances in potential health benefits of quercetin. Pharmaceuticals. 2023;16(7):1020. DOI:10.3390/ph16071020

5. Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, Liu H, Yin Y. Quercetin, inflammation and immunity. Nutrients. 2016;8(3):167. DOI:10.3390/nu8030167
6. Boots AW, Haenen GRMM, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. European Journal of Pharmacology. 2008;585(2-3):325-337. DOI:10.1016/j.ejphar.2008.03.008
7. Wang Y, *et al*. Pharmacological activity of quercetin: an updated review. Evidence-Based Complementary and Alternative Medicine. 2022;2022:3997190. https://onlinelibrary.wiley.com/doi/10.1155/2022/3997190.
8. Yang D, Wang T, Long M, Li P. Quercetin: its main pharmacological activity and potential application in clinical medicine. Oxidative Medicine and Cellular Longevity. 2020;2020:1-13. DOI:10.1155/2020/8825387
9. Di Petrillo A, Orrù G, Fais A, Fantini MC. Quercetin and its derivatives as antiviral potentials: a comprehensive review. Phytotherapy Research. 2022;36(1):266-278. DOI:10.1002/ptr.7309
10. Berkel Kaşıkçı M, Bağdatlıoğlu N. Bioavailability of quercetin. Current Research in Nutrition and Food Science Journal. 2016;4:146-151. DOI:10.12944/CRNFSJ.4.Special-Issue-October.20
11. Carullo G, Badolato M, Aiello F. Bioavailability and biochemistry of quercetin and applications to health and diseases. In: Watson RR, Preedy VR, Zibadi S, editors. Polyphenols: mechanisms of action in human health and disease. 2nd ed. London: Academic Press; 2018. p.361-371. DOI:10.1016/B978-0-12-813006-3.00026-X
12. Majhi S, Das D. Chemical derivatization of natural products: semisynthesis and pharmacological aspects—a decade update. Tetrahedron. 2021;78:131801. DOI:10.1016/j.tet.2020.131801
13. Shabir I, Kumar Pandey V, Shams R, Dar AH, Dash KK, Khan SA, Bashir I, Jeevarathinam G, Rusu AV, Esatbeyoglu T, Pandiselvam R. Promising bioactive properties of quercetin for potential food applications and health benefits: a review. Frontiers in Nutrition. 2022;9:999752. DOI:10.3389/fnut.2022.999752
14. Bouktaib M, Lebrun S, Atmani A, Rolando C. Hemisynthesis of all the O-monomethylated analogues of quercetin including the major metabolites, through selective protection of phenolic functions. Tetrahedron. 2002;58(50):10001-10009. DOI:10.1016/S0040-4020(02)01306-6
15. Lo S, Leung E, Fedrizzi B, Barker D. Synthesis, antiproliferative activity and radical scavenging ability of 5-O-acyl derivatives of quercetin. Molecules. 2021;26(6):1608. doi:10.3390/molecules26061608