	Callus induction present	
	5 mg/l - BAP	2 mg/l - 2,4 D
G1	90%	90%
G2	90%	90%
G3	100%	90%
Total	93%	90%

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Bioinformatic analysis of phytochemical constituents and in silico ADMET profiling of *Melissa officinalis* L.

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Abstract:

Melissa officinalis L. is a medicinal and aromatic plant widely valued for its rich phytochemical profile and diverse biological activities. While its chemical composition and traditional uses are well documented in the literature, bioinformatic and computational evaluations of its bioactive compounds remain limited. The present study aims to provide an integrative in silico assessment of major phytochemicals identified in *Melissa officinalis*, with a primary focus on their pharmacokinetic properties and potential molecular targets. Based on data retrieved from public chemical and biological databases, selected compounds were analyzed using established bioinformatic platforms, including PubChem, SwissADME and admetSAR. Key pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) were predicted to evaluate drug-likeness and biological availability. Special attention was given to rosmarinic acid, one of the predominant phenolic compounds in *Melissa officinalis*, due to its reported pharmacological relevance. The computational results indicated favorable drug-likeness profiles for several compounds, with rosmarinic acid showing suitable predicted ADMET parameters. Target prediction analyses suggested a potential interaction between rosmarinic acid and FYN tyrosine kinase, a protein involved in cellular signaling pathways associated with inflammatory and neuroprotective processes. These findings highlight the value of bioinformatic approaches in supporting phytochemical research and in identifying promising bioactive compounds from medicinal plants. The study contributes computational evidence that may support future experimental and biotechnological investigations on Melissa officinalis and its and its potential therapeutic relevance.

Introduction

Medicinal plants have played a fundamental role in maintaining human health since antiquity and continue to represent an important source of bioactive compounds used in both traditional and modern medicine (Petrișor et al., 2022; Miraj et al., 2016). Among these, *Melissa officinalis* L. (lemon balm) is widely recognized for its therapeutic potential and is extensively used across various regions of the world.

The biological activity of *Melissa officinalis* is mainly attributed to the presence of diverse phytochemicals, including phenolic compounds, which contribute to its antimicrobial, anti-inflammatory, antioxidant, and neuroprotective properties (Moradkhani et al., 2010; Świąder et al., 2019). Due to these effects, lemon balm has been traditionally used for the management of various disorders, particularly those related to the nervous system and inflammatory conditions. In addition, recent research has increasingly focused on identifying the molecular mechanisms underlying these biological effects, emphasizing the importance of phytochemical characterization.

Botanically, the species belongs to the Lamiaceae family and is native to the Mediterranean region, being widely cultivated and naturalized in Europe and other parts of the world (Sawicka et al., 2020; Usai et al., 2016).

Moreover, the increasing availability of bioinformatic tools provides new opportunities for evaluating phytochemicals and predicting their pharmacokinetic behavior and biological targets in a rapid and cost-effective manner.

Despite the extensive ethnopharmacological and experimental data available for *Melissa officinalis*, computational and bioinformatic studies addressing the pharmacokinetic behavior and molecular targets of its phytochemical constituents remain limited. Therefore, the present study aims to perform an in silico bioinformatic analysis of major phytochemical constituents of Melissa officinalis, with emphasis on ADMET profiling and molecular target identification.

Material and method

The bioinformatic investigation of *Melissa officinalis* was conducted using a combination of publicly available phytochemical databases and computational tools in order to identify the major bioactive compounds and to evaluate their physicochemical, pharmacokinetic, and molecular interaction profiles.

Initially, general information regarding the phytochemical composition and therapeutic uses of *Melissa officinalis* was obtained from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database, which integrates data on medicinal plants, phytochemical compounds, and associated biological activities. This database enabled the identification of known pharmacological effects and provided an overview of the potential therapeutic relevance of the plant.

Complementary information regarding the main chemical constituents and their relative concentrations was retrieved using the FooDB database, a comprehensive resource on food-derived compounds. Through FooDB, the principal organic constituents of *Melissa officinalis* were selected based on their reported abundance and relevance, forming the basis for the subsequent computational analysis.

The physicochemical properties of the selected phytocompounds were further investigated using the PubChem database. This resource allowed the extraction of key molecular descriptors, including molecular weight, lipophilicity (logP), number of hydrogen bond donors (HBD) and acceptors (HBA), number of rotatable bonds, and topological polar surface area (tPSA). These parameters are essential for understanding molecular behavior, drug-likeness, and potential biological activity.

To evaluate the pharmacokinetic profile of the identified compounds, the SwissADME web tool was employed. This platform enables the prediction of important parameters related to absorption, distribution, metabolism, and excretion, as well as drug-likeness and oral bioavailability. The SwissADME analysis provided insights into gastrointestinal absorption, blood–brain barrier permeability, and interactions with cytochrome P450 enzymes. In order to obtain a more detailed characterization of ADMET properties, the admetSAR 3.0 platform was also utilized. This tool allowed the prediction of additional endpoints, including human intestinal absorption, metabolic interactions, half-life, and a wide range of toxicity parameters such as carcinogenicity, mutagenicity, hepatotoxicity, cardiotoxicity, and ecotoxicity.

Focusing on the major phenolic compound identified, namely rosmarinic acid, the potential molecular target was predicted using the SwissTargetPrediction platform. This tool estimates likely macromolecular targets by comparing the query molecule with known bioactive compounds using both two-dimensional and three-dimensional similarity methods.

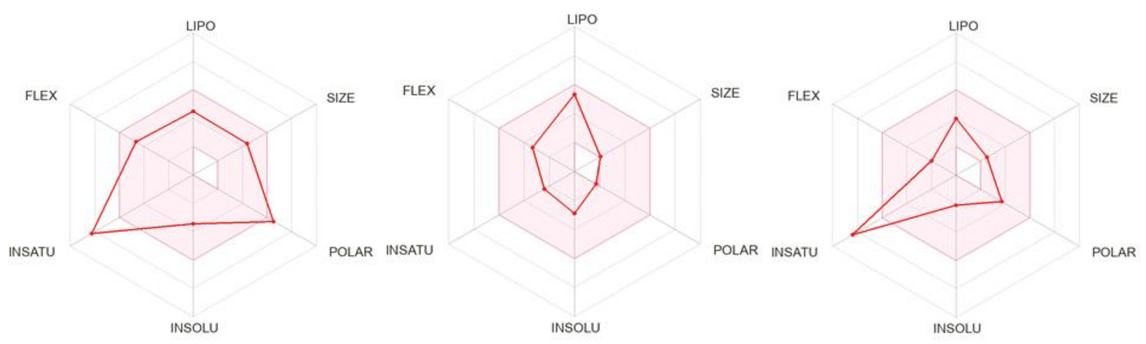
The analysis identified FYN tyrosine-protein kinase as a probable molecular target.The selected protein was subsequently characterized using the UniProt database, which provides detailed information on protein sequence, structure, function, and biological role. In order to perform structural analysis, the three-dimensional structure of the protein was retrieved from the Protein Data Bank (RCSB PDB), which contains experimentally determined structures of biomolecules. The structural file corresponding to the identified protein was used for further visualization and interpretation.

Finally, molecular visualization and structural analysis were carried out using UCSF Chimera software. This tool enabled the representation of the protein structure in three dimensions and allowed the analysis of important structural features, including surface topology, electrostatic potential, hydrophobicity distribution, and ligand positioning. These analyses contributed to a better understanding of the possible interaction between the phytochemical compounds and the predicted molecular target.

Results and Discussions

The phytochemical analysis of *Melissa officinalis* identified several major bioactive compounds, with rosmarinic acid as the predominant constituent, followed by citronellal, ferulic acid, and β-caryophyllene. These compounds generally exhibit low molecular weight and moderate lipophilicity, suggesting good membrane permeability. Physicochemical evaluation showed a low number of hydrogen bond donors and acceptors, as well as limited molecular flexibility, features that contribute to drug-likeness and stability. ADMET analysis indicated that most compounds have favorable pharmacokinetic profiles, including high gastrointestinal absorption and good predicted oral bioavailability. In contrast, rosmarinic acid showed lower absorption despite its abundance. Several compounds were predicted to cross the blood–brain barrier, suggesting potential neuroactive effects, while interactions with cytochrome P450 enzymes were generally minimal.

Overall, the studied phytochemicals display promising pharmacokinetic characteristics, supporting their potential as biologically active molecules (Figure 1).



a) rosmarinic acid b) citronellal c) ferulic acid

Figure 1. SwissADME radar plots illustrating the pharmacokinetic profiles of selected phytochemicals: rosmarinic acid – a), citronellal – b) and ferulic acid – c).

The radar plots highlight differences in drug-likeness profiles among the selected compounds. While citronellal and ferulic acid show profiles closer to the optimal range for oral drugs, rosmarinic acid deviates in several parameters, particularly polarity and size, which may explain its lower predicted bioavailability.

Target prediction analysis identified FYN tyrosine-protein kinase as a potential molecular target of rosmarinic acid. This protein plays a key role in cellular signaling pathways, including inflammatory and neurodegenerative processes, suggesting a possible mechanism underlying the biological activity of this compound (Figure 2).

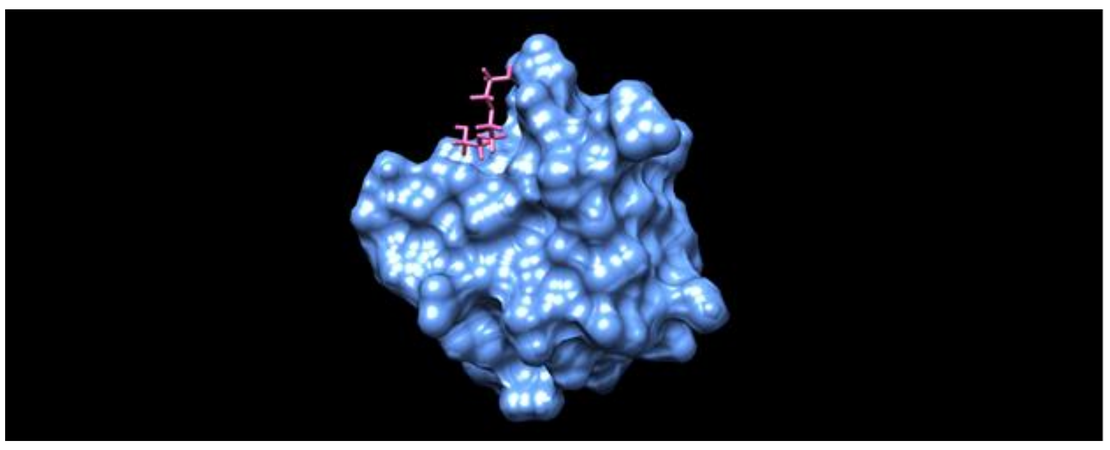


Figure 2. 3D structure of FYN tyrosine-protein kinase showing ligand positioning (visualized using UCSF Chimera).

The structural visualization reveals the surface topology of the FYN tyrosine-protein kinase and the ligand binding site, supporting its role as a potential molecular target for phytochemical interactions.

Conclusions

The present study highlights the potential of *Melissa officinalis* phytochemicals as biologically active compounds with favorable pharmacokinetic profiles. Most of the analyzed compounds exhibited suitable ADMET properties, although rosmarinic acid showed limitations in absorption despite its high abundance. Bioinformatic analysis identified FYN tyrosine-protein kinase as a potential molecular target, suggesting a possible mechanism underlying the biological activity of the plant. These findings support the relevance of computational approaches in evaluating medicinal plant compounds and guiding future experimental studies.

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