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In-Silico ADMETox Profiling of Quercetin Derivatives

[1*]Titin Sulastri, [2]Marvel Reuben Suwitono

[1]*Department of Biology, Universitas Advent Indonesia*
[2]*Department of Pharmacy, Universitas Advent Indonesia*

titin.sulastri@unai.edu

Abstract

Quercetin, a flavonoid with known pharmacological properties, has garnered significant attention for its potential therapeutic applications. To explore its derivatives for drug development, this study conducted an in-silico ADMETox (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling. A diverse set of Quercetin derivatives was obtained from computational analysis using SwissSimilarity tools. We have as much as 400 structures, which are restricted to 20 structures which have similarity higher than 90%. Key ADMETox properties, including solubility, permeability, CYP450 inhibition, and toxicity, were predicted. The results revealed that structural modifications in Quercetin derivatives significantly influenced their ADMETox profiles. Specific structural features were identified that correlated with improved or worsened properties. These findings provide valuable insights for the rational design of Quercetin derivatives with optimized pharmacokinetic and safety profiles, paving the way for their potential development as therapeutic agents.

Keywords: quercetin, ADMETox, similarity, computational

INTRODUCTION

Quercetin, a flavonoid abundant in various plants, has emerged as a promising compound for its potential health benefits. As a potent antioxidant, quercetin helps neutralize harmful free radicals, reducing oxidative stress associated with chronic diseases. Additionally, its anti-inflammatory properties can alleviate inflammation linked to conditions like arthritis and cardiovascular disease. Studies have also suggested that quercetin may contribute to cardiovascular health by lowering blood pressure and improving cholesterol levels. Moreover, its neuroprotective and anticancer potential make it a subject of ongoing research, exploring its potential as a natural compound for promoting overall well-being and preventing chronic diseases (Carrillo-Martinez et al., 2024). Common plant sources of quercetin include onions, apples, berries (such as blueberries and cranberries), tea (especially green and black), and red wine. The specific quercetin content can vary depending on factors like plant variety, growing conditions, and processing methods (Anand David et al., 2016)

A flavonoid known as quercetin possesses a unique chemical structure that serves as the foundation for a diverse array of derivatives. These derivatives are generated through various modifications to the quercetin molecule, including glycosylation, methylation, and sulfation. Despite these modifications, quercetin derivatives retain a core structural similarity, which is essential for understanding their biological activities and potential therapeutic applications (Massi et al., 2017). The core structure of quercetin is characterized by 1) a flavonoid skeleton, consists of two benzene rings (A and B) connected by a three-carbon chain

(C), 2) a double bond which located between carbons 2 and 3 of the C ring, 3) a ketone group located at carbon 4 of the C ring, and 4) hydroxyl groups which attached to various positions on the A and B rings (Lam et al., 2024).

In-silico ADMETox (Absorption, Distribution, Metabolism, Excretion, Toxicity) profiling is a valuable computational tool for predicting the pharmacokinetic and toxicological properties of molecules. By applying these methods to quercetin, researchers can gain insights into its absorption, distribution, metabolism, and potential toxicity (Austin et al., 2023).

Quercetin exhibits moderate oral bioavailability, allowing for its absorption from the gastrointestinal tract into the bloodstream. Computational methods can be employed to predict the permeability of quercetin across biological membranes, which is a crucial factor in its absorption. Moreover, the solubility of quercetin in both aqueous and lipid environments can influence its absorption efficiency (Yi et al., 2021). The distribution of quercetin in the body is influenced by its binding to plasma proteins. A higher degree of protein binding can limit the availability of free quercetin for distribution to various tissues and organs. Computational models can assist in predicting the distribution of quercetin to different body compartments, providing valuable insights into its pharmacokinetics (Muñoz-Reyes et al., 2021).

Metabolic transformations of Quercetin undergo in the body primarily through phase I and phase II reactions. Computational tools can aid in identifying potential metabolites of quercetin, which can provide valuable information about its metabolic fate. Additionally, predicting the metabolic stability of quercetin can help understand its clearance rate from the body, affecting its overall pharmacokinetic profile (Michala & Pritsa, 2022). Quercetin is primarily excreted from the body through the kidneys, with a portion also being eliminated through the bile. Computational methods can be utilized to assess the potential toxicity of quercetin, including its genotoxicity and hepatotoxicity. The predicted toxicity profile can inform the safety evaluation of quercetin and its derivatives. By conducting in-silico ADMETox profiling, researchers can gain valuable insights into quercetin's pharmacokinetic properties and potential toxicity, guiding the development of therapeutic applications and ensuring its safe use (Qi et al., 2022).

The exploration of quercetin derivatives is motivated by the potential to enhance the pharmacological properties of the parent molecule. By modifying the chemical structure of quercetin through derivatization, researchers aim to address limitations such as low bioavailability, rapid metabolism, and potential toxicity. Derivatives may exhibit improved solubility, increased stability, or altered bioactivity compared to quercetin. Additionally, derivatization can potentially broaden the therapeutic applications of quercetin, targeting specific diseases or conditions.

METHODOLOGY

The methodology for identifying quercetin derivatives involved a combined approach of similarity and structure fishing. A comprehensive chemical database (n = 400) was utilized to search for compounds similar to quercetin, using a similarity threshold of 90% to ensure a high degree of structural similarity. Additionally, specific substructures within the quercetin molecule were defined to identify compounds with desired structural features.

To initiate the search for structurally similar compounds of quercetin, the SwissSimilarity interface was accessed. This online platform provides a user-friendly environment for conducting similarity searches against a vast database of chemical compounds. This query structure served as the reference point for the subsequent similarity search, allowing

the database to identify compounds that shared structural similarities with quercetin. SwissSimilarity is a powerful online tool for chemical structure fishing. It allows researchers to efficiently identify compounds that share structural similarities with a given query molecule, and exhibit a high degree of structural similarity (Bragina et al., 2022). Each derivatives structure was validated at EMBL's European Bioinformatics Institute (EMBL-EBI) site.

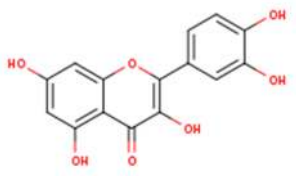
Once a set of structurally similar quercetin derivatives has been identified using SwissSimilarity, the next step is to assess their ADME (Absorption, Distribution, Metabolism, Excretion) properties. SwissADME is a comprehensive in-silico tool that can predict various ADME parameters, including oral bioavailability, permeability, protein binding, metabolism, and excretion (Daina et al., 2017). By inputting the structures of the identified derivatives into SwissADME, researchers can obtain valuable insights into their potential pharmacokinetic behavior and identify promising candidates for further investigation and development.

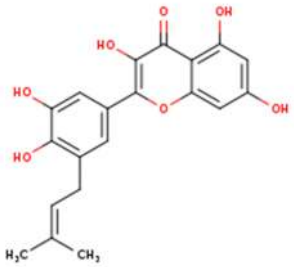
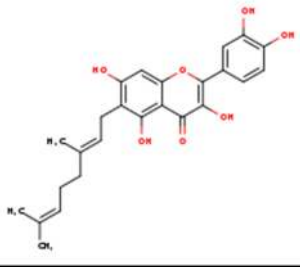
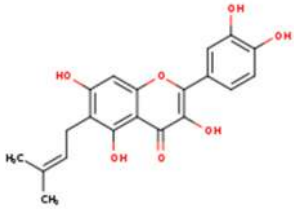
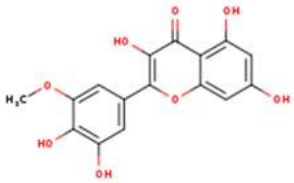
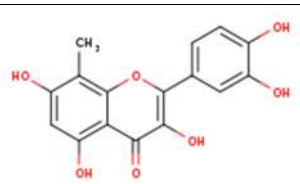
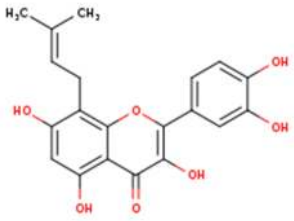
Following the identification of structurally similar quercetin derivatives using SwissSimilarity and the prediction of their ADME properties using SwissADME, a comprehensive data collection and analysis process is necessary. This involves gathering information on the predicted ADME parameters, such as oral bioavailability, permeability, protein binding, metabolism, and excretion. The collected data can then be analyzed to identify trends, correlations, and potential relationships between structural features and ADME properties. Statistical analyses, such as correlation analysis or regression analysis, can be employed to quantify these relationships and gain a deeper understanding of how structural modifications in quercetin derivatives influence their pharmacokinetic behavior.

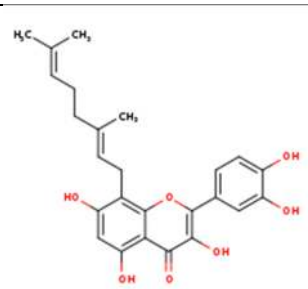
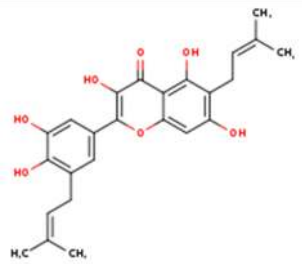
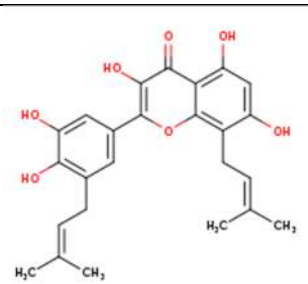
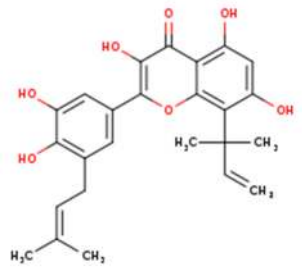
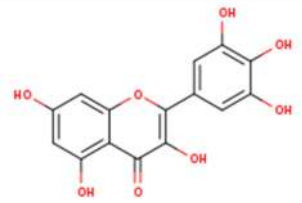
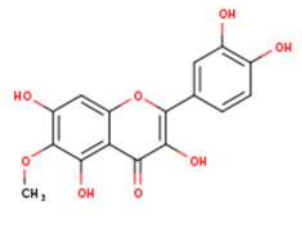
Results and Discussion

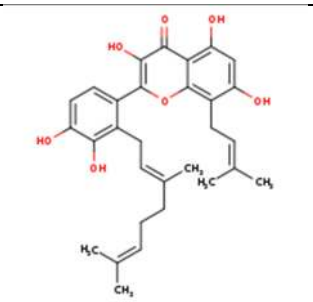
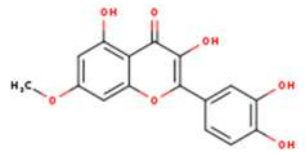
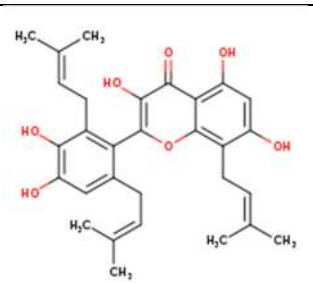
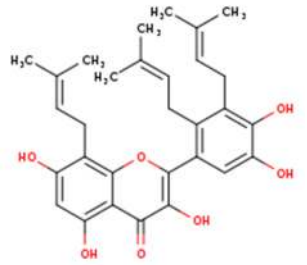
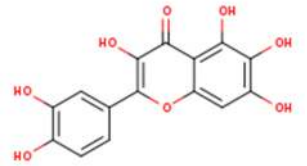
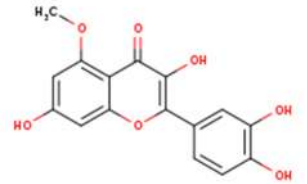
A total of 20 quercetin derivatives were identified using SwissSimilarity with a 90% similarity threshold out of 400 structures where similarity higher than 60% (Table 1). These derivatives exhibited a diverse range of structural modifications, including glycosylation, methylation, and sulfation. To validate the accuracy of the SwissSimilarity results, the identified structures were cross-referenced with the EMBL-EBI database. The majority of the identified derivatives were confirmed to have high structural similarity to quercetin, further validating the effectiveness of the SwissSimilarity approach.

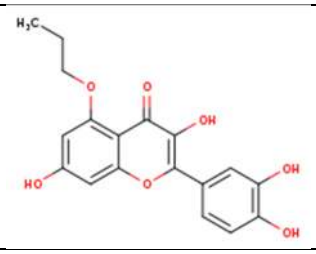
Table 1
Quercetin derivatives with higher than 90% similarit

No.	ID	SMILES	Name	Structure	Similarity
1	CHEMBL1173475	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	● Quercetin ● 3'-Hydroxykaempferol ● Corvitin ● Lipoflavon ● Meletin		1.000

2	CHEMBL113833	CC(=CCc1cc(cc(c1O)O)c1oc2cc(O)cc(c2c(=O)c1O)O)C	● Uralenol ● 3,5,7,3',4'-Pentahydroxy-5'-isoprenylflavone ● 2-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-3,5,7-trihydro xychromen-4-one		0.984
3	CHEMBL457261	C/C(=C\Cc1c(O)cc2c(c1O)c(=O)c(c(o2)c1ccc(c(c1)O)O)O)/CCC=C(C)C	● 5,7,3',4'-tetrahydroxy-6-geranylflavonol		0.962
4	CHEMBL463452	CC(=CCc1c(O)cc2c(c1O)c(=O)c(c(o2)c1ccc(c(c1)O)O)O)C	● Gancaonin P ● 6-prenylquercetin ● 2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-6-(3-methylbut-2-enyl) chromen-4-one		0.962
5	CHEMBL2260151	COc1cc(cc(c1O)O)c1oc2cc(O)cc(c2c(=O)c1O)O	● Laricytrin ● Larycitrin ● 3'-Methylmyricetin ● 3'-O-Methylmyricetin		0.958
6	CHEMBL382937	Oc1cc(ccc1O)c1oc2c(C)c(O)cc(c2c(=O)c1O)O	● 8-methylquercetin ● 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-8-methyl-4H-chromen-4-one		0.956
7	CHEMBL193059	CC(=CCc1c(O)cc(c2c1oc(c1ccc(c(c1)O)O)c(c2=O)O)O)C	● 8-Prenylquercetin ● 2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-8-(3-methylbut-2-enyl) chromen-4-one ● 8-prenyl-quercetin		0.956

8	CHEMBL3617858	C/C(=C\Cc1c(O)cc(c2c1oc(c1ccc(c(c1)O)O)c(c2=O)O)O)/CCC=C(C)C	• 2-(3,4-dihydroxyphenyl)-8-[(2E)-3,7-dimethylocta-2,6-dienyl]-3,5,7-trihydroxychromen-4-one		0.956
9	CHEMBL457303	CC(=CCc1cc(cc(c1O)O)c1oc2cc(O)c(c(c2c(=O)c1O)O)CC=C(C)C)C	• Broussonol E • Papyriflavonol A • 2-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-3,5,7-trihydroxy-6-(3-methylbut-2-enyl)chromen-4-one		0.949
10	CHEMBL458762	CC(=CCc1cc(cc(c1O)O)c1oc2c(CC=C(C)C)c(O)cc(c2c(=O)c1O)O)C	• Broussonol D		0.944
11	CHEMBL323712	C=CC(c1c(O)cc(c2c1oc(c1cc(O)c(c(c1)CC=C(C)C)O)c(c2=O)O)O)(C)C	• 2-[3,4-Dihydroxy-5-(3-methyl-but-2-enyl)-phenyl]-8-(1,1-dimethyl-allyl)-3,5,7-trihydroxy-chromen-4-one		0.944
12	CHEMBL164	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1cc(O)c(c(c1)O)O	• Myricetin • Myricetol • Myricitin		0.942
13	CHEMBL465155	COc1c(O)cc2c(c1O)c(=O)c(c(o2)c1ccc(c(c1)O)O)O	• Patuletin • 6-Methoxy quercetin • Quercetagetin 6-methyl ether		0.932

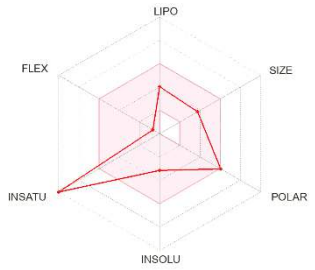
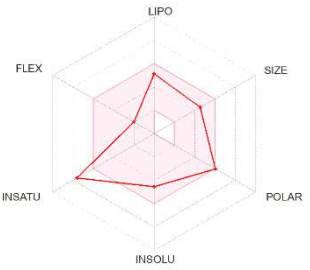
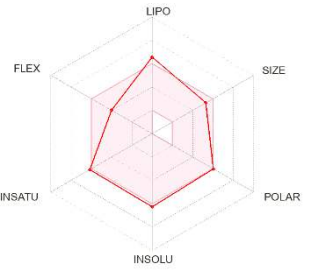
14	CHEMBL1808154	C/C(=C\Cc1c(O)c(O)ccc1c1oc2c(CC=C(C)C)c(O)cc(c2c(=O)c1O)O)/CCC=C(C)C	● Notabilisin C		0.923
15	CHEMBL312163	COc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	● Rhamnetin ● beta-Rhamnocitrin ● 7-Methoxy quercetin ● 7-O-Methyl quercetin		0.917
16	CHEMBL515360	CC(=CCc1cc(O)c(c(c1c1oc2c(CC=C(C)C)c(O)cc(c2c(=O)c1O)O)CC=C(C)C)O)C	● Petalostemumol G		0.913
17	CHEMBL516319	CC(=CCc1c(CC=C(C)C)c(O)c(cc1c1oc2c(CC=C(C)C)c(O)cc(c2c(=O)c1O)O)O)C	● Broussoflavonol G		0.908
18	CHEMBL413552	Oc1ccc(cc1O)c1oc2cc(O)c(c(c2c(=O)c1O)O)O	● Quercetagetin ● 6-Hydroxy quercetin ● 3,3',4',5,6,7-Hexahydroxyflavone		0.908
19	CHEMBL470848	COc1cc(O)cc2c1c(=O)c(c(o2)c1ccc(c(c1)O)O)O	● Azaleatin ● 5-O-Methyl quercetin ● Quercetin 5-methyl ether ● 5-O-Methyl Quercetin		0.905

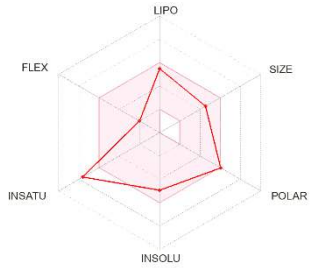
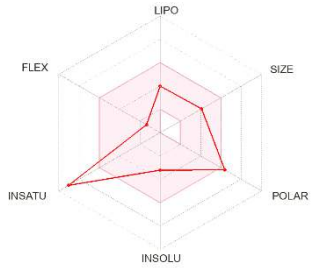
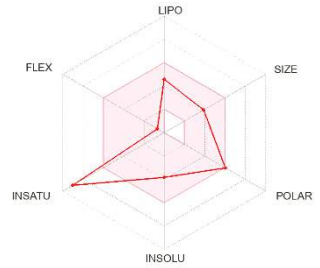
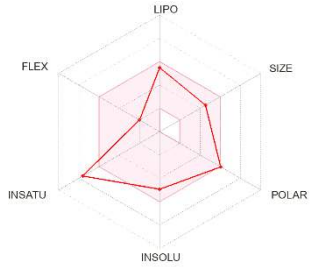
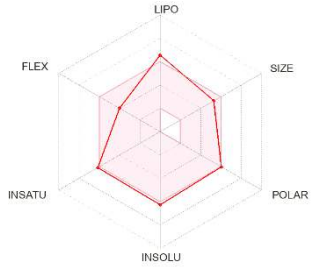
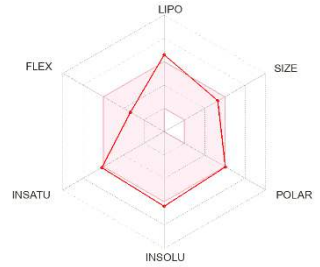
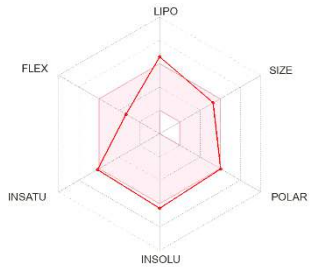
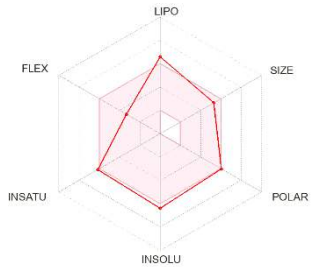
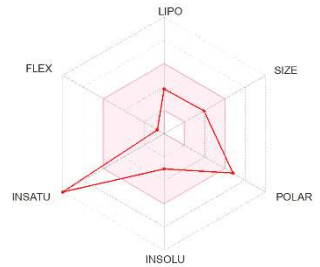
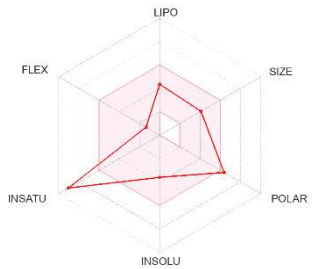
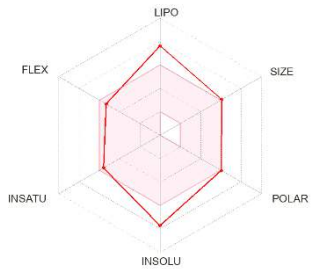
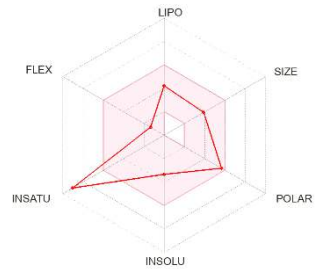
20	CHEMBL1935385	CCCOc1cc(O)cc2c1c(=O)c(c(o2)c1ccc(c(c1)O)O)O	• 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-5-propoxychromen-4-one		0.905

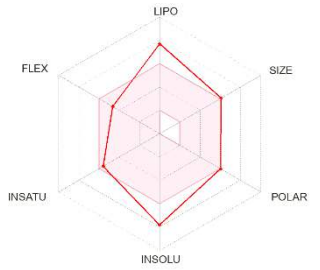
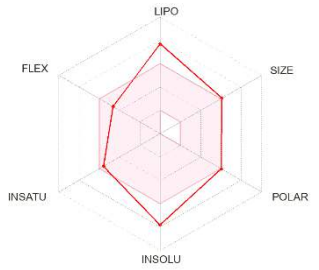
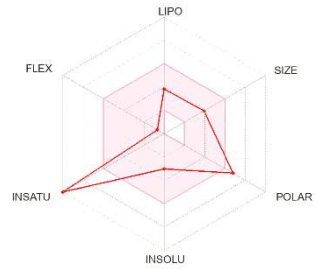
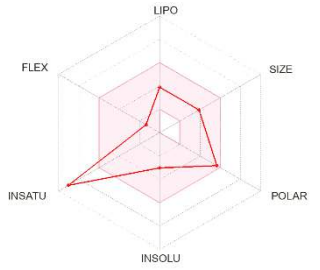
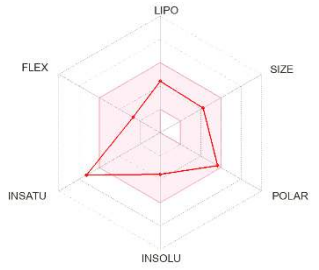
To visualize and compare the bioavailability profiles of the identified quercetin derivatives, a bioavailability radar was constructed (Table 2). This radar plot displayed various ADME parameters, such as oral bioavailability, permeability, protein binding, and clearance. Each axis of the radar represented a specific ADME parameter, and the distance from the center indicated the predicted value for that parameter. By comparing the radar plots of different derivatives, it was possible to identify trends in bioavailability and identify derivatives with favorable pharmacokinetic properties. This visual representation provided a valuable tool for evaluating the potential of quercetin derivatives as therapeutic agents.

Lipinski's Rule of Five is a set of empirical guidelines used to predict drug-likeness. To assess the drug-likeness of the identified quercetin derivatives, their adherence to Lipinski's Rule of Five was evaluated. Table 2 shows that 20 derivatives which having 90% similarity to quercetin followed to Lipinski Rule of Five, including having molecular weights lower than 500, logP values less than 5, less than five hydrogen bond donors, or less than 10 hydrogen bond acceptors. This suggests that these derivatives may have enhanced oral bioavailability and reduced potential for toxicity, making them promising candidates for further investigation and development as therapeutic agents.

Table 2
Bioavailability radar of quercetin derivatives

1. CHEMBL1173475		2. CHEMBL113833		3. CHEMBL457261	
					
MW (≤ 500)	302.24	MW (≤ 500)	370.35	MW (≤ 500)	438.47
LogP (≤ 4.15)	-0.56	LogP (≤ 4.15)	0.56	LogP (≤ 4.15)	1.56
nHA (≤ 10)	7	nHA (≤ 10)	7	nHA (≤ 10)	7
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	5
Lipinski Violation	0	Lipinski Violation	0	Lipinski Violation	0

4. CHEMBL463452		5. CHEMBL2260151		6. CHEMBL382937	
					
MW (≤ 500)	370.35	MW (≤ 500)	332.26	MW (≤ 500)	316.26
LogP (≤ 4.15)	0.56	LogP (≤ 4.15)	-0.83	LogP (≤ 4.15)	-0.31
nHA (≤ 10)	7	nHA (≤ 10)	8	nHA (≤ 10)	7
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	5
Lipinski Violation	0	Lipinski Violation	0	Lipinski Violation	0
7. CHEMBL193059		8. CHEMBL3617858		9. CHEMBL457303	
					
MW (≤ 500)	370.35	MW (≤ 500)	438.47	MW (≤ 500)	438.47
LogP (≤ 4.15)	0.56	LogP (≤ 4.15)	1.56	LogP (≤ 4.15)	1.56
nHA (≤ 10)	7	nHA (≤ 10)	7	nHA (≤ 10)	7
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	5
Lipinski Violation	0	Lipinski Violation	0	Lipinski Violation	0
10. CHEMBL458762		11. CHEMBL323712		12. CHEMBL164	
					
MW (≤ 500)	438.47	MW (≤ 500)	438.47	MW (≤ 500)	318.24
LogP (≤ 4.15)	1.56	LogP (≤ 4.15)	1.56	LogP (≤ 4.15)	-1.08
nHA (≤ 10)	7	nHA (≤ 10)	7	nHA (≤ 10)	8
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	6
Lipinski Violation	0	Lipinski Violation	0	Lipinski Violation	1
13. CHEMBL465155		14. CHEMBL1808154		15. CHEMBL312163	
					

MW (≤ 500)	332.26	MW (≤ 500)	506.59	MW (≤ 500)	316.26
LogP (≤ 4.15)	-0.83	LogP (≤ 4.15)	2.48	LogP (≤ 4.15)	-0.31
nHA (≤ 10)	8	nHA (≤ 10)	7	nHA (≤ 10)	7
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	4
Lipinski Violation	0	Lipinski Violation	1	Lipinski Violation	0
16. CHEMBL515360		17. CHEMBL516319		18. CHEMBL413552	
					
MW (≤ 500)	506.59	MW (≤ 500)	506.59	MW (≤ 500)	318.24
LogP (≤ 4.15)	2.48	LogP (≤ 4.15)	2.48	LogP (≤ 4.15)	-1.08
nHA (≤ 10)	7	nHA (≤ 10)	7	nHA (≤ 10)	8
nHD (≤ 5)	5	nHD (≤ 5)	5	nHD (≤ 5)	6
Lipinski Violation	1	Lipinski Violation	1	Lipinski Violation	1
19. CHEMBL470848		20. CHEMBL1935385			
					
MW (≤ 500)	316.26	MW (≤ 500)	344.32		
LogP (≤ 4.15)	-0.31	LogP (≤ 4.15)	0.17		
nHA (≤ 10)	7	nHA (≤ 10)	7		
nHD (≤ 5)	4	nHD (≤ 5)	4		
Lipinski Violation	0	Lipinski Violation	0		

To visually assess the overall ADME properties of the identified quercetin derivatives, SwissADME Boiled egg plots were generated (Figure 1). These plots provide a comprehensive overview of a molecule's predicted ADME profile by combining information on lipophilicity (logP), molecular weight, and hydrogen bond donors and acceptors. By analyzing the position of each derivative on the Boiled egg plot, researchers can gain insights into its potential for absorption, distribution, metabolism, and excretion. Derivatives located in the "sweet spot" of the plot are generally considered to have favorable ADME properties and may be more likely to have good oral bioavailability and reduced toxicity.

The BOILED-Egg model is a graphical classification tool that utilizes two physicochemical descriptors, WLOGP and TPSA, to predict a molecule's probability of traversing the gastrointestinal tract and penetrating the blood-brain barrier (BBB). The model visually represents the results in an egg-shaped plot, where the white oval signifies the physicochemical space for high probability of human intestinal absorption (HIA), and the

yellow circle denotes the physicochemical space for high probability of BBB permeation. As illustrated in Figure 1, the predictions indicate that none of the investigated quercetin derivatives exhibit significant BBB penetration, although some may demonstrate substantial HIA potential.

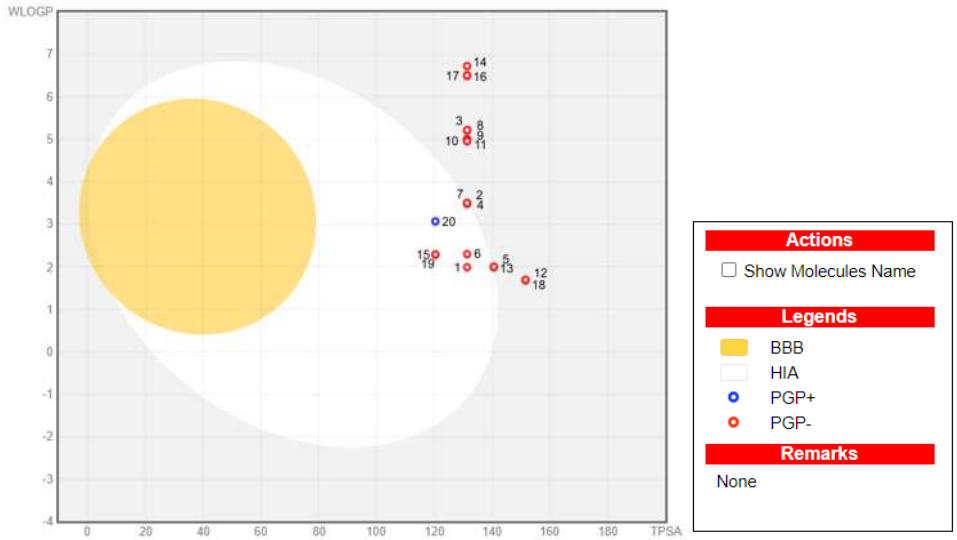


Figure 1 **ADME Boiled egg of quercetin derivatives**

WLOGP stand for Weighted LogP. It's a calculated value that estimates the lipophilicity or hydrophobicity of a molecule. In simpler terms, it predicts how well a molecule can dissolve in oil compared to water. Higher WLOGP values indicate a molecule is more lipophilic (more likely to dissolve in oil). Lower WLOGP values indicate a molecule is more hydrophilic (more likely to dissolve in water) (Tsantili-Kakoulidou & Demopoulos, 2021). TPSA stands for Topological Polar Surface Area. It's a calculated property that estimates the polar surface area of a molecule. Higher TPSA values indicate a molecule has more polar groups (such as hydroxyl, amine, and carbonyl groups). Lower TPSA values indicate a molecule has fewer polar groups (Stefaniu & Pirvu, 2022).

The BOILED-egg model provides an initial insight into the potential gastrointestinal (GI) absorption of quercetin derivatives and BBB permeation. However, to gain a more comprehensive understanding of the ADME profile, further evaluation of other parameters such as membrane permeability, metabolism by CYP enzymes, and interactions with drug transporters is crucial. This information will provide a more accurate picture of the compound's fate in the body and its potential as a drug candidate.

Table 3
ADME profile of quercetin derivatives

No.	ID	GI absorption	BBB permeant	PGP substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	CHEMBL 1173475	High	No	No	Yes	No	No	Yes	Yes
2	CHEMBL 113833	High	No	No	Yes	No	Yes	Yes	No
3	CHEMBL 457261	Low	No	No	Yes	No	No	No	No

4	CHEMBL 463452	High	No	No	Yes	No	Yes	Yes	No
5	CHEMBL 2260151	Low	No	No	Yes	No	No	Yes	Yes
6	CHEMBL 382937	High	No	No	Yes	No	No	Yes	Yes
7	CHEMBL 193059	High	No	No	Yes	No	Yes	Yes	No
8	CHEMBL 3617858	Low	No	No	Yes	No	No	No	No
9	CHEMBL 457303	Low	No	No	Yes	No	No	No	No
10	CHEMBL 458762	Low	No	No	Yes	No	No	No	No
11	CHEMBL 323712	Low	No	No	Yes	No	No	No	No
12	CHEMBL 164	Low	No	No	Yes	No	No	No	Yes
13	CHEMBL 465155	Low	No	No	Yes	No	No	Yes	Yes
14	CHEMBL 1808154	Low	No	No	No	No	No	No	No
15	CHEMBL 312163	High	No	No	Yes	No	No	Yes	Yes
16	CHEMBL 515360	Low	No	No	No	No	No	No	No
17	CHEMBL 516319	Low	No	No	No	No	No	No	No
18	CHEMBL 413552	Low	No	No	Yes	No	No	No	Yes
19	CHEMBL 470848	High	No	No	Yes	No	No	Yes	Yes
20	CHEMBL 1935385	High	No	Yes	Yes	No	No	Yes	Yes

Quercetin derivatives have been shown to exhibit varying ADME profiles (Table 3), influenced by their structural modifications. Some derivatives may be substrates of P-glycoprotein (PGP), an efflux transporter that can limit drug absorption and distribution. Additionally, certain quercetin derivatives have been identified as inhibitors of various cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. These interactions can affect the metabolism and elimination of other drugs, potentially leading to drug-drug interactions. Further investigations are necessary to fully characterize the ADME properties of individual quercetin derivatives and assess their potential for drug-drug interactions.

P-glycoprotein (Pgp) is an efflux transporter protein that is expressed in various tissues, including the gastrointestinal tract, liver, and blood-brain barrier. It plays a crucial role in limiting the absorption and distribution of certain drugs. Compounds that are substrates of Pgp can be actively pumped back into the intestinal lumen or into the bloodstream, reducing their bioavailability and limiting their entry into target tissues. This efflux mechanism can contribute to drug resistance and reduce the efficacy of certain medications. Understanding the interaction between drugs and Pgp is essential for optimizing drug delivery and minimizing drug-drug interactions (Johnston & Kennedy, 2024).

Cytochrome P450 (CYP) enzymes are crucial in metabolizing various drugs and xenobiotics. CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 are particularly important in drug metabolism. Inhibitors of these enzymes can reduce the metabolism of drugs that are substrates for them, leading to increased drug levels and potentially toxic effects. For example,

CYP1A2 inhibitors can increase the levels of caffeine and certain antidepressants. CYP2C19 inhibitors can elevate levels of clopidogrel, a blood thinner. CYP2C9 inhibitors can increase the levels of warfarin, an anticoagulant. CYP2D6 inhibitors can raise the levels of certain antidepressants and antipsychotics. CYP3A4 inhibitors can increase the levels of numerous drugs, including statins, immunosuppressants, and anti-infective agents (Zhao et al., 2021). Understanding the interactions between drugs and these CYP enzymes is essential for optimizing drug therapy and minimizing adverse drug reactions.

CONCLUSION

In-silico ADMETox profiling has proven to be a valuable tool in assessing the potential pharmacokinetic and toxicological properties of quercetin derivatives. By leveraging computational methods, researchers can efficiently identify and characterize derivatives with favorable properties, such as high bioavailability, low toxicity, and minimal drug-drug interactions.

The findings from this study highlight the potential of quercetin derivatives as promising therapeutic agents. The identified derivatives exhibited a diverse range of structural modifications, each with unique ADME profiles. Further investigations, including in vitro and in vivo studies, are warranted to validate the in-silico predictions and evaluate the therapeutic efficacy of these compounds. In conclusion, this quercetin derivatives in-silico ADMETox profiling represents a valuable approach for accelerating the drug discovery process and identifying novel quercetin derivatives with potential therapeutic applications.

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