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Physicochemical properties, medicinal chemistry, toxicity, and absorption of quercetin and its interaction with spike glycoprotein of SARS-CoV-2: Molecular docking

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ABSTRACT

Therapeutic targets of coronavirus disease 2019 (COVID-19) may be spike glycoproteins, main protease (Mpro), and RNA-dependent RNA polymerase (RdRp). The spike glycoprotein or S-glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plays critical roles in the adhesion, fusion, and entry of viruses into the host cell. In this way, this receptor can be considered as the main target for neutralization by antiviral agents. Quercetin is a plant secondary metabolite from polyphenols (groups involving flavonoids and tannic acid) significantly extracted from apples, grapes, capers, berries, and onions. This bioactive agent has antimicrobial activity against bacteria, fungi, and viruses. In the current study, we have used ADMETlab 2.0 web server to determine the physicochemical properties, medicinal chemistry, toxicity, and absorption of quercetin. In addition, the PatchDock docking server was applied for evaluating the interaction of quercetin with the S-glycoprotein of SARS-CoV-2. According to the PatchDock results, twelve amino acids including THR95, ASN99, ILE101, ARG102, GLY103, TRP104, ASN121, ALA123, LEU176, ASN188, ARG190, and PHE192 had interaction with the active site of the spike glycoprotein. In addition, score, area, and atomic contact energy (ACE) values for the best docking pose were 4304, 511.20, and -206.60, respectively.

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1. Introduction

Inhibition and eradication of life-threatening pathogenic microorganisms such as viruses and bacteria need effective formulations with suitable biocompatibility [1-6]. The viral and bacterial surfaces having complex glycan molecules including lipopolysaccharides and glycoproteins generate prominent immunological reactions, which can be considered the main therapeutic targets [7]. Spike glycoproteins, main protease (Mpro), and RNA-dependent RNA polymerase (RdRp) are possible therapeutic targets of COVID-19 [8]. Interaction of the spike glycoprotein or S-glycoprotein of SARS-CoV-2 with the human angiotensin-converting enzyme 2 (hACE2) plays critical roles in virus adhesion, fusion, and entry into the host cell [9, 10]. This receptor is expressed in most tissues of the human body, which can be considered the main target for neutralization by antiviral agents [11]. Several antimicrobial agents such as lopinavir, anidulafungin, and copper nanoparticles have been found as antiviral drugs blocking ACE2 receptor-S glycoprotein interaction [12, 13]. Herbal primary and secondary metabolites have been reported as promising therapeutic agents with biocompatibility, bioavailability, and biodegradability [5, 14]. Quercetin (formula of $C_{15}H_{10}O_7$ with a molar mass of 302.236 g/mol) is a plant flavonol from polyphenols (groups involving flavonoids and tannic acid having several phenol units) majorly isolated from apples, grapes, capers, berries, and onions [15]. A plethora of therapeutic potentials including antioxidant [16], anticancer properties [17], antidiabetic [18], anti-inflammatory [19], antibacterial [20, 21], antifungal [22], and antiviral activities[23] have been reported for this bioactive agent. In the previous investigation, the interaction of quercetin and epigallocatechin gallate metabolites with spike glycoprotein of SARS-CoV-2 was evaluated by AutoDock Vina

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1.5.7, DockThor, CB-Dock, and EDock [24]. However, in the present study, we have employed ADMETlab 2.0 web server for assessing physicochemical, toxicity, medicinal properties, and absorption as well as the PatchDock docking server as another docking server to predict the interaction of quercetin ligand with S-glycoprotein of SARS-CoV-2.

2. Materials and methods

Physicochemical properties (Figure 1 and Table 2), medicinal chemistry (Table 2), the major toxicity (Table 3), and absorption (Table 4) of quercetin were obtained from ADMETlab 2.0 web server [25]. Spike glycoprotein (PDB ID: 6VSB) and quercetin metabolite were selected as receptor and ligand, respectively. UCSF Chimera1.12 program was used for minimizing the final structures of quercetin followed by removing all the water molecules [26]. PatchDock(https://bioinfo3d.cs.tau.ac.il/PatchDock/) was employed for surveying and comparison of molecular docking. The affinity of docked quercetin with spike glycoprotein was obtained as binding energy (kcal/mol) and BIOVIA discovery studio 2016 was applied to visualize the results of the docking interaction (Figure 2).

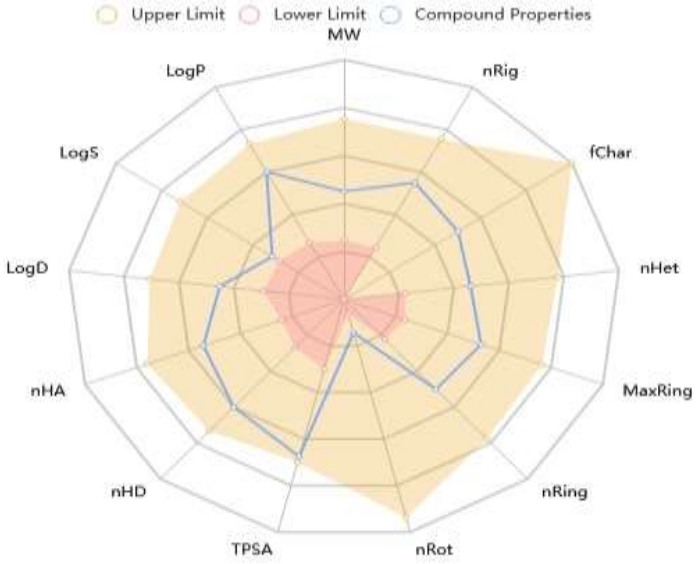


Fig. 1. Physicochemical radar of quercetin (MW: Molecular weight, nRig: Number of rigid bonds, fChar: Formal charge, nHet: Number of heteroatoms, MaxRing: Number of atoms in the biggest ring, nRing: Number of rings, nRot: Number of rotatable bonds, TPSA: Topological polar surface area, nHD: Number of hydrogen bond donors, nHA: Number of hydrogen bond acceptors, LogD: The logarithm of the n-octanol/water distribution coefficient at pH= 7.4, LogS: The logarithm of aqueous solubility value, LogP: The logarithm of the n-octanol/water distribution coefficient).

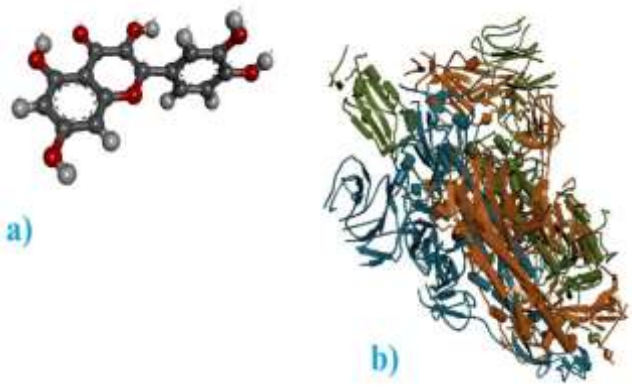


Fig. 2. a) quercetin structure (gray, pale gray, and red balls are carbon, hydrogen, and oxygen atoms, respectively) and b) spike glycoprotein (PDB ID: 6VSB).

3. Results and discussion

The number of rotatable and rigid bonds for quercetin is 1 and 18, respectively with a flexibility of 0.056. According to Table 1, quercetin has an optimal molecular weight of 302.040 g/mol. The surface area related to electronegative nitrogen and oxygen atoms and hydrogen atoms bound to these atoms is known as the polar surface area [27]. A desirable absorption and permeation of compounds can be predicted by TPSA value of ≤ 140 $Å^2$ [28, 29], which for quercetin was 131.36 $Å^2$. As presented in Table 2, information obtained from ADMETlab 2.0 web server showed poor drug-likeness (QED: 0.434). This table shows excellent synthetic accessibility score equal to 2.545 and poor Fsp3 (0.00). Additionally, the natural product-likeness score (NPscore) demonstrated a suitable probability of 1.701 (A score up to 5. exhibits a higher probability). Based on table 3, quercetin cannot cause hERG toxicity, hepatotoxicity, oral acute toxicity, carcinogenicity, eye corrosion, and respiratory toxicity. Drug-induced liver injury, skin sensitization, and eye irritation are expected for quercetin, which may be reduced by novel nanoformulations such as liposomal encapsulation technology [30-33].

Table 1. Physicochemical properties for quercetin.

Properties	Values
Molecular weight (MW)	302.040 g/mol
Van der Waals volume	282.767 $Å^3$/molecule
Density (MW / Volume)	1.068 g/m^3
nHA	7
nHD	5
nRot	1
nRing	3
MaxRing	10
nHet	7
fChar	0
nRig	18
Flexibility (nRot / nRig)	0.056
Stereo centers	0
TPSA	131.360
logS	-3.671
logP	2.155
logD	1.767

Table 4 shows the absorption of quercetin based on parameters of Caco-2 Permeability, MDCK Permeability, Pgp-inhibitor, Pgp-substrate, HIA (human intestinal absorption), $F_{20\%}$, and $F_{30\%}$. There are poor Caco-2 permeability, $F_{20\%}$, and $F_{30\%}$ for quercetin. However, MDCK permeability, Pgp-inhibitor, Pgp-substrate, and HIA are excellent for this metabolite.

Based on PatchDock results, twelve amino acids including THR95, ASN99, ILE101, ARG102, GLY103, TRP104, ASN121, ALA123, LEU176, ASN188, ARG190, and PHE192 had interaction with the active site of the spike glycoprotein (Figure 3). In addition, molecular docking scores, approximate interface area of each receptor-ligand complex, and analysis ACE (atomic contact energy: estimation of solvation- free energy changes of ligand-receptor or two proteins from the unbound state to the complex) have been presented in table 5. In this way, score, area, and ACE values for the best docking pose were 4304, 511.20, and -206.60, respectively.

In a previous study, teprotide, trandolapril, cilazapril, benazepril, quinapril, ramipril, and perindopril showed energy scores of −6.95 and −6.93, −6.35, −6.34, −6.32, −6.31, and −6.02 kcal/mol toward spike glycoprotein, respectively [34]. According to another study, nigellidine molecule blocked spike glycoprotein by −6.11 kcal/mol energy binding with the highest ACE value of −340.50 [35]. PatchDock ACE values for hydroxychloroquine, catechin, catechin gallate, epicatechin 3-O-gallate, epigallocatechin, epigallocatechin 3-gallate, gallocatechin, gallocatechin gallate, theaflavin monogallate, and theaflavin digallate towards ACE2-COVID-19 spike glycoprotein were −293.32, −266.41, −393.05, −308.25, −270.01, −407.58, −274.72, −364.16, −434.42, and −465.17, respectively. Gallocatechin, catechin , and epigallocatechin demonstrated ligand efficiencies of −0.22, −0.2, and −0.18 with binding energy values of−4.76, −4.23, and −3.94 Ki (inhibition constant) values in μmol [36].

Table 2. Medicinal chemistry of quercetin. (QED: A measure of drug-likeness on the concept of desirability, SAscore: Synthetic accessibility score, Fsp^3: The number of sp3 hybridized carbons/total carbon count, MCE-18: This measure can effectively score molecules by novelty in terms of their cumulative sp3 complexity, NPscore: The natural product-likeness score, PAINS: Pan assay interference compounds).

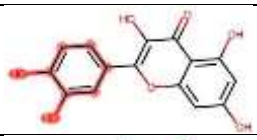
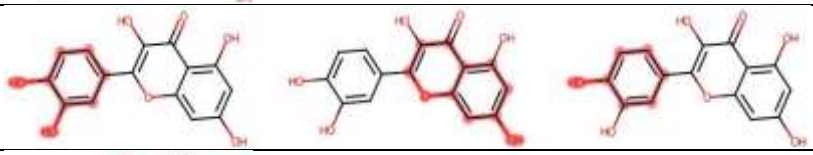
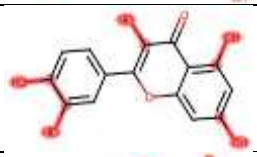
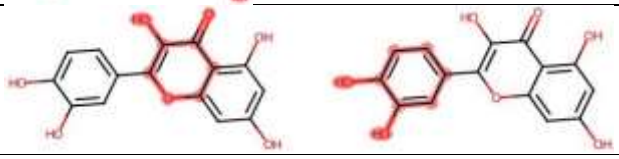
Parameters	Values
QED	0.434
SAscore	2.545
Fsp^3	0.000
MCE-18	19.000
NPscore	1.701
Lipinski Rule	Accepted
Pfizer Rule	Accepted
GSK Rule	Accepted
Golden Triangle	Accepted
PAINS	1 alert(s) 
ALARM NMR Rule	3 alert(s) 
BMS Rule	1 alert(s) 
Chelator Rule	2 alert(s) 

Table 3. The major toxicity of quercetin (hERG: The human ether-a-go-go related gene, H-HT: The human hepatotoxicity, DILI: Drug-induced liver injury, AMES toxicity: The ames test for mutagenicity, FDAMDD: The maximum daily dose showing the toxic dose threshold of compounds in humans). Excellent (---), medium (+ and -), and poor (+++)**.**

Parameters	Values
hERG Blockers	---
H-HT	---
DILI	+++
AMES toxicity	+
Rat oral acute toxicity	---
FDAMDD	-
Skin Sensitization	+++
Carcinogencity	---
Eye Corrosion	---
Eye Irritation	+++
Respiratory Toxicity	---

Table 4. Absorption of quercetin (HIA: Human intestinal absorption, F20%: The human oral bioavailability 20%, and F30%: The human oral bioavailability 30%). Excellent (---), medium (+ and -), and poor (+++)**.**

Factors	Values
Caco-2 Permeability	-5.204
MDCK Permeability	7.7e-06
Pgp-inhibitor	---
Pgp-substrate	---
HIA	---
$F_{20\%}$	+++
$F_{30\%}$	+++

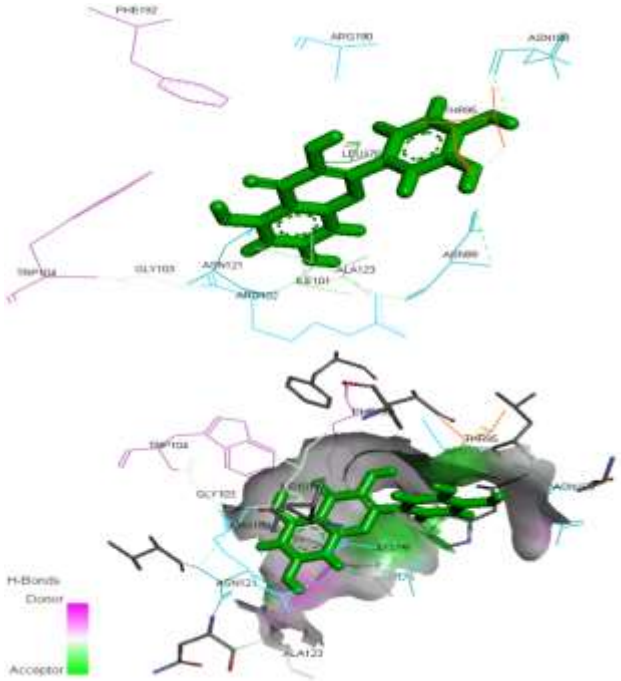


Fig. 3. Image presenting Patchdock results for the docking of quercetin ligand and transmembrane spike glycoprotein receptor of SARS-CoV-2 (In the surface of the receptor, colors of pink and green shows donor and acceptor states for H-bonds, respectively).

In a similar study, the docking of two herbal metabolites including catechin (a flavan-3-ol; $C_{15}H_{14}O_6$) and curcumin (a polyphenol; $C_{21}H_{20}O_6$) towards S protein, ACE2, and (receptor-binding domain (RBD)/ACE2-complex was evaluated by docking program AutoDock Tools 1.5.6 and docking tool of clusPro2.0. Curcumin and catechin showed the binding affinity values of -7.9 and -10.5 kcal/mol; -7.8 and -8.9 kcal/mol; and -7.6 and -9.1 kcal/mol, for the S protein, ACE2, and RBD/ACE2, respectively [37].

Table 5. Molecular docking scores for quercetin ligand and transmembrane spike glycoprotein receptor obtained from PatchDock. (SN: Solution No. and ACE: atomic contact energy).

SN	Score	Area	ACE
1	4304	511.20	-206.60
2	4274	516.20	-216.27
3	4270	496.30	-139.35
4	4266	494.20	-195.30
5	4258	533.90	-118.84
6	4196	520.80	-236.40
7	4192	513.50	-189.29
8	4160	516.80	-231.34
9	4156	510.90	-232.98
10	4152	520.20	-123.82
11	4134	486.20	-199.96
12	4132	508.30	-160.28
13	4130	456.00	-71.15
14	4124	520.10	-134.10
15	4112	483.00	-235.83
16	4102	499.20	-170.41
17	4100	434.90	-117.96
18	4100	457.70	-140.25
19	4078	512.70	-183.17
20	4070	531.80	-140.26

4. Conclusions

Growth inhibition or eradication of microbial pathogeneses specifically viruses by natural metabolites has major benefits such as suitable characteristics of biocompatibility, bioavailability, and biodegradability compared to conventional drugs. Spike glycoproteins, main protease (Mpro), and RNA-dependent RNA polymerase (RdRp) can be therapeutic targets for treatment of COVID-19. According to PatchDock results, score, area, and ACE values for the best docking pose of querectin with S-glycoprotein were 4304, 511.20, and -206.60, respectively. In the current study, we have revealed by molecular docking via the PatchDock server that quercetin as a bioactive agent can bind in the active sites of the S-glycoprotein receptor of SARS-CoV-2. Moreover, according to the obtained results of the ADMETlab 2.0 web server, quercetin with a TPSA value of 131.36 $Å^2$ has permeation and good absorption. This metabolite cannot lead to hERG toxicity, hepatotoxicity, oral acute toxicity, carcinogenicity, eye corrosion, and respiratory

toxicity. However, eye irritation, skin sensitization, and drug-induced liver injury can be expected for quercetin, which may be mitigated by the encapsulation of quercetin in nanomaterials such as liposomes. Totally, more studies are needed to improve formulations of quercetin as an effective antiviral medication.

Abbreviations

ACE: Atomic contact energy
COVID-19: Coronavirus disease 2019
fChar: Formal charge
Fsp3: The number of sp3 hybridized carbons/total carbon count,
hACE2: The human angiotensin-converting enzyme 2
LogD: The logarithm of the n-octanol/water distribution coefficient at pH= 7.4
LogP: The logarithm of the n-octanol/water distribution coefficient
LogS: The logarithm of aqueous solubility value
MaxRing: Number of atoms in the biggest ring
Mpro: Main protease
MW: Molecular weight
nHA: Number of hydrogen bond acceptors
nHD: Number of hydrogen bond donors
nHet: Number of heteroatoms
NPscore: The natural product-likeness score
nRig: Number of rigid bonds
nRing: Number of rings
nRot: Number of rotatable bonds
PAINS: Pan assay interference compounds
QED: A measure of drug-likeness on the concept of desirability
RdRp: RNA-dependent RNA polymerase
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
SAscore: Synthetic accessibility score
S-glycoprotein: Spike glycoprotein
TPSA: Topological polar surface area

Study Highlights

- Spike glycoproteins, main protease (Mpro), and RNA-dependent RNA polymerase (RdRp) can be main targets for treatment of COVID-19.
- Quercetin as a bioactive agent can bind in the active sites of the S-glycoprotein receptor of SARS-CoV-2.
- Quercetin with a TPSA value of 131.36 $Å^2$ has permeation and good absorption.
- Eye irritation, skin sensitization, and drug-induced liver injury of quercetin may be mitigated by the encapsulation of quercetin in specific nanomaterials.
- More investigations are needed to improve formulations of quercetin as an effective antiviral medication.

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution
All authors: conceptualization, preparing the first drafting, and revising the manuscript.

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