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In silico molecular docking and ADME/T analysis of Quercetin compound with its evaluation of broad-spectrum therapeutic potential against particular diseases

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ABSTRACT

Progression in computational research has made it possible for the *in silico* methods to offer epochal benefits to both regulatory needs and the pharmaceutical industry to assess the safety profile. Myriad amounts of flavonoids are present in the human diet. They showed potential therapeutic effects against a wide range of illnesses. One of the most ubiquitously distributed and extensively studied flavonoids is flavonol Quercetin (Quercetin). The current study aspires to reveal Quercetin as a potent inhibitor against Tuberculosis, Malaria, Inflammatory diseases, Breast cancer, Obesity, and Alzheimer's disease in analogy to the standard drugs of each disease. A molecular docking study of Quercetin with specific proteins associated with the diseases was done using Schrodinger Maestro (v11.1) software. The QikProp module of Schrodinger Maestro was used for ADME prediction, and the admetSAR online database evaluated the toxicity of the ligand. Molecular docking results also showed higher scores than commercially available standard drugs. Moreover, ADME properties of Quercetin are delineated with no carcinogenicity and mutagenicity along with lower rat acute toxicity & acceptable oral acute toxicity level. Quercetin possessed higher scores (−9.00, −6.36, −8.53, −7.28, −7.89, −6.68 kcal/mol) as Anti-tuberculosis, Anti-malarial, Anti-inflammatory, Antineoplastic (Breast –cancer), Anti-obesity and Anti-Alzheimers drugs, respectively when compared to the standard drugs. Therefore, from the docking score, we can conclude that Quercetin can be a more potent inhibitory potential agent against selected diseases than the drugs available in the market. However, congenial clinical and empirical studies are required to explicit Quercetin as an effectual candidate drug with equitable treatment of the above-referred diseases.

1. Introduction

QUERCETIN (primarily known as Quercetin glycosides, $C_{15}H_{10}O_7$, a polyphenolic bioflavonoid that is most copious of the flavonoid molecules and widely distributed in the plant kingdom [1,2]. It was found in Avena sativa (oats), Allium cepa (Onion), Brassica spp., tea (in the form of tannins), Allium sativum (garlic), pear, and spinach in a considerable amount [3]. Quercetin is also familiar as plant pigment. Quercetin has significant importance in ethnopharmacology such as its use as an antioxidant, anticancer and neuroprotective [4]. Much predilection and attention were primarily directed recently to various flavonoids existing in fruits, vegetables, and grains, training to numerous biological activities [5]. It does employ distinctly diverse biological activities, including anti-inflammatory, antioxidant, neurological, antiviral, anticancer, cardiovascular, antimicrobial, anti-diabetic, anti-hypertensive, hepato-protective, as protective of the reproductive system, anti-obesity agent, and anti-plasmodial (anti-malarial) agent [6]. When our immune system is activated, inflammatory cells are released. These cells fight bacteria or repair tissue injury. Chronic inflammation occurs when our bodies put out inflammatory cells even when we are not sick or damaged. Many chronic disorders, such as arthritis and Alzheimer's disease, have inflammation as a symptom.

While each person's sense is unique, the inflammation usually results

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Abbreviations

- (ADMET) Absorption, Distribution, Metabolism, Elimination & Toxicity
- (admetSAR) Absorption, Distribution, Metabolism, Elimination & Toxicity Structure Activity Relationship
- (CRP) C-reactive Protein
- (TNF-alpha) Tumour Necrosis Factor Alpha
- (IL-6) Interleukin-6
- (HER2) Human Epidermal Growth Factor Receptor 2
- (TB) Tuberculosis
- (MT) Mycobacterium Tuberculosis
- (CID) Compound Identity Number
- (OPLS3) Optimized Potentials for Liquid Simulations 3
- (RCSB) Research Collaboratory for Structural Bioinformatics
- (PDB) Protein Data Bank
- (FTO) Fat mass and Obesity
- (BACE1) Beta-site Amyloid Precursor Protein Cleaving Enzyme 1
- (pH) Potential of Hydrogen
- (RMSD) Root-Mean-Square-Deviation
- (SP glide) Standard Precision glide
- (MM/GBSA) Molecular Mechanics/Generalized Born Surface Area
- (COVID) Corona Virus Diseases
- (PfENR) Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase
- (NF-kB) Nuclear Factor Kappa B
- (DNA) Deoxyribonucleic Acid

in pain because of the swelling and accumulation of tissue press upon nerve endings. This pressure causes discomfort by sending pain signals to the brain [7]. It is infeasible to envision a world without pain relief. In the sixteenth century, laudanum, opium, was used as a painkiller. Opium was the source from which morphine was first extracted in a pure form in the early nineteenth century and used to relieve pain [8]. However, for their addictive properties, they had been prohibited from taking for this purpose. Commercially available drug-like Acetaminophen, including paracetamol or Tylenol, is used to relieve pain. Chronic inflammation has been linked to a higher risk of breast cancer recurrence in some studies, while anti-inflammatory medicines such as NSAIDs have been linked to a lower risk of breast cancer development in others [9]. Following the emergence of cancer-like sickness in the human body, people all over the world became familiar with Breast cancer, a type of cancer that develops in the cells of women's breasts. When cells begin to develop out of control cancer is being created. At present, the most commonest cause of cancer death in women worldwide is due to Breast cancer and the rates are drifting about five-fold around the world [10]. After lungs cancer, it is the second leading cause of cancer death among women [11].

Breast cancer is the most demotic malignancy of women in the United States, accounting for more than 40,000 deaths each year [12]. In women with breast cancer, altered inflammatory responses are common, and researchers have associated breast cancer with an inflammatory etiology. CRP, TNF-alpha, and IL-6 levels are higher in breast cancer patients. Clinical treatments involve radiotherapy, chemotherapy with anthracycline, endocrine therapy with tamoxifen, anti-HER2-therapy with trastuzumab, and surgery. Moreover, chemotherapy for breast cancer is linked to accelerated aging and increased Alzheimer's disease [13]. Malaria is an outrageous parasitic disease caused by infection with Plasmodium protozoa transmitted by an infective female Anopheles mosquito [14]. Approximately 228 million infected malaria cases worldwide are associated with 405,000 fatalities, according to documentation by World Malaria Report 2019 statistics [15,16]. In southeast Asia, out of about 1.4 billion people living in 11 countries, 1.2 billion (85.7%) are susceptible to the risk of malaria [17–19]. It is still a significant threat in many parts of the world, with resistance spreading to almost all classes of anti-malarials [20]. The limited aider of available anti-malarial drugs strengthens the exigent need for novel antimalarial compounds [3]. In regions where both diseases are prevalent, malaria and tuberculosis coinfection are unknown. Malaria can exacerbate tuberculosis (TB) containment and increase TB patient death [20]. Tuberculosis (TB) is a contagious disease transmitted by inhaling aerosolized droplets caused by *Mycobacterium tuberculosis* [2,20]. MT has very primitive origins: it has anointed (survived) over 70, 000 years and it currently infects nearly 2 billion people worldwide [21]; with around 10.4 million new cases of TB each year, almost one-third of the world's population are carriers of the TB bacillus and are at risk for developing the active disease [20,22]. Numerous tuberculosis foci of the breast, also known as disseminated tuberculosis mastitis, create multiple ulceration and discharge sinuses on the skin in the diffuse form of the disease, which mimics inflammatory breast cancer on mammographic results. Moreover, Patients with tuberculosis have a considerably higher risk of dementia than the general population, according to a retrospective population-based cohort study [23]. Neurodegenerative diseases are prominent causes of worldwide morbidity, disability, and decreased quality of life [24]. It is the most common disease for disability in the elder [25–27]. Alzheimer's disease, a neurodegenerative disorder, is responsible for 50–60% of dementia cases [28]. The chance of this disease increases significantly due to obesity [29]. Obesity is expected but is often a major risk factor for the growth of disparate non-communicable diseases, premature death, and significant disability [30–32]. According to a new study, inflammation in the brain is responsible for the progression of dementia and Alzheimer's disease from the existence of amyloid plaque and tau tangles to the onset of dementia and Alzheimer's disease [33].

In molecular modeling, sequence analysis platforms, and clinical training management, molecular docking has been identified as a useful technique. The discovery of new drugs relies on *in silico* tools, specifically molecular docking, to simplify the overall process since it involves several stages and workflows [34]. Docking is a computational technique that samples small molecule conformations in protein binding sites and uses scoring functions to determine which conformation best complements the protein binding site. For lead identification, molecular docking is a commonly used technique. Molecular docking, on the other hand, is an essential method in structural molecular biology and computer-assisted drug design. ligand-protein docking aims to predict the most common ligand-protein binding mode(s) [35]. Any compound's therapeutic potential can be assessed first using molecular docking, which saves time and money in drug development. For example, since Quercetin has several forms of function, the current analytical research uses a computational approach to assess its pharmacologic properties against the diseases described above [36].

2. Materials and methods

2.1. Preparation of ligand and protein

The 2D structure of Quercetin (PubChem CID: 5280343) was retrieved from PubChem online database. This compound was converted into minimized 3D structure using the LigPrep wizard of Schrödinger maestro (v11.1). With the assistance of Epik, the possible ionization state was generated at target p^H 7.0 ± 2.0 for accurate tautomer enumeration and to know the protonation state in biological status [37,38]. Completing stereoisomers at most 32 per ligand was generated by retaining specified chiralities. The force field was set to OPLS3 [39]. The

target protein used for molecular docking were downloaded from RCSB Protein Data Bank [40,41] following mycolic acid cyclopropane synthase (PDB id: 1KPI) [34] for anti-tuberculosis activity, plasmepsin II (PDB id: 1SME) for antimalarial activity, cyclooxygenase-1 (PDB id: 2OYE) [35] for an anti-inflammatory response, human estrogen receptor alpha (PDB id: 3ERT) [36] for antineoplastic (breast cancer) activity, fat mass and obesity-associated (FTO) protein (PDB id: 3LFM) [45] for gastric and pancreatic lipase inhibition activity, BACE1 (PDB id: 4IVT) [46] against Alzheimer's disease. Mycolic acid cyclopropane synthase (PDB id: 1KPI) is the drug target for tuberculosis. The mechanism of action relies on the inhibition of mycolic acid cyclopropane synthesis [34]. Plasmepsin II (PDB id: 1SME) is a key enzyme in the life cycle of the Plasmodium parasites responsible for malaria, a disease that afflicts more than 300 million individuals annually.

Since plasmepsin II inhibition leads to starvation of the parasite, it has been acknowledged as an important target for developing antimalarials [42–44]. Cyclooxygenase-1 (PDB id: 2OYE) targets many analgesic drugs to reduce pain. Blocking cyclooxygenase-1 synthesis subsequently prevents prostaglandin formation and reduces the pain [35]. Human estrogen receptor alpha (PDB id: 3ERT) is an important drug target for breast cancer. The drugs competitively inhibit estrogen binding to its receptor, which is critical for its activity in breast cancer cells [36]. Fat mass and obesity-associated (FTO) protein (PDB id: 3LFM) is responsible for an obesity-related complication. Thereby, FTO is an important target for a drug to exert an anti-obesity effect [45]. BACE1 (PDB id: 4IVT) is a prime therapeutic target for lowering cerebral A/beta concentrations in Alzheimer's disease, and clinical development of BACE1 inhibitors is intensely pursued [46].

The protein preparation wizard in Schrödinger Maestro (v11.1) was used to prepare the 3D structure of the protein. In this management, bond orders were assigned, CCD database was used, hydrogens were added, zero-order bonds to metal and disulfide bonds were created, selenomethionines were converted into methionines, water molecules were eliminated beyond 5°A from het groups, and het state was left in default pH (7.0±2.0) using Epik. Finally, restrained minimization was performed under the OPLS3 force field, which converges heavy atoms to RMSD 0.30 Å.

2.2. Identification of active site of the receptor

An active site is a specific place on the surface of the receptor where the compounds tend to bind and causes conformational changes to induce a pharmacological action [47]. The active site determination is an integral part of docking simulation because it specifies the binding site of a ligand on the receptor. The target protein's active site was selected using the PockDrug server for druggability assessment [48].

2.3. Receptor grid generation

Here the van der Waals radius scaling factor is 1, and the partial charge cutoff is 0.25, default parameters. Also, the bounding box was set, which can cover the whole target site for docking simulation.

2.4. Molecular Docking Simulation study

After the pre-requisite steps were finished, the docking simulation was carried out in the SP glide of Schrodinger maestro (v11.1) [49], considering penalties employed to non-cis/trans amide bonds. Here, the van der Waals scaling factor was set to 0.80 and the partial charge cutoff was 0.15. Energy minimized posture was employed to determine the definitive score, expressed as glide score. The score for each activity for the compound and the standard drugs was recorded.

2.5. ADMET analysis

ADME properties depict the compound accessibility throughout the body, determined by Lipinski's rule of five [50]. The standard parameter for this rule is given below:

1) Molecular weight (acceptable range:$\leq$ 500)
2) Hydrogen bond donor (acceptable range: $\leq$ 5)
3) Hydrogen bond acceptor (acceptable range: $\leq$ 10)
4) High lipophilicity (expressed as LogP, acceptable range: $\leq$ 5)
5) Molar refractivity (acceptable range: 40–130)

The QikProp module of Schrödinger maestro (v11.1) was used to determine Quercetin's ADME (Absorption Distribution Metabolism Excretion) property. In addition, the toxicity profile was evaluated using admetSAR online server-based database [51]. The block diagram of the proposed work is shown in Fig. 1.

3. Results

The two-dimensional (2D) structure of the Quercetin compound is shown in Fig. 2. This study evaluated the docking simulation of Quercetin (Fig. 1) for five distinct proteins. The regarding scores for docking simulation are shown in Table 1. This compound showed promising results for selective activity compared to their respective standard drugs. The 2D and 3D representations of the interaction between the compound and protein have shown in Fig. 3. In the 2D structure of Fig. 3, green color represents hydrogen bond, and other colors include light green (van der Waals bond), blue (pi-sigma bond), yellow (pi-sulfur bond), purple (amide-pi stacked bond), light purple (pi-alkyl bond) has also shown with the atomic distances. Table 2 indicated the binding interaction (Hydrogen and hydrophobic) between Quercetin and the receptors.

3.1. ADME/T analysis

ADME property evaluates the ability of a chemical agent to act like a drug. The pharmacokinetic profile of quercetin has shown in Table 3, which depicts that it has not violated any of the criteria for the Lipinski rule and it has no mutagenic and carcinogenic properties.

4. Discussion

Quercetin is a well-known flavonoid; the key compound analyzed in this study. Analysis of ligand binding interaction by molecular docking is a well-known method of drug discovery worldwide. The results obtained from this study would help understand the inhibitory mode and rapidly and accurately predict the activities of new inhibitors based on docking scores [52]. Molecular docking provides information about the relative orientation of a ligand molecule when it is bound to a protein [53]. The discovery of novel compounds with more potency and selectivity and understanding the pharmacological activity of natural compounds at therapeutic conditions can achieve from the information resulting from *in silico* molecular docking study. Recent docking studies showed that Quercetin also acts as a potential treatment for COVID-19-induced acute kidney injury by inhibition of inflammatory, cell apoptosis-related signaling pathways [54–57] and as an antimalarial by inhibition of Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR) [58]. Another *in silico* study revealed its anti-inflammatory and anticancer activity where Quercetin effect the NF-kB pathway and docking score was −9.7 & −9.5 kcal/mol, respectively [59]. We have carried out molecular docking and ADME/T investigation to analyze Quercetin's mechanism of action against breast cancer, Alzheimer's disease, tuberculosis, obesity, and malaria. Previous studies suggested that the higher the docking score, the higher the efficacy of the novel compound against the particular disease [60].

From the perspective of our study, it has been revealed that Quercetin possesses higher docking scores (−9.00, −6.36, −8.53, −7.28, −7.89 and −6.68 kcal/mol as Anti-tuberculosis, Anti-malarial, Anti-

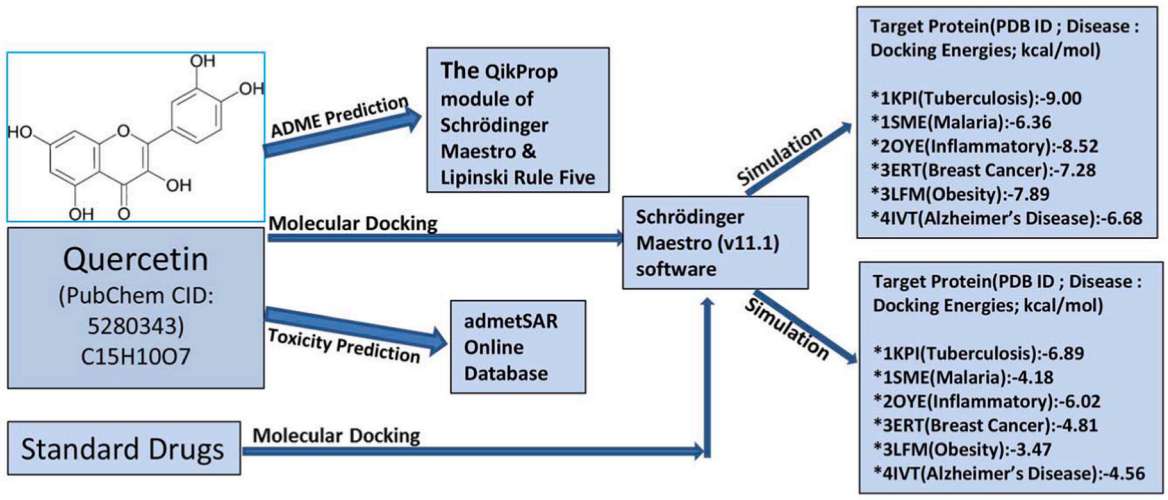

Fig. 1. In silico molecular docking and ADME/T analysis of Quercetin compound with its evaluation of broad-spectrum therapeutic potential against Tuberculosis, Malaria, Inflammatory diseases, Breast cancer, Obesity, and Alzheimer's disease.

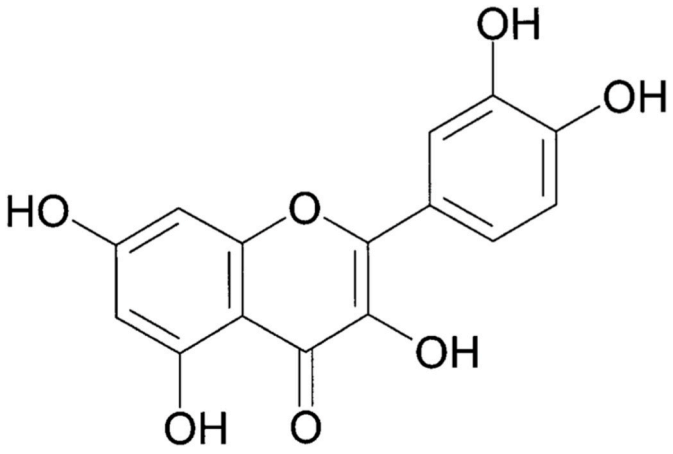

Fig. 2. Two-dimensional Structure of Quercetin compound.

inflammatory, Antineoplastic especially agents against breast cancer, Anti-obesity and Anti-Alzheimer's drug respectively) against selected diseases when compared to the available standard drugs (−6.89, −6.04, −6.60; −4.18, −5.54, −4.18; −6.02, −5.07, −4.72; −4.81, −5.49, −10.83; - 3.47, −5.73, −5.41 and −4.56, −4.30, −4.77 kcal/mol for specifically Thaicetazone, Pyrazinamide, Isoniazid; Primaquine, Tafenoquine, Chloroquine; Aspirin, Ibuprofen, Naproxen; Tamoxifen, Toremifene, Raloxifene; Orlistat, Cetilistat, Lorcaserin; Galantamine, Donepezil, and Rivastigmine respectively) in the market. Thereupon, MM-GBSA analysis reveals the stronger binding of the ligands to the receptors. The binding energy (−35.37, −41.73, −19.46, −39.03, −49.51, −45.38 kcal/mol) of Quercetin and binding energy (−30.53, −11.1, −10.98; −20.41, −47.00, −35.12; −30.90, +3.03, +5.05; −40.62, −51.69, −70.34; −18.22, −46.616, −29.53; −28.02, −31.06, −33.65 kcal/mol) of standard drugs (Thaicetazone, Pyrazinamide, Isoniazid; Primaquine, Tafenoquine, Chloroquine; Aspirin, Ibuprofen, Naproxen; Tamoxifen, Toremifene, Raloxifene; Orlistat, Cetilistat, Lorcaserin; Galantamine, Donepezil, and Rivastigmine respectively) to the selected disease-specific receptor proteins(1KPI, 1SME, 2OYE, 3ERT,3LFM & 4IVT) was yielded after MMGBSA analysis. We can assume from the above information that against tuberculosis (1KPI), malaria (1SME), obesity (2OYE), and Alzheimer's disease(3ERT), Quercetin possesses a greater score of docking as well as MM/GBSA than the standard drugs. On the other hand, In the case of Inflammation (pain)(3LFM) and breast cancer(4IVT), Quercetin possesses a greater docking score but lower MMGBSA compared to standard drugs. Overall, it can be stated from the analogy of both the scores that Quercetin can be a highly potent agent against tuberculosis, malaria, obesity, and Alzheimer's diseases and is also slightly effective against Inflammation (pain) and breast cancer.

Organic compounds can link to proteins via creating chemical bonds and non-covalent interactions between the ligand and the protein [61]. Hydrogen bond interaction and hydrophobic interaction are important considerations in evaluating binding affinity and the effectiveness of a new drug molecule to gain suitable pharmacologic properties. H-bonds play a critical role in drug-receptor interactions and the structural integrity of numerous biological components, including proteins and DNA [62]. Hydrogen bonds (H-bonds) are relatively common between ligand and protein [61]. By enabling chemical interactions, H- bonds enhance various biological functions [63]. The bond is assumed to be hydrogen if a valid hydrogen bond acceptor–donor pair is within the correct distance. The stronger the hydrogen bond, the closer it gets to perfect geometry [64]. The ligand's binding causes direct interaction with the protein to develop and the release of water molecules.

Table 1
Comparison of the Molecular Docking binding energies between Quercetin and other Standard drugs.

Activity	Quercetin(kcal/mol)	MMGBSA	Standard drug(kcal/mol)	MMGBSA	Standard drug(kcal/mol)	MMGBSA	Standard drug(kcal/mol)	MMGBSA
Anti-tuberculosis	-9.00	-35.37	-6.89 (Thiacetazone)	-30.53	-6.04 (Pyrazinamide)	-11.1	-6.60 (Isoniazid)	-10.98
Anti-malaria	-6.36	-41.73	-4.18 (Primaquine)	-20.41	-5.54 (Tafenoquine)	-47.00	-4.18 (Chloroquine)	-35.12
Anti-inflammatory	-8.52	-19.46	-6.02 (Aspirin)	-30.90	-5.07 (Ibuprofen)	+3.03	-4.72 (Naproxen)	+5.05
Antineoplastic (breast cancer)	-7.28	-39.03	-4.81 (Tamoxifen)	-40.62	-5.49 (Toremifene)	-51.69	-10.83 (Raloxifene)	-70.34
Anti-obesity	-7.89	-49.51	-3.47 (Orlistat)	-18.22	-5.73 (Cetilistat)	-46.616	-6.41 (Lorcaserin)	-29.53
Anti-alzheimer's Disease	-6.68	-45.38	-4.56 (Galantamine)	-28.02	-4.30 (Donepezil)	-31.06	-4.77 (Rivastigmine)	-33.65

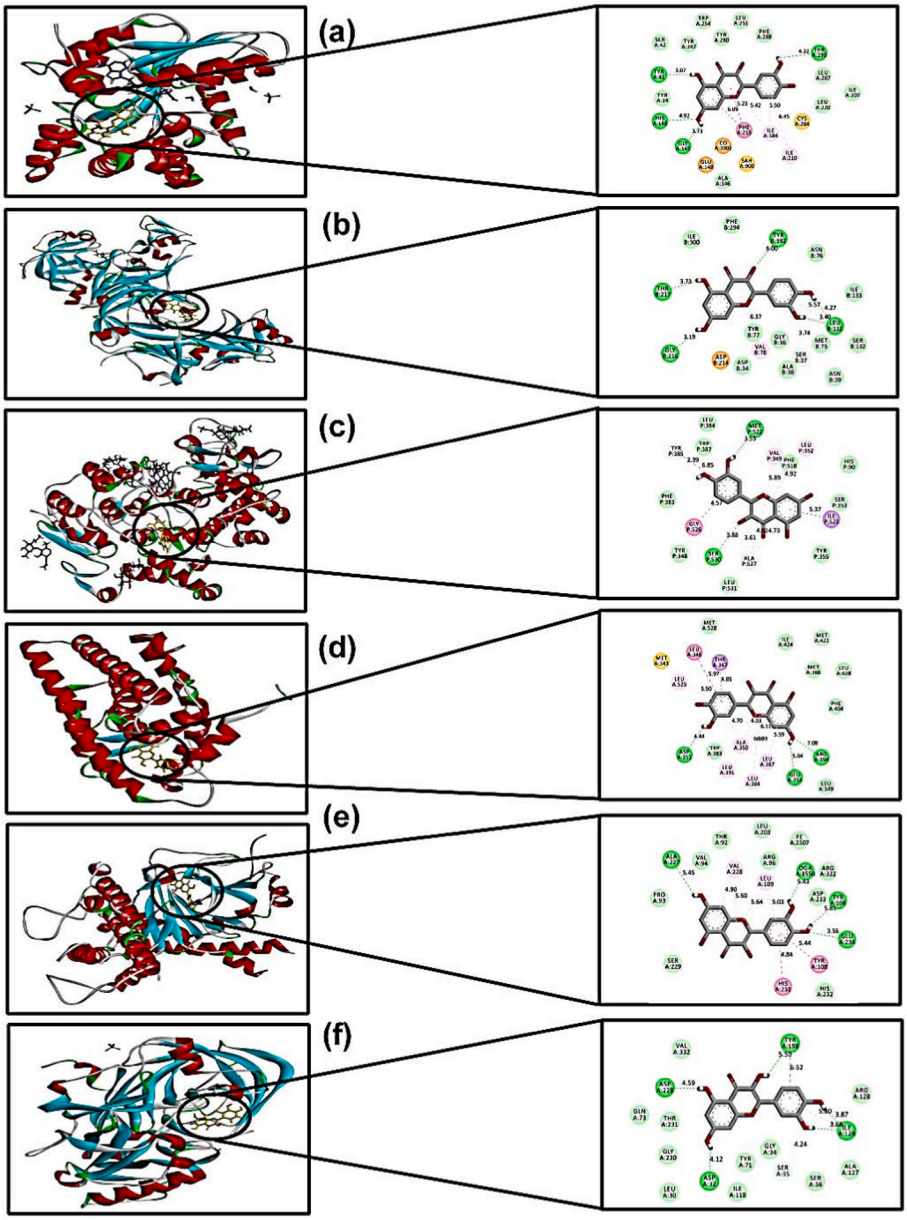

Fig. 3. Molecular Docking Simulation analysis. (a) Interaction with mycolic acid cyclopropane synthase (PDB id: 1KPI), (b) Interaction with plasmepsin II (PDB id: 1SME), (c) Interaction with cyclooxygenase-1 (PDB id: 2OYE), (d) Interaction with human estrogen receptor alpha (PDB id: 3ERT), (e) Interaction with fat mass and obesity associated (FTO) protein (PDB id: 3LFM), (f) Interaction with BACE1 (PDB id: 4IVT).

Both of these contributions are advantageous to the binding [61]. The mean donor-acceptor distances in protein secondary structure elements and those between bases in Watson-Crick pairing are close to 3.0–3.5 [65]. The majority of h-bonds in proteins are moderate. Strong h-bonds require moieties or conditions that are rare within proteins. The hydrogen atoms in moderate h-bonds often do not lie on the straight line connecting the donor to the acceptor, so donor-acceptor distance slightly underestimates the length of the h-bond [65]. In the case of Quercetin and the target proteins, the bond distance is like most of average 3.0 and in between 3.5 and 4.0, which is good enough in contrast to the available standard drugs interaction value. Hydrophobic interactions are formed when non-polar amino acid side chains of the protein and lipophilic groups on the ligand are in close contact. Hydrophobic interactions have been demonstrated to contribute significantly to the binding affinity of ligands with substantial lipophilic groups [61]. Hydrophobicity impacts a variety of biological processes, including biological molecule transport, distribution, and metabolism; molecular recognition; and protein folding. It is vital to have a parameter that defines the behavior of solutes into polar and non-polar phases to forecast the transport and action of medications, pesticides, and xenobiotics. The more the hydrophobic interactions distance, the more the bioavailability of drug molecules [66]. Based on less bond distance (Å) or energy value of Quercetin in comparison to the standard drug in case of hydrogen bond interactions and more distance value for hydrophobic interaction with the receptor's active site suggests that Quercetin has a stronger binding affinity towards most of the protein molecules as well as a suitable bioavailability property. Future critical analysis of the binding affinity is needed for a better assumption. Pharmacokinetics and toxicological studies are vital parameters in drug discovery [66]. From the ADME/T analysis of Quercetin, according to Lipinski rule - molecular mass less than 500 Da (302.24g/mol); The molecular weight of a drug is crucial because it allows it to be absorbed by the body at the right rate and amount. It is possible to spray a liquid onto small drug cores, forming a membrane that the drug must pass through before reaching

Table 2
Binding interaction (hydrogen and hydrophobic) between quercetin and the receptors.

Proteins (PDB ID)	Ligands	Hydrogen bond interactions		Hydrophobic interactions	
		Amino acid residue	Distance (Å)	Amino acid residue	Distance (Å)
1KPI	Quercetin	TYR-41	3.07	PHE-215	6.09
		HIS-149	4.92	ILE-184	5.50
		GLY-145	3.73	ILE-210	6.45
		THR-293	4.22		
1KPI	Thiacetazone	GLU-148	4.55	ILE-184	6.62
		GLY-145	3.55	LEU-220	5.01
		TYR-41	4.30	PHE-215	5.15
		TYR-24	6.54		
1SME	Quercetin	TYR-192	6.00	TYR-77	6.37
		THR-217	3.73	LEU-131	5.57
		GLY-216	3.19		
		LEU-131	3.40		
1SME	Primaquine	ASP-34	4.34	VAL-78	5.50
				ASP-214	4.53
				ASP-34	5.04
				GLY-216	4.10
				TYR-77	3.39
2OYE	Quercetin	MET-522	3.53	TYR-385	2.39
		SER-530	3.88	GLY-526	4.57
		ASP-351	4.44	ALA-527	3.61
		GLU-353	5.04	ILE-523	5.37
				VAL-349	5.89
				LEU-352	4.92
				THR-347	4.85
				LEU-346	5.97
2OYE	Aspirin			TYR-385	7.81
				GLY-526	4.78
				ALA-527	4.20
3ERT	Quercetin	ARG-394	3.68	LEU-525	5.50
		ALA-227	5.45	ALA-350	4.70
				LEU-391	6.65
		TYR-106	5.81	LEU-384	6.03
		GLU-234	3.56	LEU-387	5.59
				VAL-228	4.90
				LEU-109	5.64
3ERT	Tamoxifen	LEU-536	4.81	GLU-380	6.04
				PRO-535	4.85
				LEU-536	5.08
				LEU-354	6.89
				LEU-525	4.48
3LFM	Quercetin	TYR-198	5.50	HIS-231	4.84
		ASP-228	4.59	TYR-108	5.44
		ASP-32	4.12	ILE-126	5.80
		ILE-126	3.87	SER-35	4.24
				TYR-198	6.52
3LMF	Orlistat	SER-229	4.16	TYR-214	4.35
				TYR-108	5.23
				TYR-106	6.53
				SER-229	3.66
				TRP-230	6.18
				ILE-85	4.76
4IVT	Quercetin	ILE-126	3.87	ILE-126	5.80
		TYR-198	5.50	TYR-198	6.52
		ASP-228	4.59	SER-35	4.24
		ASP-32	4.12		
4IVT	Galantamine	ARG-235	4.16	ASP-228	5.08
		THR-72	4.16	ASP-32	4.77
				GLY-34	3.83
				PRO-70	4.26
				TYR-71	5.06
				GLN-71	4.46
				VAL-332	7.92

Abbreviation: TYR- Tyrosine, HIS-Histidine, GLY-Glycine, ARG-Arginine, ASP-Aspartic Acid, THR- Threonine, SER-Serine, ILE-Iso-leucine, LEU- Leucine, GLU-Glutamic Acid, ALA-Alanine, MET-Methionine, GLN-Glutamine, VAL- Valine, PRO-Proline, TRP-Tryptophan, PHE-Phenylalanine.

Table 3
Ligand properties of QUERCETIN.

Molecular weight	302.24 g/mol
Hydrogen bond donor	5
Hydrogen bond acceptor	7
High lipophilicity (log P)	1.23
Molar refrectivity	78.03
Mutagenicity	Non-mutagenic
Carcinogenicity	Non-carcinogenic
Acute oral toxicity	II
Rat acute toxicity	3.0200

the body.

On the other hand, hydrogen bond donor is 5, which is compatible, and also hydrogen bond receptor is less than 10 (particularly 7), which indicated good binding strength. Moreover, high lipophilicity (defined as partition co-efficient denoted as logP) is less than five or between (1.23), which indicates better absorption (Lipophilicity and molecular weight are frequently increased during drug development to improve the affinity and selectivity of the therapeutic candidate, and molar refractivity is between 40 and 130 (78.3) [67]. A drug-like molecule with a logarithm of the partition coefficient (logP) ranging from −0.4 to 5.6, a molecular weight of 160–480 g/mol, a molar refractivity of 40–130, which is proportional to the molecule's volume and molecular weight, and 20–70 atoms [68]. Thus, Quercetin satisfied all the parameters of Lipinski's five rules, including the absorption analysis, distribution, metabolism, and excretion, and exhibited good oral bioavailability. Furthermore, the toxicity analysis revealed that the compound is safe as it exhibited no mutagenic or carcinogenic properties. Also, based on the acute oral toxicity level (II) and the rat acute toxicity value is (3.020) in ADME/T analysis, the toxicity level value is within the acceptable limit in the perspective of a computer simulation study. Nevertheless, clinical investigation is needed to evaluate overall toxicity. After all, the efficacy and safety profile are quite reasonable compared to referenced drugs.

5. Conclusion

In this study, molecular docking was applied to explore the binding mechanism and correlate its docking score with the activity of the Quercetin compound. It has displayed good docking scores in comparison to the standard drugs. Quercetin and its derivatives have been studied for their pharmacological properties in recent years. We have assessed some pharmacological properties, including antineoplastic (Breast Cancer), anti-obesity, anti-inflammatory, anti-Alzheimer's disease, anti-malarial, and anti-tuberculosis. The results of our present study can be useful for the design and development of novel compounds having better inhibitory activity against several diseases. Quercetin exhibited an acceptable drug-like property with no carcinogenicity or mutagenicity. However, Quercetin and its derivatives are versatile molecules. So, this potential drug candidate can further be validated in wet lab studies for its proper function in human health with a safety profile and extensive drug interactional study should be done.

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Credit author statement

Md.Mahmudul Hasan: Conception and design, or analysis and interpretation of the data, Writing – original draft, Writing – review & editing. Zidan Khan: Conception and design, or analysis and interpretation of the data, Writing – original draft, Writing – review & editing. Mohammed Salahuddin Chowdhury: Writing– original draft, Writing –

review & editing. Md Arif Khan: Writing – review & editing, Critical Revision and comments. Mohammad Ali Moni: Writing – review & editing. Md Habibur Rahman: Writing – original draft, Writing – review & editing and Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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