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Identification of Structurally Similar Phytochemicals to Quercetin with High SIRT1 Binding Affinity and Improving Diabetic Wound Healing by Using *In silico* Approaches

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Abstract: Diabetes Mellitus is the most prevalent metabolic disorder that is increasing at an alarming rate worldwide. The unregulated glucose level leads to various types of health disorders, and one of the major diabetic complications is delayed wound healing. Due to the more side effects of synthetic drugs, there is a need to explore plants and their phytochemicals for medicinal purposes. It was found that Quercetin, a flavonoid, increases the rate of diabetic wound healing by enhancing the expression of SIRT1. This demands more insight towards Quercetin and its similar compounds, as it is hypothesized that similar compounds may have similar biological properties. Thus similarity searching was done to identify the most similar compounds of Quercetin, and then the molecular docking of the screened compounds was performed using AutoDock Vina. The unique ligands were docked into the active site of SIRT1 protein (PDB ID: 4ZZJ). The binding free energy of the interacting ligand with the protein was estimated. Six compounds were identified which possess the maximum structural similarity with Quercetin, and upon docking, it was found that gossypetin and herbacetin have similar binding modes and binding energy as that of Quercetin (-7.5 kcal/mol). Therefore, the hypothesis has been validated by in silico analysis. Our study identified two phytochemicals, Gossypetin, and Herbacetin which can prove beneficial for improving diabetic wound healing but needs to be validated further by *in vitro* and *in vivo* studies.

Keywords: diabetic wound healing; SIRT1; phytochemicals; similarity searching; molecular docking.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by raised blood sugar due to insufficient insulin secretion or action. Insulin is a hormone responsible for blood glucose regulation. Hyperglycemia is a prevalent impact of uncontrolled diabetes, resulting in serious damage to the body's nervous and blood vessel systems. Glucose is the body's primary energy source, and glucose management becomes irregular in the event of DM. The onset of DM has three significant flaws: increased glucose production in the liver, reduced pancreatic insulin secretion, and impaired insulin action. Symptoms include polyuria, polydipsia, constant hunger, weight loss, vision changes, and fatigue. DM is a critical disease that impacts

contemporary society's quality of life and has recently increased globally [1]. Protein, fat, and carbohydrate metabolism complications are the most prevalent syndrome of this chronic disease and require adequate treatment [2].

Uncontrolled diabetes leads to many types of diseases, also referred to as diabetic complications, including diabetic retinopathy, neuropathy, nephropathy, foot ulcers, and delayed wound healing [3]. Many research studies have demonstrated that hyperglycemia is responsible for delayed wound healing, and it is one of the most serious complications of diabetes [4-7]. Hyperglycemia increases the oxidative stress that is accompanied by the enhanced production of free radicals [8,9]. The increased glucose level has been shown to decrease the rate of cell proliferation and collagen production, which increases the chances of tissue injury. Thus there is an urgent need to cure diabetes so that further complications of diabetes can be controlled.

For the treatment of diabetes and wound, several synthetic drugs are available in the market, but they are of high cost and have adverse side effects. The major limitation of these drugs is an allergic reaction and drug resistance [10]. The wound healing medicines have a major proportion of polypeptide growth factors which induces increased cell proliferation and eventually leads to cancer development [11]. The high cost, toxicity, and adverse effects of synthetic drugs highlight the need to identify new and effective treatment approaches for diabetic wounds [12]. Traditionally, plants and their phytochemicals were used throughout the world because of their effectiveness, relative abundance, low cost, and fewer side effects. Thus the use of such natural therapeutic drugs with the absence of any side effects appears promising towards chronic wound healing [13,14].

Phytochemicals are non-nutritive chemicals produced by plants for self-protection and provide color and taste to fruits and vegetables [15]. Natural products contain a wide variety of chemicals, including flavonoids, polyphenols, saponins, steroids, and vitamins that have several therapeutic roles like anti-diabetic, antioxidant, anti-inflammatory, angiogenic, and cell synthesis modulating properties. The phytochemicals influence various metabolic pathways and thereby increase the release of insulin, it's production, and efficacy [16,17]. The literature survey reported that one of the most abundant plants flavonols is Quercetin which has various therapeutic effects.

Quercetin (3,3′,4′,5,7-pentahydroxyflavone), is a naturally occurring poly-phenolic flavonoid [18]. It is a part of non-steroidal compounds derived from plants, known as phytoestrogens. A large amount of Quercetin occurs in fruits and vegetables like cranberry, onion, radish leaves, broccoli, nuts, seeds, etc. [19,20]. It may exist freely or be bound with sugars, but the conjugated form is better absorbed [21]. Thus, many common foods and beverages are rich sources of Quercetin and its derivatives [18]. Various clinical and nonclinical studies have shown strong anti-diabetic activity of Quercetin, and it is due to the more proliferation of pancreatic cells that enhance insulin secretion and glucose metabolism [22]. Quercetin enhances the expression of AMP-dependent protein kinase (AMPK) and Sirtuin 1 (SIRT1) that decreases glucose production [23]. SIRT1, also called Sirtuin (silent mating type information regulation 2 homolog) 1, is a class III histone deacetylase (HDAC) that removes an acetyl group from histone protein N terminal tails and thus regulates gene expression by regulating the accessibility of the transcription factors to the specific genes. In this way, SIRT1 regulates various cellular processes like inflammation, apoptosis, cellular senescence, oxidative stress, mitochondrial biogenesis, and function [24]. High glucose or high insulin resistance leads to reduced SIRT1 expression that can cause detrimental effects like

increased oxidative stress, inflammation, impaired wound healing, etc. [25-27]. Thus potent SIRT1 activating compounds (SACs) need to be identified to overcome various diabetic complications.

Quercetin regulates various signal transduction pathways responsible for oxidative stress and thus acts as a scavenger of reactive oxygen species (ROS) [28]. ROS creates lethal effects and leads to various disorders like diabetes, cardiovascular diseases, and cancer [29]. Structurally presence of catechol groups in the ring B and free OH groups of the A ring and/or C ring is the result of its antioxidant activity [30]. The anti-inflammatory effect of Quercetin is due to the inhibition of enzymes responsible for triggering inflammation like lipoxygenase (LOX) and cyclooxygenase (COX) [31]. Thus Quercetin can improve wound healing by increasing fibroblast proliferation and reducing scar formation [32]. Quercetin also has other therapeutic effects as it acts as a potent anti-cancer agent [33]. It exerts its effect by altering the progression of the cell cycle, inhibiting the proliferation of cells, and promoting apoptosis [21,34].

In this study, we have evaluated various biological activities of Quercetin, and it has been found that Quercetin has no toxicity or side effects [35]. Thus due to the pronounced therapeutic activities of Quercetin, it has attracted more attention. Since nature is a vast reserve of phytochemicals that may have similar therapeutic activities as Quercetin but are still unexplored, there is a need to identify similar compounds that may cure diabetic wound healing. Therefore we hypothesize that structurally similar compounds can exhibit similar biological activities. Data mining and similarity searching was performed to identify the compounds similar to Quercetin. Further, Quercetin is known to enhance SIRT1 activity, so we also performed molecular docking of Quercetin and its similar compounds with SIRT1 (PDB ID: 4ZZJ) to predict their binding energies for a more confirmatory hypothesis.

2. Materials and Methods

2.1. In silico studies: data mining and similarity searching.

Quercetin was used as a query molecule for data mining and similarity searching in different open sources databases like CHEMBL, Protein Data Bank (PDB), PubChem, and DrugBank. 2D structure (Figure 1) and SMILE notation were used for searching the databases for more outputs. It was reported that if two molecules are structurally similar, then they may have the same biological activities [36,37].

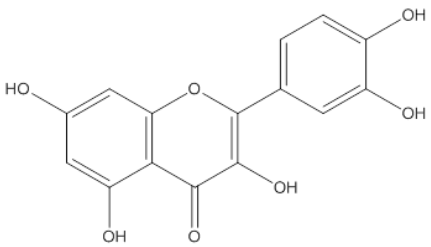


Figure 1. Structure of Quercetin.

2.2. Molecular docking.

Molecular docking is an *in silico*-approach for predicting the binding free energy of the query structure into the active site of the protein. AutoDockVina [38], a web-based server for

docking, was used for the docking studies of Quercetin and its similar compounds into the binding site of PDB protein.

Protein Data Bank online database (http://www.rcsb.org/) was used to obtain the structure of human SIRT1 (PDB ID: 4ZZJ) in the pdb format [39]. Ligand and water molecules were removed while polar hydrogen and Kollman charge were added to SIRT1 (PDB ID: 4ZZJ) so as to convert it into pdbqt. Molecular docking of the bound ligand 4TQ i.e. (3S)-1,3-dimethyl-N-[3-(1,3-oxazol-5-yl)phenyl]-6-[3-(trifluoromethyl)phenyl]-2,3-dihydropyrido[2,3-b]pyrazine-4(1H)-carboxamide) was performed to predict the binding energy of the reference molecule. Then the molecular docking of the molecules obtained by virtual screening was performed to evaluate the binding energy of each using AutoDock Vina. Certain parameters of docking was set, grid box 40 X 40 X 40 , grid centre (-0.827, 45.618, -0.853) and grid spacing 0.375Å. This study gives an idea about how similar molecules can bind to the active site of the same protein.

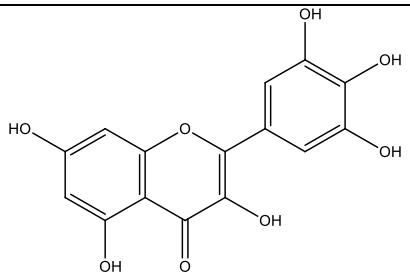
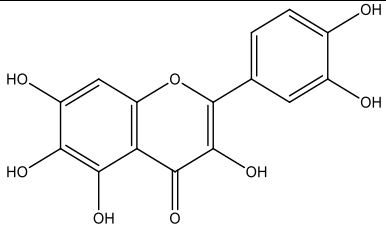
2.3. PyMOL software.

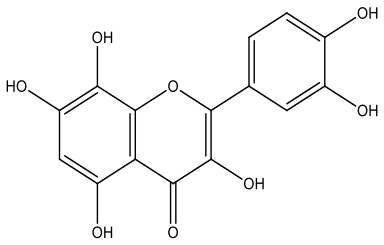
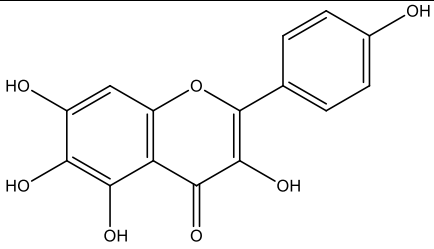
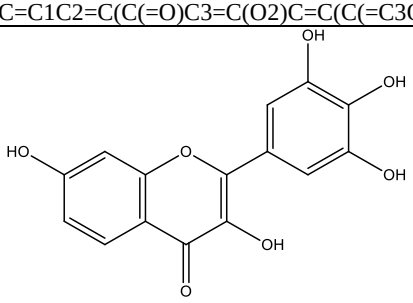
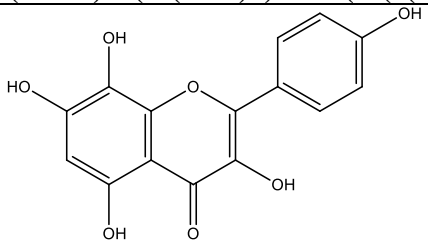
To better visualize the binding interactions of ligand and protein, the docking results are visualized using PyMOL software. This software also helps in predicting the distance between ligand and interacting amino acids.

3. Results and Discussion

Structural similarity searching identified various molecules with more than 80% similarity with Quercetin, out of which six compounds with the highest (>95%) similarity (i.e., Myricetin, Quercetagetin, Gossypetin, 6-Hydroxykaempferol, Robinetin, and Herbacetin) were chosen for molecular docking (Table 1).

Table 1. Similarity searching using Quercetin as a query molecule.

Compound	Structure	Similarity (%)
Myricetin	 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one **ChEMBL ID:** CHEMBL164 **Canonical SMILES:** C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O	99.53
Quercetagetin	 2-(3,4-dihydroxyphenyl)-3,5,6,7-tetrahydroxychromen-4-one **ChEMBL ID:** CHEMBL413552 **Canonical SMILES:** C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C(=C3O)O)O)O)O)O	98.88

Gossypetin	 2-(3,4-dihydroxyphenyl)-3,5,7,8-tetrahydroxychromen-4-one **ChEMBL ID:** CHEMBL253570 **Canonical SMILES:** C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C(=C(C=C3O)O)O)O)O)O	98.70
6-Hydroxykaempferol	 3,5,6,7-tetrahydroxy-2-(4-hydroxyphenyl)chromen-4-one **ChEMBL ID:** CHEMBL455504 **Canonical SMILES:** C1=CC(=CC=C1C2=C(C(=O)C3=C(O2)C=C(C(=C3O)O)O)O)O	97.86
Robinetin	 3,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one **ChEMBL ID:** CHEMBL170405 **Canonical SMILES:** C1=CC2=C(C=C1O)OC(=C(C2=O)O)C3=CC(=C(C(=C3)O)O)O	97.76
Herbacetin	 3,5,7,8-tetrahydroxy-2-(4-hydroxyphenyl)chromen-4-one **ChEMBL ID:** CHEMBL611029 **Canonical SMILES:** C1=CC(=CC=C1C2=C(C(=O)C3=C(O2)C(=C(C=C3O)O)O)O)O	97.68

3.1. Molecular docking.

The redocking of the ligand 4TQ with the macromolecule 4ZZJ revealed an output of -8.0 kcal/mol. Out of the six similar compounds, the binding energy of Gossypetin and Herbacetin is found to be -7.5 kcal/mol, which is similar to the binding affinity of the query structure, i.e., Quercetin (-7.5 kcal/mol) with SIRT1 (4ZZJ) (Table 2). Thus it can be hypothesized that Gossypetin and Herbacetin, having structural similarity with Quercetin and the same binding affinity towards 4ZZJ macromolecule (Figure 2), may have similar biological activities also. The docking results of bound ligand (4TQ), Gossypetin, and Herbacetin were visualized through PyMOL software for a better pictorial resolution of binding interactions (Figure 3, 4, 5).

Table 2. Estimated binding free energy of the structurally similar compound with SIRT1 (PDB ID: 4ZZJ).

Compound	Binding Free Energy (kcal/mol)	Interacting Amino Acids
Quercetin (query structure)	-7.5	ARG274 VAL657 GLU467 ARG649 GLU477 PHE474 PRO470 PRO468 LEU469
Gossypetin	-7.5	VAL657 ARG274 LYS444 PRO468 LEU469 SER442
Herbacetin	-7.5	LEU469 PRO468 HIS471 LYS444 ARG274 VAL657
Myricetin	-7.2	ARG274 VAL657 LYS444 SER442 PRO468 LEU469
6-Hydroxykaempferol	-7.2	VAL657 ARG274 GLU467 PRO468 HIS471 LEU469
Quercetagetin	-7.1	ARG199 LEU202 LYS203 LEU206 THR209 ILE210
Robinetin	-7.1	GLU477 ARG649 PRO468 PRO470 HIS473 PHE474

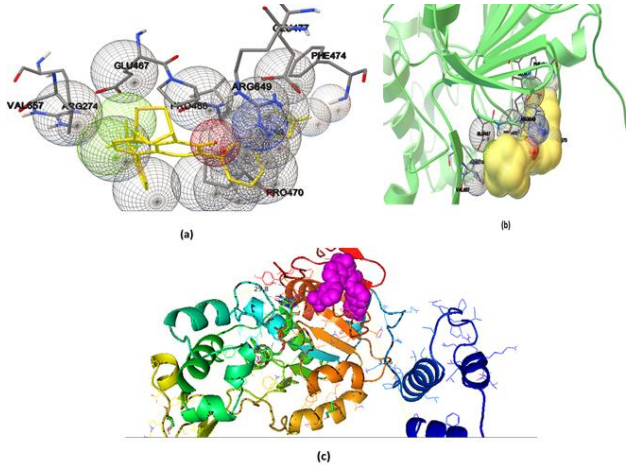


Figure 2. Molecular docking of bound ligand 4TQ into the active site of protein (PDB ID:4ZZJ): (a) Binding interactions between the target protein and ligand (yellow); (b) Binding interactions between the surface view of ligand and secondary structure of target protein; (c) Visualization of binding interactions between target protein (cartoon structure) and ligand (magenta sphere) using Pymol software.

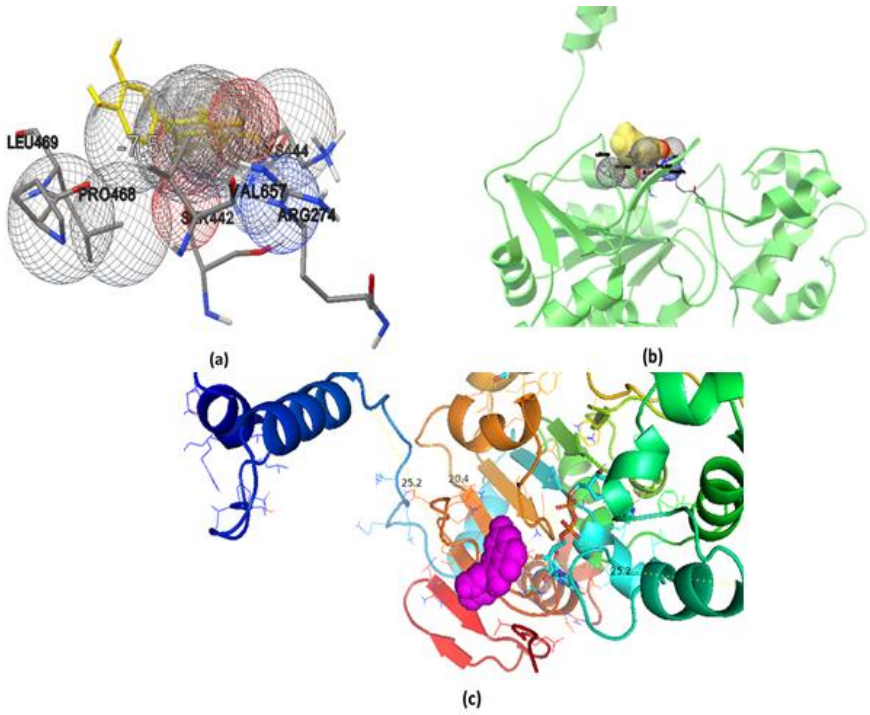


Figure 3. Molecular docking of query structure, i.e., Quercetin into the active site of protein (PDB ID:4ZZJ): (a) Binding interactions between the target protein and ligand (yellow); (b) Binding interactions between the surface view of ligand and secondary structure of target protein; (c) Visualization of binding interactions between target protein (cartoon structure) and ligand (magenta sphere) using Pymol software.

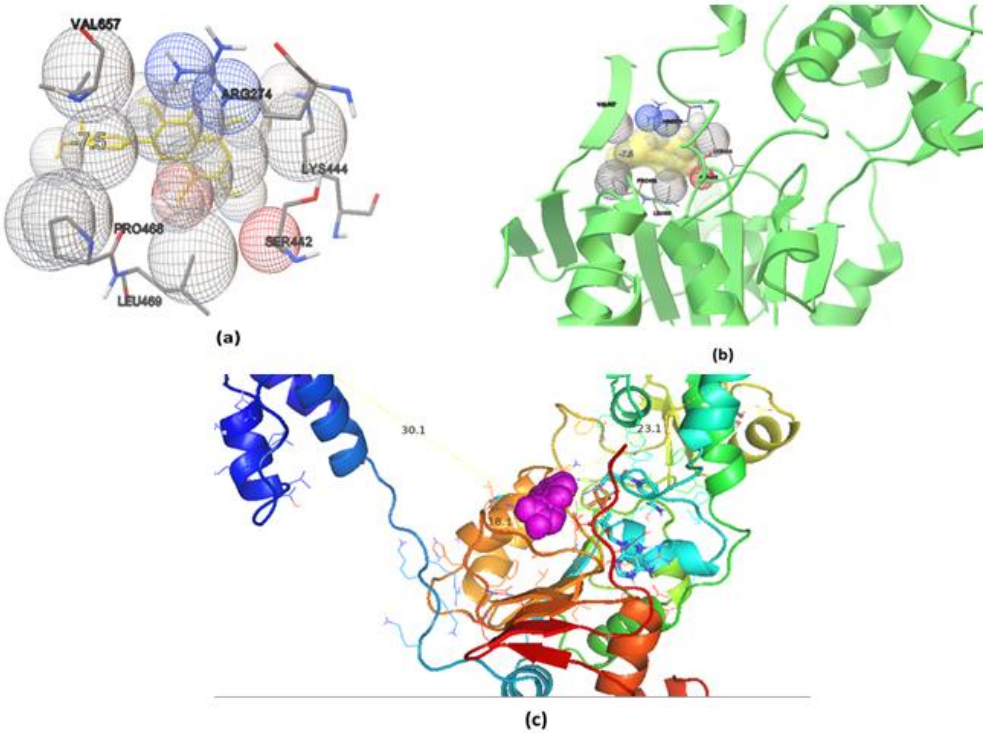


Figure 4. Molecular docking of unique ligand gossypetin into the active site of protein (PDB ID:4ZZJ): (a) Binding interactions between the target protein and ligand (yellow); (b) Binding interactions between the surface view of ligand and secondary structure of target protein; (c) Visualization of binding interactions between target protein (cartoon structure) and ligand (magenta sphere) using Pymol software.

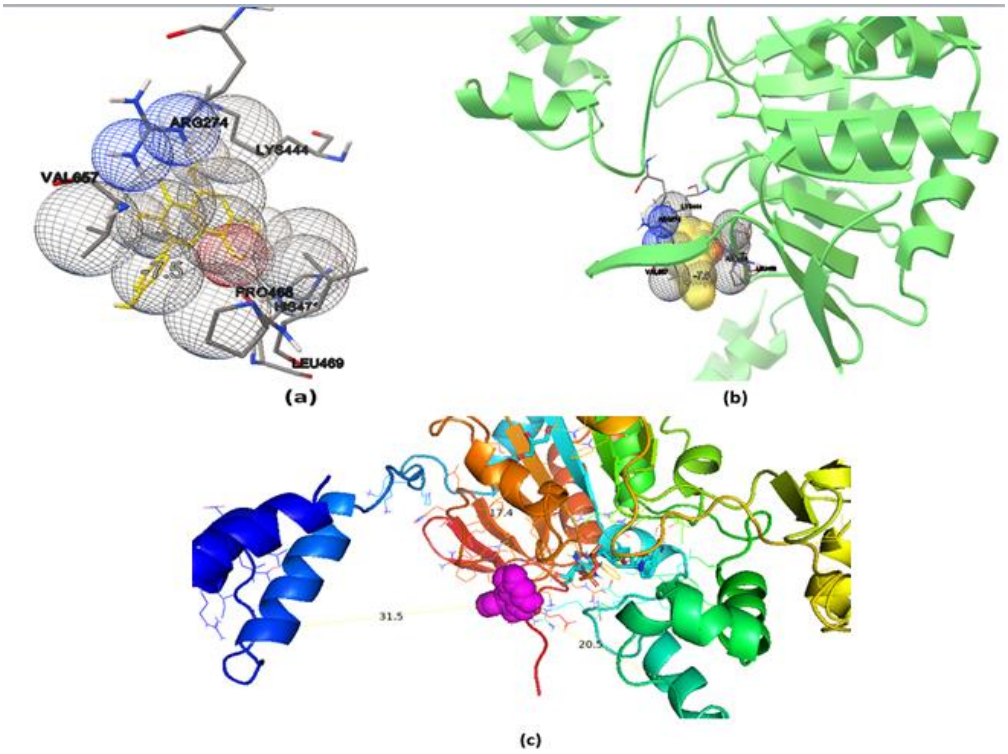


Figure 5. Molecular docking of unique ligand Herbacetin into the active site of protein (PDB ID:4ZZJ): (a) Binding interactions between the target protein and ligand (yellow); (b) Binding interactions between the surface view of ligand and secondary structure of target protein; (c) Visualization of binding interactions between target protein (cartoon structure) and ligand (magenta sphere) using Pymol software.

3.2. Discussion.

The occurrence of chronic wounds is a significant problem for diabetic people, which increases healthcare costs [40]. No effective strategies are available for the treatment of this complication. Currently, SIRT1 is emerging as an important therapeutic target for increasing diabetic wound healing. Lower expression of SIRT1 was observed in streptozocin (STZ)-induced diabetic mice and diabetes patients with reduced wound healing. Treating the wounds with a synthetic SIRT1 activator (SRT1720) locally increased angiogenesis and improved wound healing. Furthermore, SRT1720 was also found to increase the proliferation, migration, and in vitro tube formation ability by human umbilical vein endothelial cells (HUVECs). The SIRT1 activator mediates the protective effect by reducing oxidative stress injury [41].

Many natural phytochemicals are evaluated as effective SACs. Reports have emphasized that dietary supplementation of polyphenols enhances the deacetylase activity of SIRT1 and protects against metabolic diseases. Traditional Chinese medicine includes many active molecules which are potent SIRT1 activators [42]. Diabetes-associated impaired tissue regeneration, and reduced wound healing often gets translated to end-stage complications like diabetic foot disease and foot ulceration. It was estimated by the International Diabetes Federation (IDF, 2015) that around 9.1 million to 26.1 million diabetic people develop foot ulcers every year worldwide [43]. Endothelial progenitor cells (EPCs) are a central role player in angiogenesis, and their dysfunction is directly linked with diabetic wound healing [44]. They significantly contribute to tissue repair by migrating to different sites and proliferating to form new capillaries from the previous ones on receiving angiogenic stimuli [45]. Quercetin, a natural flavonoid, had been reported to protect EPCs against high glucose-induced impaired cell migration by increasing SIRT1 expression and Sirt1-dependent eNOS upregulation.

Sirtinol, a chemical antagonist of SIRT1, abolished these protective effects of Quercetin [46]. Due to the beneficial roles of Quercetin, similarity searching was done to identify similar compounds. Since the similarity index is chosen to be more than 80%, which means the compounds whose structure resembles 80% and more to Quercetin will be fetched, six compounds with maximum similarity with Quercetin were chosen. The similar compounds were then docked with SIRT1 protein (PDB ID: 4ZZJ) to evaluate the binding energies. The study showed that similar compounds interacted in the same manner as the query structure into the active site of 4ZZJ. The interacting amino acids present in the active site of bound ligand, i.e., 4TQ and Quercetin, are the same, which infers Quercetin is also binding with the SIRT1 activator protein just like 4TQ. Also, the resemblance of amino acids with Quercetin is found in the identified phytochemicals (PRO468, LEU469, VAL657, ARG274); thus, it is predicted that those phytochemicals will have the same properties as that of Quercetin since their binding interactions are nearly the same. Some of the interacting amino acids are hydrophobic (VAL657, LEU469, PRO468, PHE474), while some are hydrophilic (ARG274, THR209, GLU467) in nature, and they show van der Waals interaction and few hydrogen bonds while binding with the ligand. Quercetin or similar phytochemicals are SIRT1 activators that show HDAC activity. Thus they promote transcription of various signaling molecules that help in improving diabetic wound healing.

The above study revealed that similar structures (Gossypetin and Herbacetin) are binding with the SIRT1 activator protein equivalent to Quercetin; thus, the in silico analysis gives an insight that the similar compounds will have the same biological activities. Gossypetin is a hexahydroxyl flavone, first isolated from the Hibiscus species (*H. vitifolius* and *H. furcatus*). The plant extracts were traditionally used to cure diabetes, jaundice, and inflammation and possess antioxidant activity [47-49]. Herbacetin, a pentahydroxyl flavone, occurs naturally in *Rhodiola rosea* [50] and cotton [51]. Herbacetin shows antioxidant, antitumor [52,53] and anti-inflammatory properties [54]. The diabetic wound healing activity of Herbacetin and Gossypetin as of Quercetin have been proved through *in silico* analysis and can be further investigated through *in vivo* and *in vitro* analysis.

4. Conclusions

Nutraceuticals and phytochemicals are emerging as promising elements for promoting health due to fewer side effects, relative abundance, and less cost. Several plant secondary metabolites like stilbenes, flavones, anthocyanidins, and chalcones are best known for their beneficial therapeutic activities. Our study highlights the biological activities of phytochemicals Herbacetin and Gossypetin, which possess high structural similarity with biologically active Quercetin and thus may prove beneficial for improving diabetic wound healing. Both the phytochemicals also possess a high binding affinity with the active site of SIRT1, similar to Quercetin. To the best of our knowledge, this is the first report to identify Quercetin's similar compounds and evaluate their binding energies using the molecular docking approach and further validating the results through PyMOL visualization. Further *in vitro* and *in vivo* analysis of these similar identified compounds can authenticate the *in silico* results.

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Conflicts of Interest

The authors declare no conflict of interest.

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