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Investigation of The Efficacy of *Plantago Major* Flavonoids in The Healing of Diabetic Foot Wound in *Silico* Analysis

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ABSTRACT
Diabetes is a chronic disease that is rapidly increasing worldwide due to insulin deficiency. Diabetic foot ulcer is one of the most important complications of diabetes. There are many synthetic and natural treatment methods in the treatment of these wounds. Among the possible side effects of synthetic drugs, the use of natural flavonoids such as Quercetin is preferred in the treatment of diabetic wounds. In this study, *Plantago's major* flavonoids, which can be an alternative to Quercetin, were investigated *in silico*. Whether *Plantago major* and its flavonoids show similar properties with Quercetin was investigated *in silico* with the help of AutoDockTools software. The ADME study of flavonoids was investigated with the help of SwissAdme, an open-access web tool. The results of the *in silico* study of *Plantago major*'s flavonoids and Quercetin's 4ZZJ, one of the SIRT 1 receptors that play a role in diabetic wound healing; Plantago major flavonoids luteolin (-4.81 kcal.mol^{-1}), apigenin (-4.74 kcal.mol^{-1}) and Hispidulin (-4.58 kcal.mol^{-1}) are better than Quercetin (-4.56 kcal.mol^{-1}). showed that it has binding energy. In conclusion, this *in silico* study showed that *Plantago major* flavonoids luteolin, apigenin and hispidulin could be natural alternatives to Quercetin for diabetic wound healing.

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Diyabetik Ayak Yarası Iyileşmeside Plantago Majör Flovonoidlerin Etkinliğinin *In Silico* Olarak Araştırılması

ÖZET
Diyabet, insülin eksikliğine bağlı olarak tüm dünyada hızla artan kronik bir hastalıktır. Diyabetik ayak ülseri diyabetin en önemli komplikasyonlarından biridir. Bu yaraların tedavisinde sentetik ve doğal birçok tedavi yöntemi bulunmaktadır. Sentetik ilaçların olası yan etkilerinden dolayı Quercetin gibi doğal flavonoidlerin kullanımı diyabetik yaraların tedavisinde tercih edilmektedir. Bu çalışmada Quercetine alternatif olabilecek *Plantago major* flavonoidleri *in silico* olarak araştırılması amaçlanmıştır. *Plantago major* ve flavonoidlerinin Quercetin ile benzer özellikler gösterip göstermediği AutoDockTools yazılımı yardımıyla *in silico* olarak araştırılmıştır. Flavonoidlerin ADME çalışması, açık erişimli bir web aracı olan SwissAdme yardımıyla araştırılmıştır. Plantago major'un flavonoidleri ile Quercetin'in diyabetik yara iyileşmesinde rol oynayan SIRT 1 reseptörlerinden 4ZZJ'nin *in silico* çalışmasının sonuçları; *Plantago major* flovonoidlerinden luteolin (-4,81 kcal.mol^{-1}), apigenin (-4,74 kcal.mol^{-1}) ve Hispidulin'in (-4,58 kcal.mol^{-1}) Quercetin'den (-4,56 kcal.mol^{-1}) daha iyi bağlanma enerjisine sahip olduğunu göstermektedir. Sonuç olarak, bu *in silico* çalışma *Plantago major* flavonoidleri luteolin, apigenin ve hispidulinin diyabetik yara iyileşmesi için Quercetine doğal alternatifler olabileceğini göstermiştir

Moleküler Biyoloji

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INTRODUCTION

Diabetes is described as a chronic disease that occurs when the pancreas no longer produces insulin adequately or when the body cannot effectively use the insulin it produces (Lazzarini et al., 2023; Doğan et al., 2022). The inability to produce insulin or use it effectively leads to an increase in glucose levels in the blood. In the long term, high glucose levels cause damage to the body and deterioration of various organs and tissues (IDF, 2022). According to the International Diabetes Federation (IDF) 2021 atlas, approximately 537 million adults (aged 20-79) worldwide live with diabetes. It is also estimated that the total number of people living with Diabetes will increase to 643 million by 2030 and to 783 million by 2045 (IDF, 2021). Additionally, diabetes accounts for approximately 9% of total global health expenditure on adults and is responsible for 6.7 million deaths worldwide (IDF, 2021). Both the number of cases and the prevalence of diabetes have been increasing steadily over the past few decades (Uslu et al., 2022). When comparing the data of the "Turkey Diabetes, Hypertension, Obesity, and Endocrinological Diseases Prevalence Study-II (TURDEP-II)" completed in 2010 in our country with the TURDEP-I data from 12 years ago, it is evident that the prevalence of diabetes has increased by 90%. The study reveals that the prevalence of diabetes in the Turkish adult population has risen from 7.2% to 13.7% (Satman et al., 2013).

One of the most common complications in diabetic patients is diabetic foot ulcers, which occur at a rate of 25%. These ulcers can lead to infection, gangrene, amputation, and even death (Chirico et al., 2016; Najafian et al., 2019). The most common risk factors are neuropathy (86% of cases), peripheral arterial disease (49% of cases), trauma and foot deformities (Salvo et al., 2017). In addition, diabetic foot wounds are the main cause of hospitalization and amputation in diabetic patients (Chirico et al., 2016; Salvo et al., 2017).

Wound healing and repair of damaged tissue are very important for diabetes patients (Vyas & Vasconez, 2014). The wound healing process includes a series of overlapping phases such as hemostasis, inflammation, proliferation, and remodeling, which can be inhibited by the presence of free oxygen radicals, microbial infection, and high blood glucose (Patel et al., 2019). Chemical or herbal medicines that can modulate one or more of these phases are shown as candidates for wound healing agents in normal or hyperglycemic conditions (Kartini et al., 2021). Routinely, wound healing is a quick and uncomplicated process, but causes such as diabetes and infection make it difficult for these wounds to heal (Khaire et al., 2023). Elevated glucose levels in diabetic patients decrease cell proliferation and collagen production while increasing the likelihood of tissue injury (Sanganalmath et al., 2023).

The high cost, toxicity and side effects of synthetic drugs have revealed the need for new and effective treatment approaches for diabetic wounds (Dubey et al., 2021). Many people's concerns about the side effects of newly released drugs have increased interest in plant-based treatments as an alternative system to modern medicine (Ghanadian et al., 2022).

In traditional Asian medicine, *Plantago major* has been used for thousands of years as a potent and non-toxic therapeutic agent in the prevention of inflammation (Al Baihaqi et al., 2022). *Plantago major* is a plant belonging to the Plantaginaceae family, found in a wide region including Europe, Asia, North Africa, and North America (Ghanadian et al., 2022). *In vivo* and *in vitro* studies have shown that this herb is beneficial in wound healing (Amini et al., 2010; Gonçalves & Romano, 2016; Mahmood & Phipps, 2006; Zubair et al., 2012). *Plantago major* contains many effective phytochemicals such as flavonoids in its leaves, anthocyanins in its flowers, iridoids in its roots and cinnamic acid in its aerial parts (Abate et al., 2022; Al Baihaqi et al., 2022).

Phytochemicals increase insulin secretion, production and efficiency by affecting various metabolic mechanisms (Salla et al., 2020). *Plantago major* is known to have antioxidant, antiulcerative, antidiabetic, anti-inflammatory, and antimicrobial effects due to its polyphenolic compounds, which contribute to its healing wound properties (Kartini et al., 2021). Literature research studies have shown that *Plantago major* is used as a phytotherapeutic plant in the healing of acute and chronic wounds in many parts of the world (Adom et al., 2017; Gonçalves & Romano, 2016; Hosseinkhani et al., 2017; Jarić et al., 2018; Jivad et al., 2016; Khaire et al., 2023).

In the design of new drugs for wound treatment, not only *in silico*, *in vitro*, and *in vivo* studies but also nursing care applied in clinical settings is important. Therefore, multidisciplinary approaches are prominent in new drug designs (Figure 1). It is predicted that these multidisciplinary approaches will reduce costs and improve the quality of life in the treatment of diabetic foot ulcers (Eraydın, 2019).

Advancements in computer technology over the past quarter century have significantly contributed to multidisciplinary research. One such area is molecular docking, which encompasses the disciplines of physics, chemistry, and biology. Molecular docking studies conducted *in silico* on computer platforms are cost-

effective in terms of time, expense, and safety. New drug designs frequently use these studies to provide insights into *in vitro*, *in vivo*, and clinical trials.

SIRT1 receptors, which are involved in insulin regulation, are one of the signalling proteins involved in metabolic regulation.

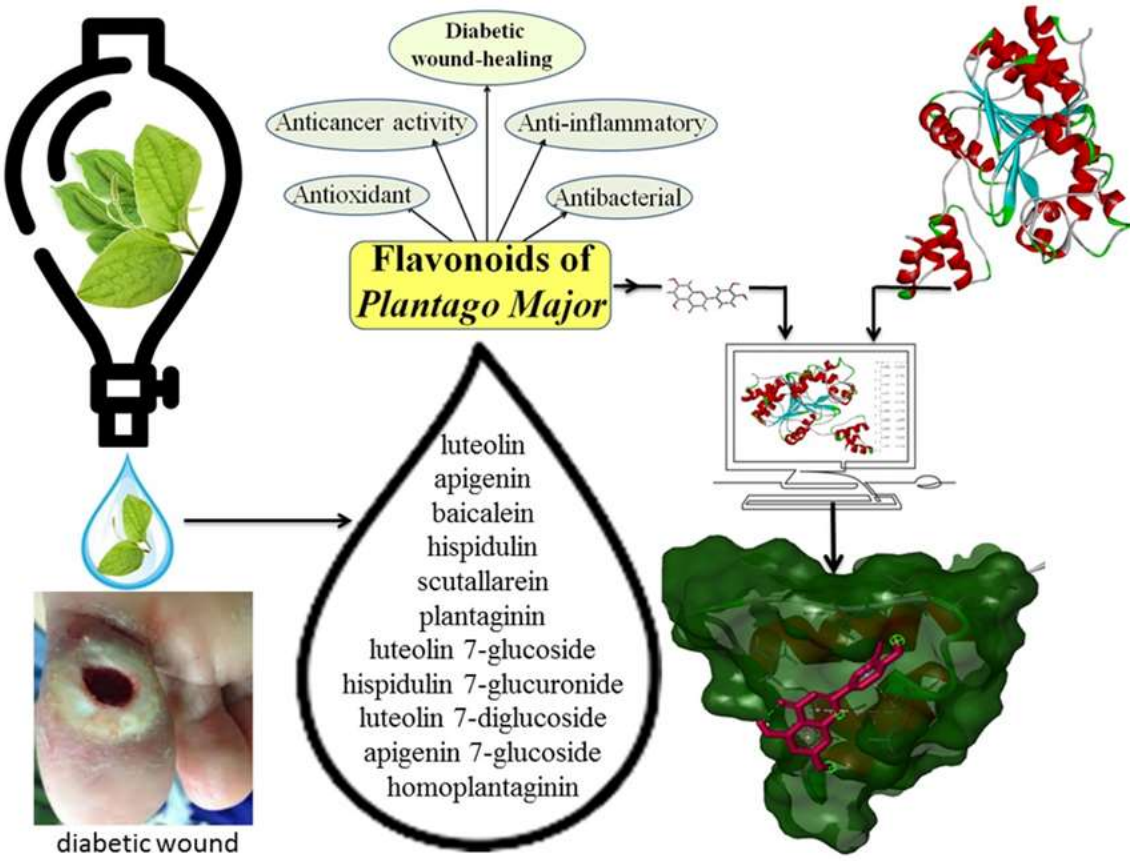


Figure 1: Multidisciplinary approach to new drug designs for diabetic foot wound.
Şekil 1: Diyabetik ayak yaraları için yeni ilaç tasarımlarına multidisipliner yaklaşım.

In this study, the binding of flavonoids found in the leaves of *Plantago major* from SIRT1 receptors to 4ZZJ PDB-encoded receptors were studied *in silico* with the help of computer-aided molecular docking study to provide an insight into new drug designs.

MATERIALS and METHODS

Theoretical and experimental studies conducted on diabetic wound healing have demonstrated the positive effects of Quercetin on reducing glucose production and increasing the expression of 5'-adenosine monophosphate-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) (Khursheed et al., 2020). As nature has a large reserve of phytochemicals that may have similar therapeutic activities as Quercetin but are still unexplored, there is a need to identify similar compounds that could improve diabetic wound healing. One of these similar compounds is thought to be the leaves of the Plantogo major plant, which has been used for wound healing for many years.

In this study, the interactions between the flavonoids found in the leaves of *Plantago major* and the allosteric region of SIRT1, shown in red in Figure 2, were investigated *in silico*. The results obtained *in silico* were compared with the *in silico* results of Quercetin for the discovery of new phytotherapeutic biochemicals effective in diabetic wound healing.

Ligands typically interact with the amino acid residues in the active site of enzymes, thereby altering their mechanisms. On the other hand, some enzymes possess regulatory centers called allosteric sites, where they can interact with effector molecules outside the active site. These effectors, by binding to the allosteric site, exhibit regulatory effects by inhibiting or activating the enzyme's activity. The conformational changes resulting from this interaction cause the enzyme mechanism to change (Srinivasan et al., 2014). Luteolin [1], apigenin [2] (Kawashty et al., 1994; Nishibe et al., 1995), baicalein [3], hispidulin [4], scutallarein [5] (Sanz et al., 1994), plantaginin [6] (Yuting et al., 1990), luteolin 7-glucoside [7], hispidulin7-glucuronide [8], luteolin 7-diglucoside [9], apigenin 7-glucoside [10] (Kawashty et al., 1999), and

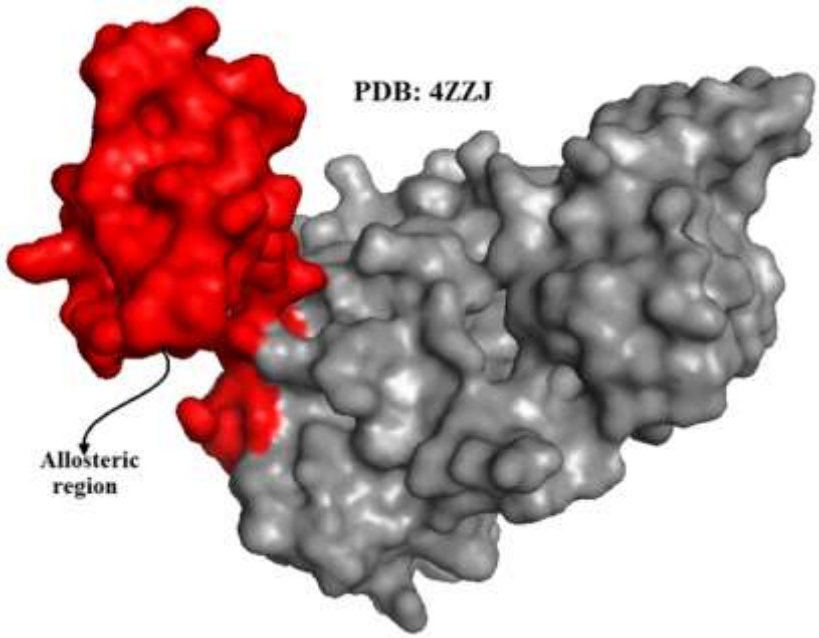
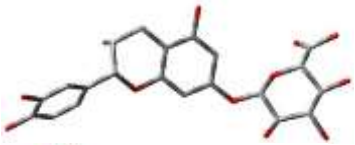
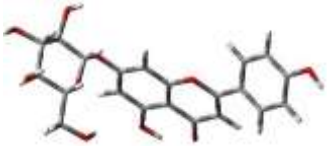
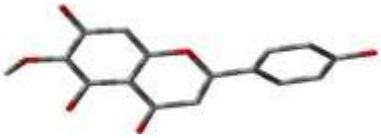
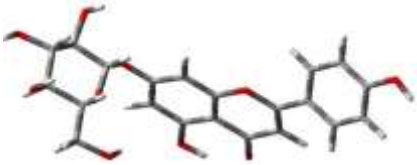
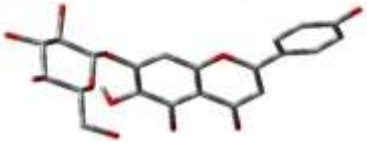


Figure 2. The 3D solid surface structure of the 4ZZJ receptor (allosteric region of the receptor shown in red)
Şekil 2. 4ZZJ reseptörünün 3D katı yüzey yapısı (reseptörün allosterik bölgesi kırmızı ile gösterilmiştir)

Table 1. Flavonoids in the leaves of Plantago major and their molecular structures
Çizelge 1. Plantago major yapraklarındaki flavonoidler ve moleküler yapıları

No	Flavonoids	Molecular structure	No	Flavonoids	Molecular structure
1	Luteolin:		7	Luteolin 7-glucoside:	
2	Apigenin:		8	Hispidulin 7-glucuronide:	
3	Baicalein:		9	Luteolin 7-diglucoside:	
4	Hispidulin:		10	Apigenin 7-glucoside	
5	Scutallarein:		11	Homoplantaginin	
6	Plantaginin:				

homoplantaginin [11] (Skari et al., 1999). These are flavonoids isolated from the leaf structure of Plantago Major. These flavonoids and their chemical structures are taken from the literature and listed in Table 1.

Drug-likeness Properties

There are certain criteria such as Lipinski's rule of five, Veber's rules, and Egan's criteria to determine whether compounds have a structure similar to drugs and their activity in living organisms. In this study, the drug-likeness properties of flavonoids from *Plantago major* were investigated using Lipinski's rule of five. An analytical technique called Lipinski's rule of five is used to assess a substance's drug-likeness and decide if a chemical compound with a particular pharmacological or biological activity can be taken orally by people as a medication (Lipinski, 2004). According to Lipinski's criteria, an orally active drug is expected not to violate multiple of the following criteria. Based on these criteria, chemical structure limitations are defined as ≤500 for molecular weight, ≤10 for hydrogen bond counts, ≤5 for hydrogen bond donor counts, and ≤5 for compound lipophilicity (log P or clog P).

Molecular Docking Study

The chemical structures of flavonoids, which are ligand molecules for *in silico* studies, were obtained from the open-access PubChem database. For the molecular docking study, the SIRT1 family protein with the PDB code 4ZZJ, known to play a role in the healing mechanism of diabetic wounds, was selected as the target receptor. The crystal structure of the 4ZZJ receptor was retrieved from the protein database.

Water molecules, hetatoms and ligand groups were extracted from the structure of the 4ZZJ protein using BIOVIA Discovery Studio software. Polar hydrogen atoms and Kollman charges were introduced to the 4ZZJ protein using AutoDockTools-1.5.6. The grid box settings were adjusted to encompass the active amino acid residues Leu206, Thr209, Pro211, Pro212, Gln222, Ile223, Asn226, Ile227, and Glu230, located in the allosteric region of the 4ZZJ protein, completing the pre-docking procedures. Molecular docking focused on the allosteric region of 4ZZJ was performed using AutoDockTools-1.5.6. The best binding modes and protein-ligand interactions were analyzed by visualizing with Biovia Studio Visualizer (Hubbard et al., 2013).

RESULTS and DISCUSSION

Drug-likeness Properties

The drug-likeness properties of flavonoids isolated from the leaf structure of *Plantago major* were calculated according to Lipinski's rule of five using the SwissADME web tool, and the relevant parameters are provided in Table 2. As seen in Table 2, the 7-glucoside flavonoids of luteolin, apigenin, baicalein, hispidulin, and apigenin complied with the Lipinski criteria. These results indicate that these five compounds can be used as orally active drugs in living organisms. On the other hand, scutallarein, plantaginin, luteolin 7-glucoside, hispidulin 7-glucuronide, luteolin 7-diglucoside, and homoplantaginin flavonoids have two violations.

Table 2. Lipinski criteria agreement table for drug-likeness properties of flavonoids
Çizelge 2. Flavonoidlerin ilaca benzerlik özellikleri için Lipinski kriterleri uyum tablosu

No	Compounds	Molecular weight (≤500 Da)		LogP (≤5)		H-Bond Donor (≤5)		H-Bond Acceptor (≤10)	
1	Luteolin	286.24	✓	1.86	✓	4	✓	6	✓
2	Apigenin	270.24	✓	1.89	✓	3	✓	5	✓
3	Baicalein	270.24	✓	2.43	✓	3	✓	5	✓
4	Hispidulin	300.26	✓	2.27	✓	3	✓	6	✓
5	Scutallarein	462.36	✓	1.11	✓	7	X	12	X
6	Plantaginin	462.36	✓	1.11	✓	7	X	12	X
7	Luteolin 7-glucoside	448.38	✓	1.83	✓	7	X	11	X
8	Hispidulin 7-glucuronide	466.39	✓	-0.09	✓	8	X	12	X
9	Luteolin 7-diglucoside	466.39	✓	-0.09	✓	8	X	12	X
10	Apigenin 7-glucoside	432.38	✓	2.17	✓	6	X	10	✓
11	Homoplantaginin	462.40	✓	2.29	✓	6	X	11	X

✓: Accept X: Violation

Molecular Docking Study

Studies conducted on Quercetin (3,3',4',5,7-pentahydroxyflavone) have demonstrated that it is one of the most abundant polyphenolic flavonoids in nature and exhibits diabetic wound healing activity (D'Andrea, 2015; Mahabady et al., 2021). In addition, Quercetin is a highly remarkable natural flavonoid not

only for its therapeutic activities, but also for its lack of known toxicity or side effects (Ebrahimpour et al., 2020).

In docking studies between *Plantago major* flavonoids, Quercetin effector and the allosteric region of 4ZZJ, the interactions of effectors with active residues and the calculated binding energies are given in Table 3. As can be seen from Table 3, *Plantago's major* flavonoids interacted with the same active amino acid residues in the allosteric region, similar to Quercetin. Hydrophobic interactions between active amino acid residues and flavonoids in the allosteric region of the receptor have been interpreted as indicative of the selectivity of the 4ZZJ receptor towards flavonoids.

As a result of the molecular docking study, the binding energy between Quercetin and the 4ZZJ receptor was found to be -4.56 kcal/mol. 2D and 3D images of the interactions between Quercetin and the allosteric region of 4ZZJ were presented in Figure 3a. As seen in Figure 3a, Quercetin performed hydrophobic interaction with amino acids Ile223 and Ile227 in the allosteric region of 4ZZJ, and acceptor hydrogen bond interaction (HBA) with amino acids Asn226, Glu230 and Thr219.

As seen in Table 3, the flavonoid compounds with the best binding energies are luteolin with -4.81 kcal/mol and apigenin with -4.74 kcal/mol. The results of docking of luteolin with active amino acid residues in the allosteric region of 4ZZJ were given in Figure 3b. The luteolin compound performed hydrophobic interactions with the active amino acid residues Ile223 and Ile227 of the allosteric region, and acceptor hydrogen bond interactions (HBA) with residues Asn226, Glu230 and Thr219.

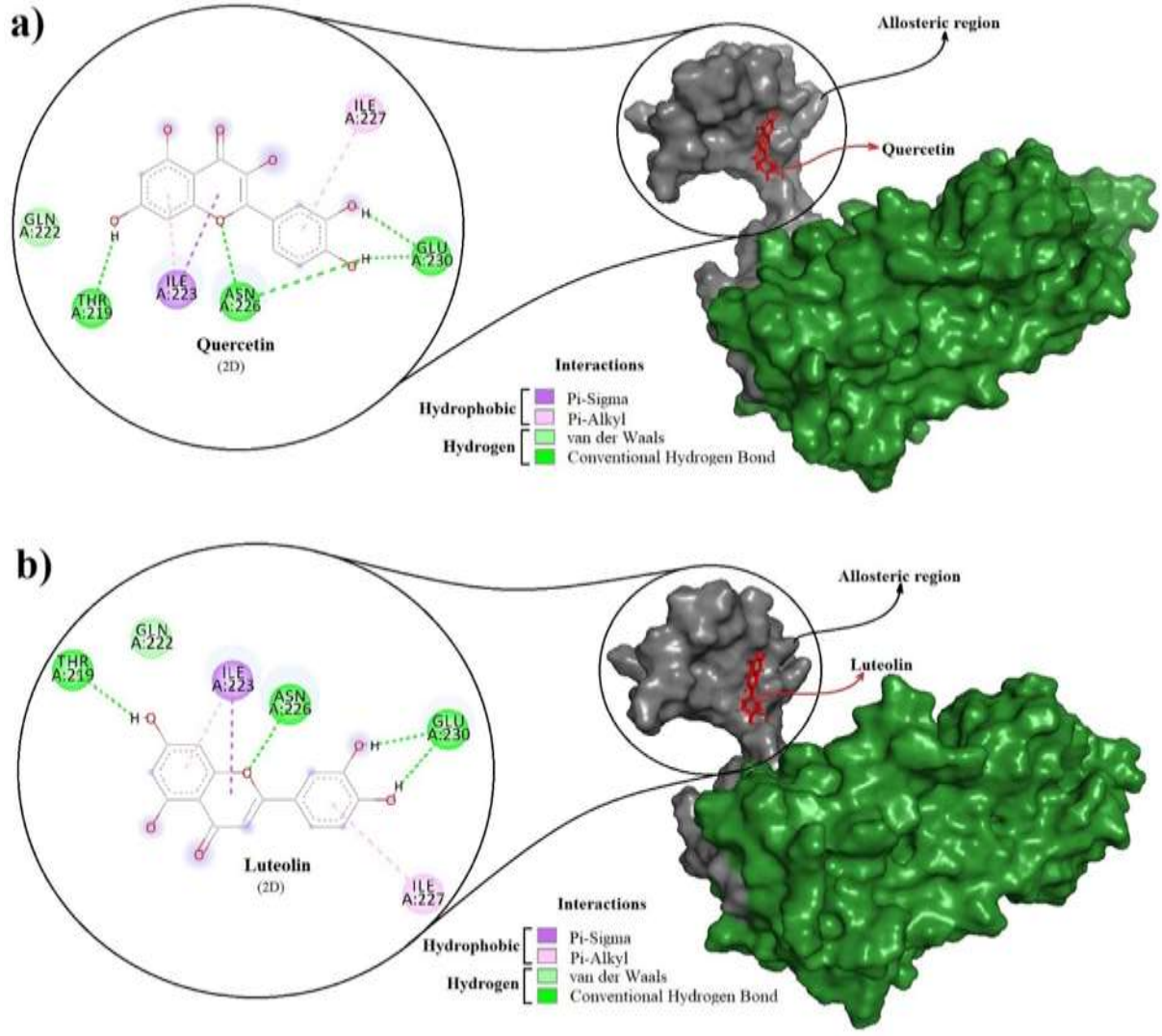


Figure 3. 3D and 2D binding modes of interactions of Quercetin and Luteolin in the allosteric region of 4ZZJ. a)Quercetin, b)Luteolin

Şekil 3. Quercetin ve Luteolin'in 4ZZJ'nin allosterik bölgesindeki etkileşimlerinin 3D ve 2D bağlanma modları. a)Quercetin, b)Luteolin

Table 3. Summative results of molecular docking Plantago major flavonoids and Quercetin with 4ZZJ.
Çizelge 3. Plantago majör flavonoidleri ve Quercetin'in 4ZZJ ile moleküler kenetlenmesinin özet sonuçları

Ligand No	ΔG (kcal/mol)	Conventional and Carbon Hydrogen Bonds Interaction	Hydrophobic Interactions	Van der Waals Interactions
Quercetin	-4.56	Asn226(1.84), Glu230(1.89), Asn226(3.07), Glu230(1.77), Thr219(2.01)	Ile223(3.69), Ile223(3.86) Ile227(5.36)	Gln222
1	-4.81	Asn226(1.75), Glu230(1.85), Glu230(1.78), Thr219(1.99)	Ile223(3.72), Ile223(3.85), Ile227(5.32)	Gln222
2	-4.74	Asn226(1.82), Asn226(2.94), Glu230(2.11), Thr219(1.92)	Ile223(3.72), Ile223(3.81) Ile227(5.16)	Gln222
4	-4.58	Asn226(2.54), Gln222(2.19), Glu230(2.16)	Asn226(4.40), Ile223(4.30), Ile223(4.12), Ile227(5.01)	Leu206, Thr219
3	-4.32	Glu230(1.80), Glu230(1.78)	Asn226(5.50), Asn226(4.15), Ile223(4.62), Ile223(4.14),	Leu206, Thr219, Ile227
7	-3.81	Asn226(1.84), Glu230(1.84), Glu230(2.11), Glu214(2.12), Glu214(2.51)	Leu215(3.62), Leu215(3.41), Ile223(3.58), Ile223(3.75), Ile223(3.79), Pro212(4.71)	Leu206, Thr209, Ile227
10	-3.79	Asn226(2.54), Thr219(2.13), Ile210(1.94)	Thr209(3.84), Ile223(3.58), Ile223(3.93), Pro211(5.42), Pro212(5.45)	Leu206, Gln222, Ile227
6	-3.73	Glu230(1.88), Glu230(1.97), Glu214(1.85)	Leu215(3.25), Ile223(3.55), Ile223(3.85), Pro212(5.16)	Leu206, Thr219, Ile227, Gln222, Asn226
11	-3.26	Asn226(1.84), Ile210(2.10), Ile227(2.24), Ile223(3.64)	Ile223(4.84), Ile223(4.60), Ile227(3.73)	Leu206, Thr209, Pro211 Pro212 Leu215, Glu230
8	-3.06	Asn226(2.04), Glu230(2.77), Glu230(2.17), Glu214(1.88), Glu214(1.93), Pro212(3.13)	Leu215(4.00), Leu215(3.54), Ile223(3.77), Ile223(3.50), Pro212(4.61)	Leu206, Thr209, Pro211, Ile227
9	-1.37	Glu208(2.00-2.32), Leu205(2.18), Thr209(2.03)		
5	-2.64	Ile210(2.11), Gln222(1.98), Pro212(3.35)	Ile223(3.38), Ile223(4.77), Ile223(4.82),	Leu206, Thr209, Pro211, Ile227, Thr219, Asn226

Luteolin(1), Apigenin(2), Baicalein(3), Hispidulin(4), Scutellarin(5), Plantaginin(6), Luteolin_7_glucoside(7), Hispidulin_7_glucuronide(8), Luteolin_7_diglucoside(9), Apigenin_7_glucoside(10), Homoplantaginin(11)
Bold are active amino acid residues of 4ZZJ.

Molecular docking studies between 4ZZJ and flavonoids revealed that the important active residues involved in the allosteric region in hydrophobic interactions are Ile223 Ile227 and Asn226. These results are consistent with previous *in silico* studies for SIRT1 (Azminah et al., 2019). When Table 3 was

examined, it was determined that other flavonoids also interacted with similar active amino acid residues in the allosteric region of the receptor. According to Table 3, it was seen that flavonoids luteolin, apigenin and hispidulin exhibited higher binding affinity than Quercetin.

CONCLUSION

The flavonoids of *Plantago major*, luteolin, apigenin, hispidulin and apigenin 7-glucoside gave positive results in drug similarity studies. A molecular docking study to elucidate the interaction mechanisms between the compounds and the receptor has shown *in silico* that flavonoids can be as effective as Quercetin as a potential phytochemical in the healing of diabetic foot wounds. These results are important as they provide a promising prediction for *in vitro* studies on *Plantago major* flavonoids.

Contribution Rate Statement Summary of Researchers

The authors declare that they have contributed equally to the article.

Conflict of Interest Statement

The authors of the article declare that there is no conflict of interest between them.

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