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Orlistat'a Alternatif Olarak Doğal Bir Bileşik Olan Scutellarinin *İn Silico* Değerlendirilmesi: Moleküler Docking Çalışması ve ADMET Analizi

In-Silico Evaluation of Scutellarin, a Natural Compound as an Alternative to Orlistat: Molecular Docking Study and ADMET Analysis

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Öz

Dünya sağlık örgütü (DSÖ), obeziteyi sağlığı bozabilecek şekilde vücutta anormal veya aşırı miktarda yağ birikimi olarak ifade etmektedir. Obeziteye tedavi etmek için önerilen en etkin ilacın orlistat olduğu ifade edilmektedir. Bu araştırma, orlistat'a alternatif olabilecek, Plantago major flavonoidlerinden Scutellarin'in, 5NN8 PDB kodlu reseptöre bağlanma potansiyeli ve yeni ilaç tasarımlarına ışık tutma amacı ile *in silico* olarak araştırılmıştır. Scutellarin ve Orlistat bileşiklerinin kompleks karbonhidratların glikoza dönüştürülüp hızlıca emilimini sağlayan α-glukozidaz enzimlerini inhibisyon potansiyeli, UCSF Chimera-1.17.3 ve AutoDockTools-1.5.6 yazılımları kullanılarak araştırılmıştır. Sonuçların görselleştirilerek kenetlenme mekanizmalarının aydınlatılmasında BIOVIA Discovery Studio yazılımı kullanılmıştır. Bu çalışmada protein data bank'tan alınan 5NN8 proteini ile kontrol bileşiği olan Orlistat ve Scutellarinin arasında gerçekleştirilen moleküler kenetlenme çalışması sonuçları; 5NN8 ile Orlistat arasındaki bağlanma skoru -6.0 kcal/mol olarak hesaplanırken 5NN8 ile Scutellarinin arasındaki bağlanma skoru ise -7.5 kcal/mol olarak hesaplanmıştır. Scutellarinin α-glukozidaz'a karşı inhibitör aktivitesi, standart inhibitör olan Orlistat ile karşılaştırılarak değerlendirildi. Moleküler kenetlenme çalışması ile bulunan Scutellarin bileşiğinin bağlanma skoru -7.5 kcal/mol ile Orlistat'tan -6.0 kcal/mol daha iyi olduğu gösterilmiştir. Ayrıca çalışılan bileşiklerin farmakolojik ve toksikolojik özellikleri, ilaç benzerliği ve ADMET analizi yardımıyla *in silico* olarak incelenmiştir. ADMET çalışması Scutelleranin'in toksik olmayan bir yapıya sahip olduğunu göstermiştir. Bu sonuçlar her ne kadar Scutellarinin obezite inhibitörü olma potansiyeli taşıyabileceğini göstersede yinede daha fazla *in vivo* ve *in vitro* çalışmaya ihtiyaç duyacağı açıktır.

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Abstract

The World Health Organisation (WHO) defines obesity as an abnormal or excessive accumulation of fat in the body that may impair health. It is stated that the most effective drugs recommended to treat obesity is orlistat. In this study, the binding potential of Scutellarin, a Plantago major flavonoid that may be an alternative to orlistat, to the 5NN8 PDB coded receptor was investigated *in silico* in order to shed light on new drug designs. The inhibition potential of Scutellarin and Orlistat compounds on α-glucosidase enzymes that enable rapid absorption of complex carbohydrates by converting them into glucose was investigated using UCSF Chimera-1.17.3 and AutoDockTools-1.5.6 software. BIOVIA Discovery Studio software was used to visualise

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the results and elucidate the docking mechanisms. In this study, the results of the molecular docking study performed between the 5NN8 protein obtained from the protein data bank and the control compounds Orlistat and Scutellarinin; the binding score between 5NN8 and Orlistat was calculated as -6.0 kcal/mol, while the binding score between 5NN8 and Scutellarinin was calculated as -7.5 kcal/mol. The inhibitory activity of Scutellarin against α-glucosidase was evaluated in comparison with the standard inhibitor Orlistat. It was shown that the binding score of Scutellarin compound found by molecular docking study was -7.5 kcal/mol, which is better than Orlistat -6.0 kcal/mol. In addition, the pharmacological and toxicological properties of the studied compounds were studied *in silico* with the help of drug-likeness and ADMET analysis. ADMET study showed that Scutelleranin has a non-toxic structure. Although these results show that Scutellarin may have the potential to be an obesity inhibitor, it is clear that further *in vivo* and *in vitro* studies will be needed.

1. INTRODUCTION

The World Health Organisation (WHO) defines obesity as an abnormal or excessive accumulation of fat in the body that may impair health (Blüher, 2019; Cho et al., 2021; Uğur et al., 2016). Obesity is increasing rapidly worldwide and has become a major health problem not only among adults but also among children and adolescents (Emerenziani et al., 2019). Factors such as industrialisation and urbanisation cause significant changes in people's lifestyles that may predispose them to obesity. In addition, factors such as abundance and cheapness of food, high fat and sugar content, increased consumption of ready-to-eat foods, fast eating habits and decreased physical activity also contribute to obesity (Uyar & Esim, 2018; Keleş, 2019). According to World Health Organisation data, obesity has been reported to be an important factor in the formation of chronic diseases such as diabetes, heart disease, chronic respiratory diseases, stroke and cancer (Boiko et al., 2021; Kuang et al., 2022). In recent years, increasing cardio-metabolic morbidity and mortality due to overweight and obesity has become a public health problem of global concern (Blüher, 2019; Kotsis et al., 2018; Ogunyemi et al., 2023). Therefore, the search for preventive measures and treatments to reduce the risk of obesity, hypertension, type 2 diabetes, hypercholesterolaemia, hyperlipidaemia and thrombosis is increasing (Alpcan & Durmaz, 2015). Methods such as diet and medical applications are frequently preferred for obesity. As a medical application, the most effective drug recommended by the American Food and Drug Administration (FDA) is orlistat (Qi, 2018; Tak & Lee, 2021). Orlistat inhibits the enzyme lipase produced in the pancreas and stomach, which helps break down triglycerides into fatty acids. This causes fat absorption to decrease by almost 30% (Uyar & Esim, 2018; Daneschvar et al., 2016; Koh et al., 2019). Targeted inhibition of pancreatic digestive enzymes is also reported to be useful in the

prevention of overweight and obesity (Lankatillake et al., 2021; Luo et al., 2019; Ogunyemi et al., 2023). Alpha-glycosidase and alpha-amylase are two specific pancreatic enzymes involved in the digestion of carbohydrates. These enzymes play a crucial role in catalysing the hydrolysis (breakdown) of complex carbohydrates into simpler sugars such as maltose and glucose (Ogunyemi et al., 2023). Alpha-glycosidase inhibitors are medicines used to manage blood glucose levels in diabetes (Ogunyemi et al., 2023). These alpha-glucosidase inhibitors slow down the activity of alpha-glucosidase enzymes in the small intestine. Thus, they delay the digestion and absorption of carbohydrates, especially complex carbohydrates, resulting in a slower rise in blood glucose levels after a meal (İzol & Yapici, 2023; Israili, 2011; Lankatillake et al., 2021). In addition, a-glucosidase inhibitors may effectively treat other clinical conditions associated with carbohydrate metabolism, such as obesity, hepatitis, cancer and hyperlipoproteinaemia (Hamedifar et al., 2023; Luo et al., 2019; Wang et al., 2020). Reducing diet-related hyperglycaemia is an important goal in the prevention of obesity and diabetes (Ogunyemi et al., 2023). In recent years, some anti-obesity drugs such as orlistat have been used to treat obesity; however, most of these drugs have been withdrawn from the market due to serious cardiovascular-related side effects (Tak & Lee, 2021). Therefore, pharmacotherapy for the prevention and treatment of obesity is gaining more and more attention in Turkey as well as all over the world (Ince et al., 2020; Newman & Cragg, 2016; Noor et al., 2019). Scutellarin, a natural flavonoid, is a constituent of the nervine plant (*Plantago major*) (Zhakipbekov et al., 2023). In a study on the reactivity of *Plantago major* flavonoids by Density Functional Theory (DFT) method, it was stated that Scutellarin was the most reactive of the flavonoid compounds (Bayrakdar & Keleş, 2024; Kitadokoro et al., 2020). Molecular docking studies are an approach used in bioinformatics that allows the study of protein-ligand interactions at the atomic level. This approach plays a key role in the process of identifying potential targets in the active sites of proteins and understanding the mechanism of action (Van et al., 2022). Ligands can bind to proteins by differentiated types of radiation. This binding process is defined by the binding affinity, which determines the interaction strength of the ligand with the protein (Sivashanmugam et al., 2013; Vardhan & Sahoo, 2020).

The oral use of drug designs in living organisms and their bioactivities on living organisms are analysed using ADMET (Absorption, Distribution, Metabolism, Elimination and Toxicological) parameters performed *in silico*. These studies provide important information on

the efficacy and safety of a drug by examining factors such as how a drug is absorbed, metabolised, distributed in circulation and excreted in the body. This information is critical for the selection, design and optimisation of potential drug candidates in the drug development process. Therefore, ADMET studies are an important part of the drug discovery and development process. In this study, the binding potential of Scutellarin, a Plantago major flavonoid that may be an alternative to Orlistat, to the 5NN8 PDB coded receptor was investigated *in silico* to shed light on new drug designs with drug-likeness properties and ADMET analysis.

2. MATERIAL VE METOD

2.1. Molecular Docking Study

In this study, the inhibitory activity of Scutellarin against α-glucosidase was evaluated *in silico* in comparison with the standard inhibitor Orlistat. The inhibition potential of Scutellarin and Orlistat compounds against α-glucosidase enzymes, which enable the rapid absorption of complex carbohydrates into glucose, was investigated by molecular docking study using UCSF Chimera-1.17.3 and AutoDockTools-1.5.6 software (Pettersen et al., 2004). BIOVIA Discovery Studio software was used to visualise the results and elucidate the docking mechanisms. The molecular structures of Orlistat and Scutellarin used in the study were obtained from pubchem. On the other hand, the human lysosomal acid-alpha-glucosidase enzyme, 5NN8 pdb coded receptor, which will be used in the molecular docking study, was taken from the protein data bank. Prior to the molecular docking study, the standard procedure used in our previous studies for the preparation of proteins and compounds was applied (Bayrakdar et al., 2024; Cengiz et al., 2023).

2.2. Drug-Likeness and ADMET Analysis

It is important in terms of time and cost to evaluate the physicochemical properties of new candidates to predict whether they can be used as drugs. There are many criteria known in the literature on this subject. One of the most well-known of these criteria is the criteria proposed by Lipinski. Lipinski stated that for drug-likeness, the molecular weight, total solubility, hydrogen bond acceptor and donor number values of the compounds should comply with the limitations of <500 Da, ≤10 and ≤5, respectively (Lipinski et al., 1997). In this study, the evaluation of drug-likeness properties was carried out with the help of the open

access SwissADME web tool. In addition, ADMET analysis, which covers a series of studies including the evaluation of further pharmacokinetic (ADME) and toxicological (T) properties about the drug candidate compound, was performed with the help of open access pkCSM web tools.

3. RESULTS AND DISCUSSION

Nowadays, theoretical approaches emerging as a result of multidisciplinary studies are frequently used in order to provide insights into clinical studies, which can be quite costly. Molecular docking study is one of the theoretical tools used to elucidate the interaction mechanisms between proteins and compounds.

3.1. Molecular Docking Study

In this study, 2D and 3D structures of the docking mechanisms resulting from the molecular docking study between the 5NN8 protein obtained from the protein data bank and the control compounds Orlistat and Scutellarinin are given in Figures 1 and 2, respectively. In addition, detailed information about the interaction mechanisms is presented in Table 1.

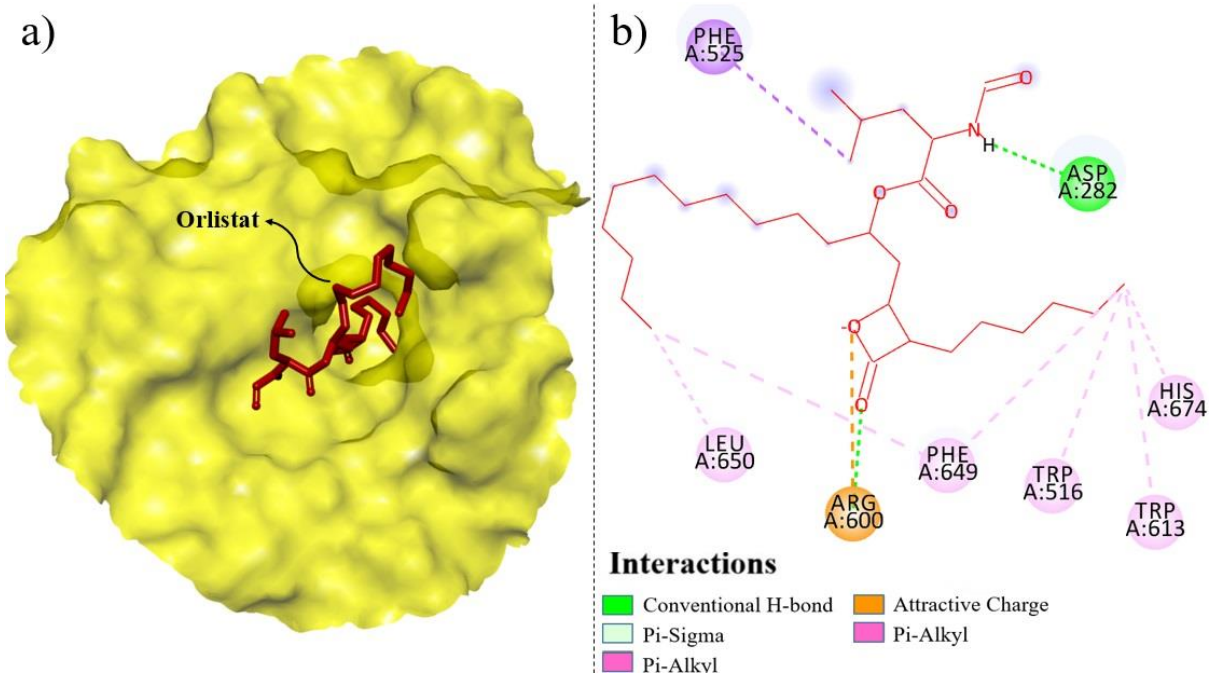

Figure 1. Molecular docking mechanism between 5NN8 and Orlistat, a)3D and b)2D interactions

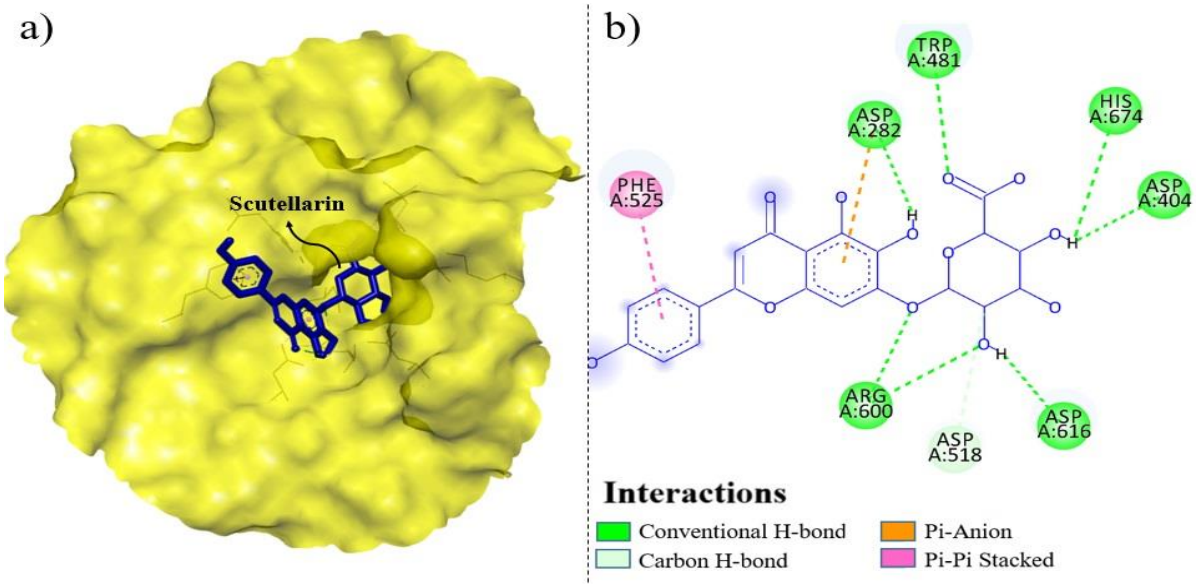

Figure 2. Mechanism of molecular docking between 5NN8 and Scutellarinin, a)3D and b)2D interactions

In the molecular docking study, the binding score between 5NN8 and Orlistat was calculated as -6.0 kcal/mol, while the binding score between 5NN8 and Scutellarinin was calculated as -7.5 kcal/mol. The most important active residues for 5NN8 receptor are Asp282, Trp376, Asp404, Leu405, Ile441, Asp443, Trp481, Trp516, Asp518, Met519, Phe525, Arg600, Trp613, Gly615, Asp616, Asp645, Phe649, Arg672 and His674 amino acids. (Abdullah et al., 2024).

Table 1. Summarative results of molecular docking of Orlistat and Scutellarin with the 5NN8 receptor.

Compounds	ΔG (kcal/mol)	Hydrogen Bond interactions (Å)	Hydrophobic interaction (Å)	Electrostatic interaction (Å)
Orlistat	-6.0	**Conventional H-Bond** Asp282(2.06), Arg600(2.82)	**Pi-Sigma** Phe525(3.95) **Alkyl** Leu650(5.48) **Pi-Alkyl** Trp613(5.31-5.12), Phe649(4.9-4.39), Trp516(5.09), His674(4.56)	**Attractive Charge** Arg600(3.99)
Scutellarin	-7.5	**Conventional H-Bond** Asp616(1.89), Asp404(2.55), His674(2.85), Asp282(1.97), Trp481(2.79, Arg600(2.8-3.2) **Carbon H-Bond** Asp518(3.1)	**Pi-Pi T-stacked** Phe525(3.91)	**Pi-Anion** Asp282(3.61)

The 3D docking mechanisms shown in **Figures 1a** and **2a** clearly show that both compounds dock to the same active site of the 5NN8 protein. The 2D visualisation of the

interaction mechanism given in Figure 1b clearly reveals that Orlistat binds to the active site by interacting with Asp282, Trp516, Phe525, Arg600, Trp613, Phe649, Leu650 and His 674 residues. On the other hand, the 2D visualisation of the interaction mechanism given in Figure 2b shows that Scutellarin binds to the active site by interacting with Asp282, Asp404, Trp481, Asp518, Phe525, Arg600, Asp616 and His 674 residues. The types of interactions of the compounds with residues in the active site of 5NN8 are summarised in **Table 1.**

3.2. Drug-Likeness and ADMET Analysis

The drug-likeness properties of the Scutellarin compound are evaluated according to the criteria known as Lipinski's rule of five and are given in **Table 2**. **Table 2** clearly showed that the number of hydrogen bond acceptors and hydrogen bond donors of Scutellarin compound were 12 and 7, respectively. The drug-likeness study showed that Scutellarin violated the Lipinski criteria twice. When many FDA-approved drugs were evaluated according to the Lipinski criteria, it was reported that although it exceeded the standard molecular weight, hydrogen bond donors and hydrogen bond acceptors values, it did not have dramatic effects on the transport and diffusion of the drug compound (Mullard, 2018). Therefore, the biological activity and therapeutic potential of this compound should be evaluated together with other factors.

Table 2. Drug-likeness properties of Scutellarine

Lipinski's criteria	**Accepted range**	**Value**	**result**
Molecular Weight (Da)	≤500	462.36	✓
H-bond donors	≤5	7	x
H-bond acceptors	≤10	12	x
LogP	≤5	0.99	✓

ADMET predictions for the pharmacological properties of Scutellarin and Orlistat compounds, including blood-brain barrier (BBB) penetration, CNS permeability, AMES toxicity, and intestinal absorption, were performed using pkCSM web tools and are presented in **Table 3**. The parameter of human intestinal absorption indicates the rate of absorption of orally administered drugs through the small intestine. A value of absorption greater than 30% is considered indicative of good absorption for molecules (Pires et al., 2015). As shown in **Table 3**, Scutellarin (18.658%) has a lower absorption compared to the control compound Orlistat (90.315%). Skin permeability parameter is considered good for logKp values greater than -2.5

(Pires et al., 2015). As shown in **Table 3**, the logKp values of Scutellarin (-2.735) and Orlistat (-2.714) compounds demonstrate their possession of good the skin permeability. The parameter VDss is a measure of the distribution of drugs in the body. A value of log VDss > 0.45 indicates a high volume of distribution, which means that there is good distribution from the plasma towards the tissues, and log VDss < -0.15 indicates that the distribution is not good. The VDss estimates given in Table 3 indicated that the compounds did not have a good distribution, however Scutellarinin was better than Orlistat. The fact that the drug compounds do not have any toxicity or mutagenic effects is evident from the estimates of AMES toxicity values in **Table 3**. The metabolism estimates for the compounds were calculated by ADMET study and given in **Table 3**. The hepatotoxicity parameter refers to the damage that compounds entering the body can cause in the liver (Gombar & Hall 2013). In the ADMET study conducted, it was estimated that Scutellarin would not cause liver damage, while Orlistat was estimated to be likely to cause damage.

Table 3. ADMET analysis results for the compounds.

	Compounds	
	Scutellarin	**Orlistat**
Absorption		
Human intestinal absorption (HIA+, %)	18.658	90.315
Skin Permeability (log *K*p)	-2.735	-2.714
Distribution		
VDss (human) (log L/kg)	-0.121	-0.59
BBB permeability (log BB)	-1.925	-1.013
CNS permeability (log PS)	-4.802	-3.131
Metabolism		
CYP2D6 substrate	No	No
CYP3A4 substrate	No	Yes
CYP1A2 inhibitior	No	No
CYP2C19 inhibitior	No	No
CYP2C9 inhibitior	No	No
CYP2D6 inhibitior	No	No
CYP3A4 inhibitior	No	No
Excretion		
Total Clearance (log ml/min/kg)	0.762	1.679
Toxicity		
AMES toxicity	No	No
Hepatotoxicity	No	Yes

Clearance parameter, which expresses the rate at which drug molecules are excreted from the body, is measured by the proportionality constant CLtot. Clearance values less than 5 mL/min/kg are considered slow excretion (Pires et al., 2015; Sarkar, Alheety & Srivastava 2023) the clearance parameters in **Table 3** show that the compounds are not immediately eliminated from the body. The parameter logBB is employed in predicting the behavior of drug compounds when they encounter the blood-brain barrier (BBB). A logBB value less than -1 indicates poor penetration ability into the BBB (Pires et al., 2015). The logBB predictions have indicated that both compounds have low penetration abilities. The parameter logPS represents the ability of compounds to penetrate the Central Nervous System (CNS). A logPS value greater than -2 predicts potential penetration into the CNS, while a logPS value less than -3 suggests inability to penetrate (Pires et al., 2015). The values provided in Table Y, namely -4.802 (Scutellarin) and -3.131 (Orlistat), indicate a low potential for CNS penetration.

4. CONCLUSIONS

In this study, the inhibition effect of Scutellarin compound on obesity was investigated by molecular docking study. The inhibitory activity of Scutellarin against α-glucosidase was evaluated in comparison with the standard inhibitor Orlistat. The binding score of Scutellarin compound found by molecular docking study was -7.5 kcal/mol, which was better than Orlistat (-6.0 kcal/mol). At the same time, the molecular docking study showed that both compounds interacted with almost identical active amino acid residues by travelling to the same binding pocket on the protein. Drug-likeness and ADMET analyses performed *in silico* for Scutelleranin revealed that Scutelleranin exhibited mediocre behaviour. Therefore, these results suggest that Scutelleranin requires additional *in vitro* and *in vivo* studies before it can be used in the development of medicinal products

Conflict of Interest

There is no conflict of interest among the article authors.

REFERENCES

Abdullah, S., Iqbal, A., Ashok, A. K., Kaouche, F. C., Aslam, M., Hussain, S., . . . Ashraf, M. (2024). Anti-enzymatic and DNA docking studies of montelukast: A multifaceted molecular scaffold with *in vitro* investigations, molecular expression analysis and molecular dynamics simulations. *Heliyon, 10*(2).

Bayrakdar, A, . & Keleş, İ. (2024, 12-13 March 2024). *Investigation of Chemical Reactivity of Plantago Major Flavonoids by HOMO-LUMO Molecular Orbital Analysis Method.* Paper presented at the 4th International Conference on Innovative Academic Studies, Konya, Turkey.

Alpcan, A., & Durmaz, Ş. A. (2015). Çağımızın dev sorunu: çocukluk çağı obezitesi. *Turkish Journal of Clinics and Laboratory, 6*(1), 30-38.

Bayrakdar, A., Magudeeswaran, S., Manivannan, P., & Bangaru, S. (2024). Spectroscopic, DFT investigation and active site analysis of 2, 2-diphenyl-1, 3-propanediol against estrogen receptor EPR gamma. *Research on Chemical Intermediates*, 1-20.

Blüher, M. (2019). Obesity: global epidemiology and pathogenesis. *Nature Reviews Endocrinology, 15*(5), 288-298.

Boiko, A. S., Pozhidaev, I. V., Paderina, D. Z., Bocharova, A. V., Mednova, I. A., Fedorenko, O. Y., . . . Bokhan, N. A. (2021). Search for possible associations of fto gene polymorphic variants with metabolic syndrome, obesity and body mass index in schizophrenia patients. *Pharmacogenomics and personalized medicine*, 1123-1131.

Cengiz, M., Gür, B., Sezer, C. V., Cengiz, B. P., Gür, F., Bayrakdar, A., & Ayhancı, A. (2023). Alternations in interleukin-1β and nuclear factor kappa beta activity (NF-kB) in rat liver due to the co-exposure of Cadmium and Arsenic: Protective role of curcumin. *Environmental Toxicology and Pharmacology, 102*, 104218.

Cho, H.-W., Chung, W., Moon, S., Ryu, O.-H., Kim, M. K., & Kang, J. G. (2021). Effect of sarcopenia and body shape on cardiovascular disease according to obesity phenotypes. *Diabetes & metabolism journal, 45*(2), 209.

Daneschvar, H. L., Aronson, M. D., & Smetana, G. W. (2016). FDA-approved anti-obesity drugs in the United States. *The American journal of medicine, 129*(8), 879. e871-879. e876.

Emerenziani, S., Pier Luca Guarino, M., Trillo Asensio, L. M., Altomare, A., Ribolsi, M., Balestrieri, P., & Cicala, M. (2019). Role of overweight and obesity in gastrointestinal disease. *Nutrients, 12*(1), 111.

Hamedifar, H., Mohammadi-Khanaposhtani, M., Sherafati, M., Noori, M., Moazam, A., Hosseini, S., . . . Erdogan, M. K. (2023). Design, synthesis, α-glucosidase inhibition, pharmacokinetic, and cytotoxic studies of new indole-carbohydrazide-phenoxy-N-phenylacetamide derivatives. *Archiv der Pharmazie, 356*(6), 2200571.

Gombar, V. K., & Hall, S. D. (2013). Quantitative structure–activity relationship models of clinical pharmacokinetics: clearance and volume of distribution. *Journal of chemical information and modeling*, 53(4), 948-957.

Ince, N., Kaya, Ş., Yıldız, İ. E., Parlak, E., & Bayar, B. (2020). Use of complementary and alternative medicine in patients with chronic viral hepatitis in Turkey. *Complementary therapies in medicine, 48*, 102229.

Israili, Z. H. (2011). Advances in the treatment of type 2 diabetes mellitus. *American journal of therapeutics, 18*(2), 117-152.

İzol, E., & Yapici, İ. (2023, October 2023). EFFECT of α-GLUCOSIDASE and α-AMYLASE ENZYMES on DIABETES. Paper presented at the 6. Internatıonal Marmara Scıentıfıc Research And Innovatıon Congress, İstanbul-Turkey.

Keleş, İ. (2019). *Ratlarda yüksek yağlı diyet ile indüklenen obezite oluşumu üzerine silymarin'in engelleyici etkisinin histopatolojik ve biyokimyasal olarak araştırılması.* (Tüksek Lisans), Van Yüzüncü Yıl Üniversitesi, Van-Türkiye.

Kitadokoro, K., Tanaka, M., Hikima, T., Okuno, Y., Yamamoto, M., & Kamitani, S. (2020). Crystal structure of pathogenic Staphylococcus aureus lipase complex with the anti-obesity drug orlistat. *Scientific reports, 10*(1), 5469.

Koh, Y.-M., Jang, S.-W., & Ahn, T.-W. (2019). Anti-obesity effect of Yangkyuksanwha-tang in high-fat diet-induced obese mice. *BMC complementary and alternative medicine, 19*, 1-12.

Kotsis, V., Tsioufis, K., Antza, C., Seravalle, G., Coca, A., Sierra, C., . . . Redon, J. (2018). Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part B: obesity-induced cardiovascular disease, early prevention strategies and future research directions. *Journal of hypertension, 36*(7), 1441-1455.

Kuang, M., Sheng, G., Hu, C., Lu, S., Peng, N., & Zou, Y. (2022). The value of combining the simple anthropometric obesity parameters, Body Mass Index (BMI) and a Body Shape Index (ABSI), to assess the risk of non-alcoholic fatty liver disease. *Lipids in health and disease, 21*(1), 104.

Lankatillake, C., Luo, S., Flavel, M., Lenon, G. B., Gill, H., Huynh, T., & Dias, D. A. (2021). Screening natural product extracts for potential enzyme inhibitors: Protocols, and the standardisation of the usage of blanks in α-amylase, α-glucosidase and lipase assays. *Plant Methods, 17*, 1-19.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews*, 23(1-3), 3-25.

Luo, S., Gill, H., Dias, D. A., Li, M., Hung, A., Nguyen, L. T., & Lenon, G. B. (2019). The inhibitory effects of an eight-herb formula (RCM-107) on pancreatic lipase: enzymatic, HPTLC profiling and *in silico* approaches. *Heliyon, 5*(9).

Mullard, A. (2018). Re-assessing the rule of 5, two decades on. Nature reviews. *Drug discovery*, 17(11), 777.

Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. *Journal of natural products, 79*(3), 629-661.

Noor, Z. I., Ahmed, D., Rehman, H. M., Qamar, M. T., Froeyen, M., Ahmad, S., & Mirza, M. U. (2019). *In vitro* antidiabetic, anti-obesity and antioxidant analysis of Ocimum basilicum aerial biomass and *in silico* molecular docking simulations with alpha-amylase and lipase enzymes. *Biology, 8*(4), 92.

Ogunyemi, O. M., Gyebi, G. A., Ibrahim, I. M., Esan, A. M., Olaiya, C. O., Soliman, M. M., & Batiha, G. E.-S. (2023). Identification of promising multi-targeting inhibitors of obesity from Vernonia amygdalina through computational analysis. *Molecular Diversity, 27*(1), 1-25.

Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera—a visualization system for exploratory research and analysis. *Journal of computational chemistry, 25*(13), 1605-1612.

Pires, D. E., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of medicinal chemistry*, 58(9), 4066-4072.

Qi, X. (2018). *Review of the clinical effect of orlistat.* Paper presented at the IOP Conference Series: Materials Science and Engineering.

Sarkar, P., Alheety, M. A., & Srivastava, V. (2023, February). Molecular Docking and ADMET Study of Spice-Derived Potential Phytochemicals against Human DNA Topoisomerase III Alpha. *In Macromolecular Symposia* (Vol. 407, No. 1, p. 2200108).

Sivashanmugam, T., Muthukrishnan, S., Umamaheswari, M., Asokkumar, K., Subhadradevi, V., Jagannath, P., & Madeswaran, A. (2013). Discovery of potential cholesterol esterase inhibitors using *in silico* docking studies. *||| Bangladesh Journal of Pharmacology, 8*(3), 223-229.

Tak, Y. J., & Lee, S. Y. (2021). Anti-obesity drugs: long-term efficacy and safety: an updated review. *The world journal of men's health, 39*(2), 208.

Uğur, K., Şener, Y. S., & Özkan, Y. (2016). Obezitenin Tanımı, Epidemiyolojisi ve Klinik Önemi. *Türkiye Klinikleri Kozmetik Dermatoloji Özel Dergisi, 9*(2).

Uyar , A., & Esim, E. (2018). Yüksek Yağlı Diyet ile Beslenen Ratlarda Mate (Ilex paraguariensis) Çayının Obeziteyi Önleyici Etkisinin Histopatolojik ve Biyokimyasal Olarak Araştırılması. *Harran Üniversitesi Veteriner Fakültesi Dergisi, 7*(2), 154-161.

Van, L. V., Pham, E. C., Nguyen, C. V., Duong, N. T. N., Le Thi, T. V., & Truong, T. N. (2022). *In vitro* and *in vivo* antidiabetic activity, isolation of flavonoids, and *in silico* molecular docking of stem extract of Merremia tridentata (L.). *Biomedicine & Pharmacotherapy, 146*, 112611.

Vardhan, S., & Sahoo, S. K. (2020). *In silico* ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19. *Computers in biology and medicine, 124*, 103936.

Wang, J., Lu, S., Sheng, R., Fan, J., Wu, W., & Guo, R. (2020). Structure-activity relationships of natural and synthetic indole-derived scaffolds as α-glucosidase inhibitors: a mini-review. *Mini Reviews in Medicinal Chemistry, 20*(17), 1791-1818.

Zhakipbekov, K., Turgumbayeva, A., Issayeva, R., Kipchakbayeva, A., Kadyrbayeva, G., Tleubayeva, M., . . . Serikbayeva, E. (2023). Antimicrobial and Other Biomedical Properties of Extracts from Plantago major, Plantaginaceae. *Pharmaceuticals, 16*(8), 1092.