Research Article
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In-silico and toxicology assessment on anti-obesity effects of cinnamon spice use in animal products for the development of functional foods

Abstract

Obesity is a complex, chronic disease that requires a multifaceted approach. This research focuses on evaluating the anti-obesity efficacy and potential toxicity of natural compounds and approved drugs through computational docking and LD50 analysis. The study included 20 compounds, such as phentermine and topiramate, as well as flavonoids, phenolic acids, and other natural substances, prepared for molecular docking using the Ligprep module. The PDB ID 6C9F crystal structures related to obesity were obtained for docking using Glide in Schrödinger Suite 2023. The ADMET properties were predicted using SwissADME and ProTox-II servers. Docking scores ranged from -9.809 to -3.561, with flavonoids like isoquercetin, rutin, astragalin, quercetin, and kaempferol showing the strongest binding affinities. LD50 values spanned from 28 mg/kg for benzaldehyde to 5000 mg/kg for several flavonoids and phenolic acids. Phentermine fell into toxicity class 3, while topiramate was class 5. Flavonoids, which exhibited strong docking scores, tended to have lower toxicity classes. Molecular docking revealed key interactions, with phentermine and topiramate binding to GLU 102, and flavonoids interacting with multiple amino acids, such as GLU 102, ASN 146, and LYS 47. ADME analysis showed that phentermine had the lowest molecular weight (149.23 g/mol) and high GI absorption, whereas flavonoids had higher molecular weights (286.24 to 610.52 g/mol) and lower GI absorption. Only phentermine crossed the blood-brain barrier (BBB). Phentermine had fewer drug-likeness violations and alerts for PAINS and Brenk compared to flavonoids, indicating better drug-likeness and ease of synthesis (synthetic accessibility score of 1). However, compounds like phentermine, benzyl benzoate, and coumarin showed higher toxicity and neurotoxic potential, with risks for neurological disorders, carcinogenicity, and ecotoxicity. Flavonoids like quercetin, kaempferol, and caffeic acid demonstrated safer profiles, suggesting potential applications in medicine and nutrition.

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Introduction

Obesity defined by the World Health Organization (WHO) as a condition characterized by inordinate accumulation of body fat and as a public health problem that leads to serious social, physical, and psychological problems. The body mass index (BMI) of 30 kg/m2 is the cut-off point for obesity, which have associated with increased risk for chronic diseases, morbidity, and mortality.[1] According to European studies, a growing health problem includes child obesity, especially in countries around the Mediterranean Sea that have shown very high rates of overweight and obesity. Surveys in Greece have noted that child obesity levels are the highest in Europe.[2] Although food portion control is very important issue for weight management, the exhortation of people to eat less of all foods may not lead to desirably results, given the fact that the high-energy-dense foods disproportionately increase energy intake in comparison with those with lower content in energy density. A more adequate strategy might be the encouragement of people increasing the consumption of low-energy-dense foods and limiting the consumption of high-energy-dense foods, in parallel with following a balanced diet, such as the Mediterranean diet, in combination with increase of physical activity.[3]

Obesity is a metabolic disease, which has become a problem of epidemic spread at European and global level and is related with other chronic degenerative or inflammatory diseases and metabolic consequences.[4] Increased food consumption, decreased physical activity, positive energy balance, and food addiction are parameters that may lead to increased obesity levels globally. The often consumption of foods that are of high content in sugar and fat, in combination with strong cravings or compulsions, is characterized as food addiction.[5,6] The strategies for weight control management and obesity prevention or treatment include increase of energy expenditure and following of a balanced diet in order to achieve negative energy balance. In recent years, it has been observed that an increase in efforts has been made for finding and applying alternative ways to prevent obesity, in order to decrease the impact and the cost of its metabolic consequences. The scientific community, based mainly on clinical and epidemiological studies, highlights the importance and the possible health effects of certain foods, so-called functional foods. The incorporation into a diet of several natural or processed foods with possible health effects, such as functional foods, may contribute to the weight management, if they are combined with the following of a balanced diet.[4,7] In recent study, with 300 healthy volunteers, the authors noticed a decreased BMI in those who often consumed gojiberry, cranberry, and pomegranate in contrast to those who had never consumed these functional foods.[4] In addition, scientific data support that the consumption of specific functional foods and bioactive compounds, such as b-glucane, glucomanane, foods with reduced fat and sugar content, etc., may contribute to weight management and metabolic consequences in obese people and could be part of a balanced diet for obesity management or treatment. However, the scientific data underline that these specific

functional foods and bioactive compounds cannot contribute to weight control if consumed unilaterally and in large quantities. Obesity is characterized by increased body and fat mass, hormonal disturbances, food intake (eating pattern), and genetic factors.[1] Obesity is a significant contributor to the global burden of several chronic diseases such as diabetes mellitus type 2, cardiovascular diseases, asthma, etc., which affect the human body. It has been proclaimed a global pandemic with a death rate of approximately 2.8 million people annually.[2,3] Since fat is present all over the body, it is not possible to measure it directly. Therefore, body mass index (BMI) is used to observe the relationship between weight and height. Whereas waist circumference, waist/hip ratio, skinfold thickness, and bioimpedance help to assess obesity and overweight.[8] Suppose the BMI of the person lies in the range of overweight, the chances of getting affected by other diseases such as diabetes mellitus type 2, hypertension, cardiovascular diseases, gallstones, etc., increase. For obesity class 1, the chances are moderate, while in the case of obesity class 2, the chances are severe. In the case of extreme obesity, the chances are very high, particularly if the person is affected by other obesity-related diseases.[9] According to the survey performed by the Organisation for Economic Co-operation and Development (OECD) in 2017, the United States of America is ranked first, followed by China and India in obesity. From 1999 to 2000 and 2015 to 2016, there has been a remarkable increase in obesity. In 2016, the World Health Organization (WHO) reported that over 1.9 billion adults who were either 18 years old or above were overweight, and among these 1.9 billion, 650 million were suffering from obesity.[2] According to a survey, 25 million people die annually because of obesity or being overweight.[5]

According to another study by WHO (World Health Organization) in 2019, 38.2 million children under the age of 5 were either suffering from obesity or overweight.[6] Even in India, the prevalence of obesity varies from urban to rural and state-wise. It was reported that the prevalence of obesity in males was higher in urban areas (37.5%) compared to rural areas (20.78%).[10] Some of the states of India affected by obesity are Jharkhand, Kerala, Pondicherry, Chhattisgarh, Madhya Pradesh, Bihar, and Andhra Pradesh.[10,11] The vital factor that plays a headway role in the case of obesity is the person's lifestyle and eating habits.[11] Most food items with high fat and sugar are responsible for increasing body weight, and such food materials have low micronutrients.[12,13] Consumption of excessive refined grains, junk foods, and soft drinks can lead to a big waist: hip ratio, and the person's fat mass also increases (Nohara *et al.,* 2019). Molecular docking is a computational method used to predict the interaction of two molecules generating a binding model. In many drug discovery applications, docking is done between a small molecule and macromolecule for example, protein-ligand docking.[14] More recently, docking is also applied to predict the binding mode between two macromolecules, for instance protein-protein docking. Currently, molecular mechanics is the basis for most docking programs. Molecular mechanics involves the description of a polyatomic system using classical physics. Experimental parameters such as charges, torsional and geometrical angles are used to narrow down the difference between experimental data and molecular mechanics predictions.[15] Due to shortcomings and limitations of experimental parameters, mathematical equations may often be parametrized on the basis of quantum-mechanical semiempirical and ab initio theoretical calculations.

As such, molecular force fields are sets of equations with different parameters with the final purpose of describing the systems. As force fields may use different considerations and simplifications, the description of the system may be inaccurate due to the level of theory involved (classical physics). Most force fields rely on five terms, all of which have a physical interpretation: potential energy, torsional terms, bond geometry, electrostatic terms, and Lenard-Jones potential.[16] Examples of prominent force fields are AMBER, GROMOS, MMFF94, CHARMM, and UFF. An indepth discussion on force fields and their limitations is beyond the scope of this review but the following references provide for further reading.[15] With the use of force fields, molecular and protein modeling was accomplished in the early 1980s. A natural extension of these methods was the modeling of molecular processes such as protein-ligand binding. Two general methodologies were developed. First, the rigid body approach that is closely related to the classic model of Emil Fischer. In this model, the ligand and receptor are regarded as two independent bodies that recognize each other based on shape and volume. The second approach is flexible docking. This approach considers a reciprocal effect of protein-ligand recognition on the conformation of each part.[17] The main aim of this study is to evaluate cinnamon spices in the development of functional foods against obesity disease.

Materials and methods

Experimental site

This research was carried out at the Animal Products Unit Laboratory of the Department of Animal Production, Faculty of Agriculture, University of Jos.

Ligand preparation

The Ligprep module Schrödinger Suite 2023 was accustomed to prepare a total of 22 phytocompounds of cinnamon identified from ethnobotanical databases for molecular docking. The 3D structures were created on low energy with the proper chiralities. At a physiological pH of 7.2± 0.2, the possible ionization states for every ligand structure were generated. Each ligand's stereoisomers were calculated by keeping certain chiralities constant while varying others. The canonical SMILES of compounds were converted to PDB format using Schrödinger Suite 2023 while the structure data file (SDF) format of standard ligands cinnamon was obtained from PubChem database. The SDF format of compounds and standard ligands were uploaded to Schrödinger Suite 2023 worksheet. The output files were minimized to obtain the minimum energy for the ligand docking.

Protein preparation

The crystal structures of the obesity were obtained from the RCSB protein data bank (PDB) with PDB ID of 6C9F method: X-RAY diffraction, with a resolution of 2.59 Å, R-Value free 0.245, R-Value work 0.228 and R-Value observed 0.229. The PDB format of the structures were uploaded to Schrödinger Suite 2023 workspace and the non-standard residues including ions, water and bounded ligands were first removed.

Receptor grid generation

For ligand docking, receptor grid generation allows determining the position and size of the protein's active region. Using the receptor grid construction tool in Schrödinger Maestro 13.5, the scoring grid was defined supported by the co-crystalized ligand GK.

Molecular docking

Molecular docking of the prepared ligands and proteins were performed using the glide ligand docking in Schrödinger Suite

2023. The target proteins were loaded into receptor grid generation in Schrödinger Suite 2023, The standard inhibitors and the test compounds were imported. The grid box was set as follows: Grid box center X : 29.46, Y: -6.63 and Z: -29.62 and grid dimensions(angstrom) X : 21.79, Y: 21.79, Z: 21.79 were set for 6C9F. The docking scores were obtained from the project table on Schrödinger Suite 2023. The 3D and 2D views of the molecular interactions were generated using ligand interaction on Schrödinger Suite 2023. Protein-Ligand Docking. Only the ligands that bind at the same site with the standard inhibitor were selected as the potential inhibitors. Protein–ligand interactions were visualized using the Schrödinger Suite 2023 to further understand the amino acid and the kinds of bonds interacting in the binding sites

Binding free energy calculation

The Prime Molecular Mechanics-Generalized Born area MM-GBSA tool (Schrödinger suite version 2020–3) was accustomed to determine the steadiness of protein-ligand complexes according to their binding free energy. The ligands were prepared beforehand using ligprep, and therefore the relevant proteins were prepared using the protein preparation wizard, as detailed previously. Sitemap anticipated the active sites of the proteins. Glide standard precision (SP) docking was then accustomed to dock the chemicals with proteins. The MM-GBSA technology offered with Prime was utilized to work out binding free energy for ligand-protein complexes utilizing the Prime MM-GBSA panel. The OPLS_2005 physical phenomenon was chosen, and therefore the continuum solvent model was VSGB. The default settings for the opposite options were selected.

ADMET Predictions

The absorption, distribution, metabolism, excretion and toxicity (ADMET) properties (lipophilicity (log Po/w), water solubility (log S), drug likeness, bioavailability score, pharmacokinetics and toxicity profile) of the test compounds were determined using in silico integrative model predictions at the SwissADME and ProTox-II online servers. Lipophilicity was measured using the partition coefficient between n-octanol and water (log Po/w) according to XLOGP, WLOGP, MLOGP, iLOGP and SILICOS-IT predictive models. The arithmetic mean of the values predicted by the five models is the consensus log P. Water solubility was estimated as the logarithm of the molar solubility in water (log S) using the SILICOS-IT predictive model. Drug likeness was according to the rule-based filters namely Lipinski and Verber. Pharmacokinetic properties predicted include: skin permeation, gastrointestinal (GI) absorption permeation, blood brain (BBB) permeation, substrate and inhibitor of permeability glycoprotein (P-gp) and cytochrome p450 (CYP) respectively. Toxicity properties considered are: Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity, Cytotoxicity and Heat Shock Factor Response Element (HSE).

Results

Docking score, LD50 and toxicity class

Table 1 shows the docking scores, LD50, and toxicity classes. Phentermine has a docking score of -5.546, LD50 of 160 mg/kg, and is moderately toxic (class 3). Topiramate, with a score of -3.561 and LD50 of 4000 mg/kg, is in class 5. Isoquercetin (-9.809) and Rutin (-9.683) have LD50s of 5000 mg/kg, placing them in class 5. Astragalin (-9.638), Quercetin (-9.057), and Kaempferol (-8.497) vary in toxicity, with Quercetin moderately toxic (159 mg/kg, class 3) and the others in class 5. Neochlorogenic Acid (-7.205), Coumarin (-7.099), and Benzyl Benzoate (-7.059) show varying toxicity, with Coumarin moderately toxic (196 mg/kg, class 3) and the others in classes 4 or 5. Benzaldehyde (-6.799) is highly toxic (LD50 28 mg/kg, class 2), while Eugenol (-6.260), Alpha-Terpineol (-6.220), Benzoic Acid (-6.200), and Coniferaldehyde (-6.188) range from moderate (class 3) to slight toxicity. Cinnamyl Acetate (-6.098), Cinnamyl Alcohol (-5.486), Caffeic Acid (-5.048), p-Coumaric Acid (-4.818), and Cinnamic Acid (-4.536) are all low toxicity (class 5) (Table 1).

Table 1 Compound cid and docking score

Ligand	Compound ID	Docking score	LD50 (mg/kg)	Toxicity class
Phentermine	4771	-5.546	160	3
Topiramate	5284627	-3.561	4000	5
Isoquercetin	5280804	-9.809	5000	5
Rutin	5280805	-9.683	5000	5
Astragalin	5282102	-9.638	5000	5
Quercetin	5280343	-9.057	159	3
Kaempferol	5280863	-8.497	3919	5
Neochlorogenic acid	5280633	-7.205	5000	5
Coumarin	323	-7.099	196	3
Benzyl Benzoate	2345	-7.059	1000	4
Benzaldehyde	240	-6.799	28	2
Eugenol	3314	-6.260	1930	4
alpha-TERPINEOL	17100	-6.220	2830	5
Benzoic Acid	243	-6.200	290	3
Coniferaldehyde	5280536	-6.188	1560	4
Cinnamyl acetate	5282110	-6.098	3300	5
Cinnamyl Alcohol	5315892	-5.486	2000	4
Caffeic Acid	689043	-5.048	2980	5
p-coumaric acid	637542	-4.818	2850	5
Cinnamic Acid	444539	-4.536	2500	5

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The interaction between ligands and amino acid

Table 2 shows the ligand-amino acid interactions and their effects on charge. Phentermine and Topiramate form salt bridges with GLU 102, creating a negative charge. Isoquercetin and Rutin interact with several amino acids, resulting in complex charge distributions. Astragalin and Kaempferol contribute to negative charges through different amino acid interactions. Quercetin and Neochlorogenic acid show a mix of charges and hydrophobic interactions, while Coumarin and derivatives mainly interact hydrophobically with VAL 98. The most commonly bound amino acid in the interactions described in Table 2 is **GLU 102,** which is involved in binding with multiple ligands, including Phentermine, Topiramate, Isoquercetin, Rutin, and Neochlorogenic acid. This indicates that GLU 102 plays a significant role in the interactions of these ligands, contributing to charge distribution and binding affinity (Table 2) (Figure 1- Figure 19).

Table 2 The interaction between ligands and amino acid

Ligands	Amino acid	Bond	Charge
Phentermine	GLU 102,	Hydrogen, salt bridge	Negative charge
Topiramate	GLU 102,	Hydrogen, salt bridge	Negative charge
Isoquercetin	GLU 102,ASN 146,ASP 15, LYS 47,VAL 98,VAL 26	Hydrogen	Negative charge, polar, positive charge, hydrophobic
Rutin	GLU 102,ASN 146,ASP 15, LYS 47,VAL 99		Negative charge, positive charge, hydrophobic
Astragalin	GLU 102,ASP 159,ASN 146,	Hydrogen	Negative charge, polar
Quercetin	VAL 98,ASP 159, LYS 47	Ydrogen	Negative,positive,hydrophobic
Kaempferol	GLU96,VAL98,ASP159	Hydrogen	Negative,hydrophobic
Neochlorogenic acid	GLU96,GLU 145, GLU102,VAL26	Hydrogen	Negative,hydrophobic
Coumarin	VAL 98	Hydrogen	Hydrophobic
Benzyl Benzoate	VAL 98	Hydrogen	Hydrophobic
Benzaldehyde	VAL 98	Hydrogen	Hydrophobic
Eugenol	VAL 98	Hydrogen	Hydrophobic
alpha-TERPINEOL	VAL 98	Hydrogen	Hydrophobic
Benzoic Acid	VAL 98	Hydrogen	Hydrophobic
Coniferaldehyde	GLU 96, LYS 47	Hydrogen	Positive and negative charge
Cinnamyl acetate	LYS 47, PHE160	Hydrogen	Positive , hydrophobic
Cinnamyl Alcohol	ALA 158	Hydeogen	Hydrophobic
Caffeic Acid	LYS 47, PHE160	Hydrogen, salt bridge	Positive , hydrophobic
p-coumaric acid	LYS 47, PHE160	Hydrogen, salt bridge	Positive , hydrophobic
Cinnamic Acid	LYS 47, PHE160	Hydrogen, salt bridge	Positive , hydrophobic

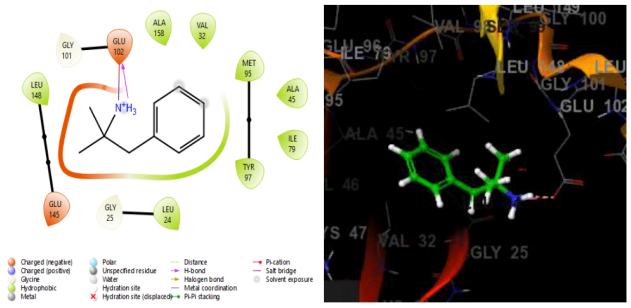

Figure 1 2D and 3D Crystal Structure of Phentermine.

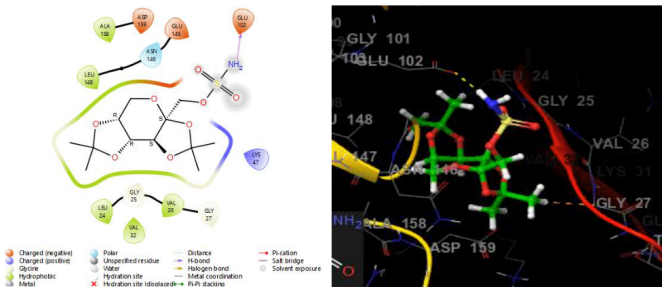

Figure 2 2D and 3D Crystal Structure of Topiramate.

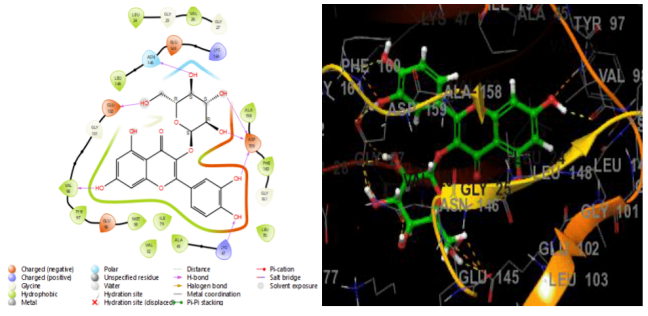

Figure 3 2D and 3D Crystal structure of isoquercetin.

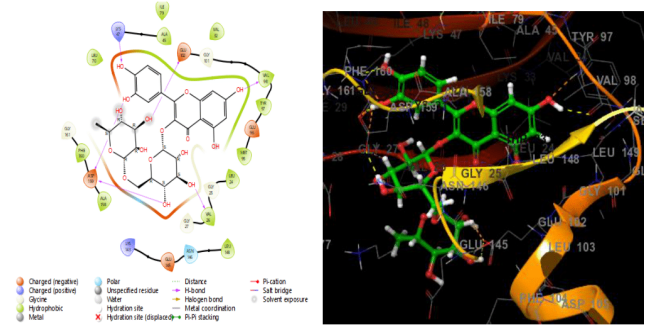

Figure 4 2D and 3D Crystal structure of rutin.

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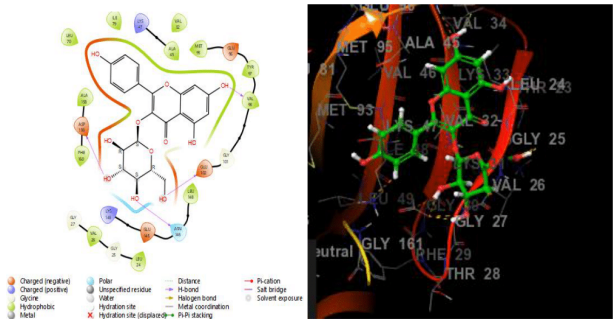

Figure 5 2D and 3D Crystal structure of astragalin.

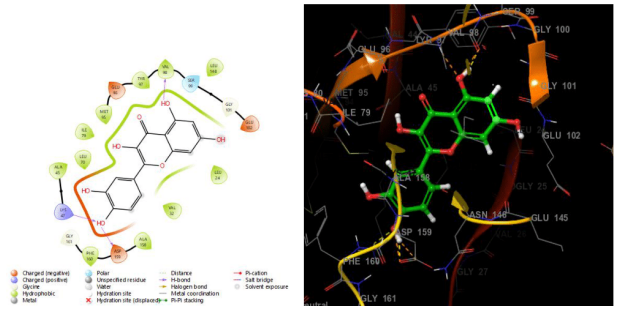

Figure 6 2D and 3D Crystal structure of quercetin.

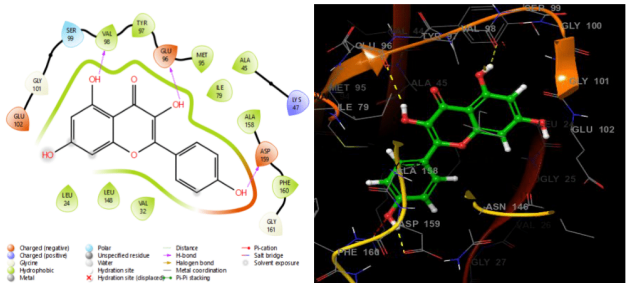

Figure 7 2D and 3D Crystal structure of kaempferol_with amp-activated protein kinase (ampk).

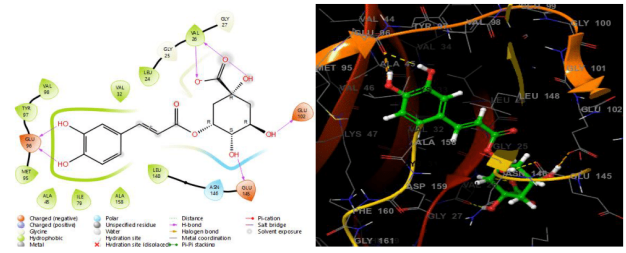

Figure 8 2D and 3D Crystal structure of neochlorogenic acid.

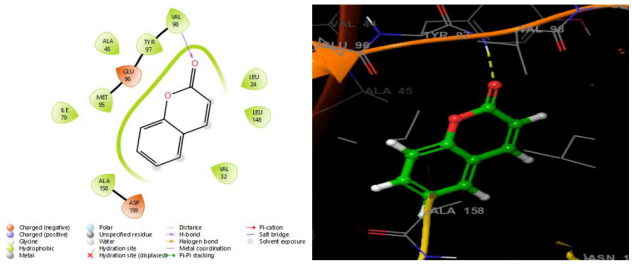

Figure 9 2D and 3D Crystal structure of coumarin.

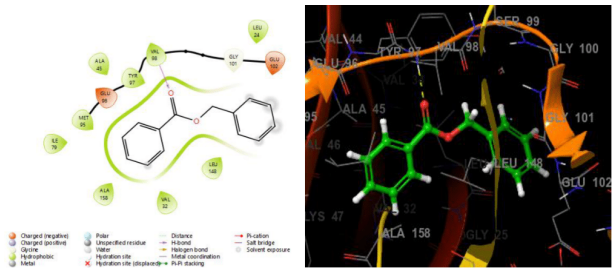

Figure 10 2D and 3D Crystal structure of benzyl benzoate.

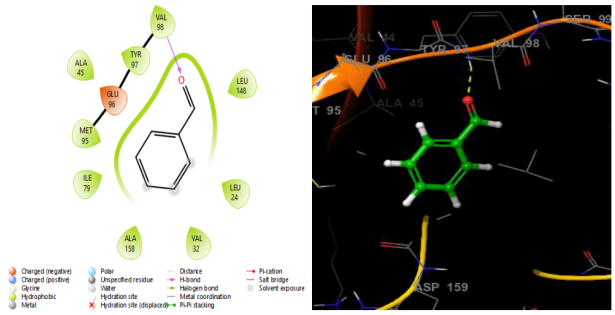

Figure 11 2D and 3D Crystal structure of benzaldehyde.

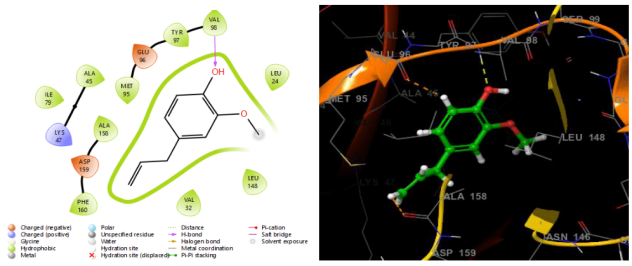

Figure 12 2D and 3D Crystal structure of eugenol.

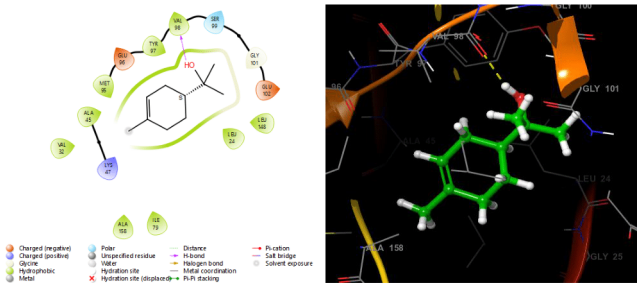

Figure 13 2D and 3D Crystal structure of alpha-terpineol.

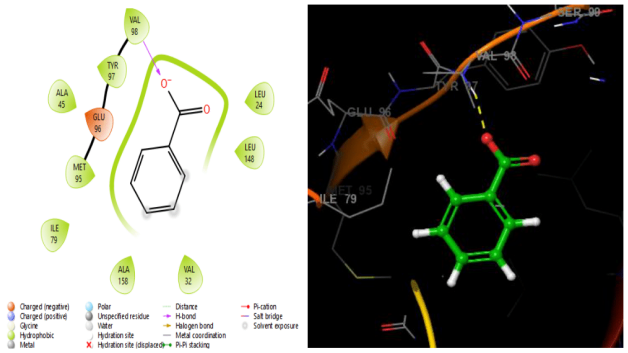

Figure 14 2D and 3D Crystal structure of benzoic acid.

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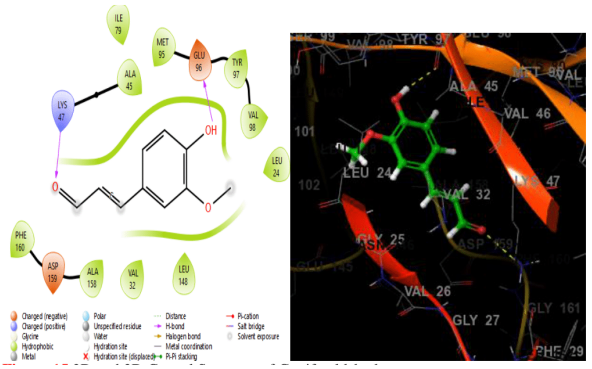

Figure 15 2D and 3D Crystal Structure of Coniferaldehyde.

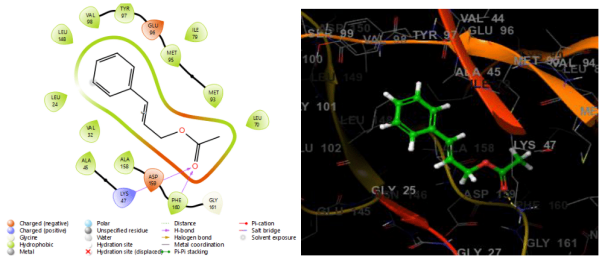

Figure 16 2D and 3D Crystal structure of cinnamyl acetate.

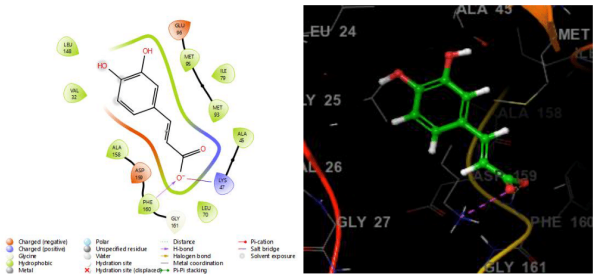

Figure 17 2D and 3D Crystal structure of caffeic acid.

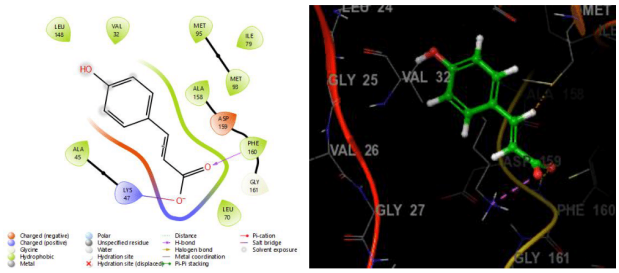

Figure 18 2D and 3D Crystal structure of p-coumaric acid.

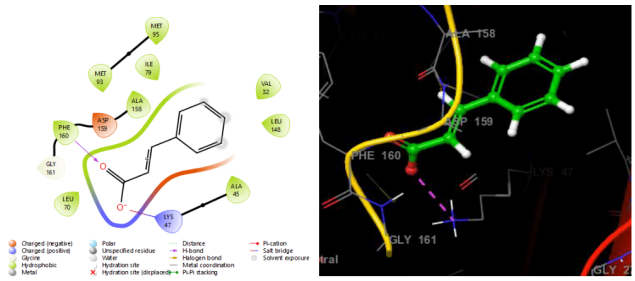

Figure 19 2D and 3D Crystal structure of cinnamic acid.

ADME (Absorption, Distribution, Metabolism, Excretion) properties of ligands

Table 3 compares the ADME properties of several ligands, including phentermine, topiramate, isoquercetin, rutin, astragalin, quercetin, and kaempferol. Phentermine has the lowest molecular weight (149.23 g/mol), while the flavonoids range from 286.24 to 610.52 g/mol. Both phentermine and the flavonoids are generally soluble or moderately soluble. Phentermine shows high gastrointestinal (GI) absorption, while flavonoids exhibit low absorption. Only phentermine is permeable to the blood-brain barrier (BBB). Phentermine has fewer violations of drug-likeness rules, fewer alerts for PAINS and Brenk, and higher lead-likeness compared to the flavonoids. It also has better synthetic accessibility, indicating ease of synthesis (Table 3).

Table 3 ADME (Absorption, Distribution, Metabolism, Excretion) properties of ligands

Molecule	Phentermine	Topiramate	Isoquercetin	Rutin	Astragalin	Quercetin	Kaempferol
MW	149.23	339.36	464.38	610.52	448.38	302.24	286.24
ESOL Class	Soluble	Very soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Ali Class	Soluble	Very soluble	Moderately soluble	Moderately soluble	Moderately soluble	Soluble	Soluble
Silicos-IT class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	High	High	Low	Low	Low	High	High
BBB permeant	Yes	No	No	No	No	No	No
Lipinski #violations	0	0	2	3	2	0	0
Ghose #violations	1	0	1	4	0	0	0
Veber #violations	0	0	1	1	1	0	0
Egan #violations	0	0	1	1	1	0	0
Muegge #violations	2	0	3	4	3	0	0
Bioavailability Score	0.55	0.55	0.17	0.17	0.17	0.55	0.55
PAINS #alerts	0	0	1	1	0	1	0
Brenk #alerts	0	0	1	1	0	1	0
Leadlikeness #violations	1	0	1	1	1	0	0
Synthetic Accessibility	1	4.94	5.32	6.52	5.29	3.23	3.14

Table 3 Continued...

Molecule	Neochlorogenic acid	Coumarin	Benzyl Benzoate	Benzaldehyde	Eugenol	alpha-TERPINEOL	Benzoic Acid
MW	354.31	146.14	212.24	106.12	164.2	154.25	122.12
ESOL Class	Very soluble	Soluble	Soluble	Very soluble	Soluble	Soluble	Soluble
Ali Class	Soluble	Very soluble	Moderately soluble	Very soluble	Soluble	Soluble	Soluble
Silicos-IT class	Soluble	Soluble	Moderately soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	Low	High	High	High	High	High	High
BBB permeant	No	Yes	Yes	Yes	Yes	Yes	Yes
Lipinski #violations	1	0	0	0	0	0	0
Ghose #violations	1	2	0	3	0	1	3
Veber #violations	1	0	0	0	0	0	0
Egan #violations	1	0	0	0	0	0	0
Muegge #violations	2	1	0	2	1	2	1
Bioavailability Score	0.11	0.55	0.55	0.55	0.55	0.55	0.85
PAINS #alerts	1	0	0	0	0	0	0
Brenk #alerts	2	1	0	1	1	1	0
Leadlikeness #violations	1	1	2	1	1	1	1
Synthetic Accessibility	4.16	2.74	1.44	1	1.58	3.24	1

Molecule	Coniferaldehyde	Cinnamyl acetate	Cinnamyl Alcohol	Caffeic Acid	p-coumaric acid	Cinnamic Acid
MW	178.18	176.21	134.18	180.16	164.16	148.16
ESOL Class	Soluble	Soluble	Soluble	Very soluble	Soluble	Soluble
Ali Class	Soluble	Soluble	Very soluble	Soluble	Soluble	Soluble
Silicos-IT class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	No	Yes	Yes
Lipinski #violations	0	0	0	0	0	0
Ghose #violations	0	0	1	0	0	2
Veber #violations	0	0	0	0	0	0
Egan #violations	0	0	0	0	0	0
Muegge #violations	1	1	2	1	1	1
Bioavailability Score	0.55	0.55	0.55	0.56	0.85	0.85
PAINS #alerts	0	0	0	1	0	0
Brenk #alerts	2	0	0	2	1	1
Leadlikeness #violations	1	1	1	1	1	1
Synthetic Accessibility	1.88	1.98	1.5	1.81	1.61	1.67

Toxicity evaluation of ligands

Table 4 shows toxicity properties of ligands the Compounds like Phentermine, Benzyl Benzoate, and Coumarin show a high toxicity profile, with multiple "Active" entries across different categories. This indicates a potential risk for human health and environmental impact. Topiramate and Phentermine show neurotoxic potential, which may lead to neurological disorders or cognitive impairment. Coumarin and Benzaldehyde have a high carcinogenic potential, indicating a possible link to cancer development. Compounds like Eugenol, Cinnamyl acetate, and Cinnamyl Alcohol show ecotoxicity, which may harm aquatic life and ecosystems. Compounds with multiple "Active" entries, like Phentermine and Benzyl Benzoate, raise safety concerns for human consumption or exposure. Compounds like Quercetin, Kaempferol, and Caffeic Acid, with mostly "Inactive" entries, may have potential applications in medicine or nutrition due to their relatively safe profile (Table 4).

Table 4 Toxicity properties of ligands

Discussion

Phentermine and topiramate are approved drugs for obesity treatment, several natural compounds show promising anti-obesity activity in silico with potentially lower toxicity. Phentermine is a commonly prescribed medication for short-term treatment of obesity. It has a docking score of -5.546 and an LD50 of 160 mg/kg, placing it in toxicity class 3.[18] Phentermine works as an appetite suppressant by increasing the release of norepinephrine, dopamine and serotonin in the brain. However, it can cause side effects like increased heart rate, high blood pressure, insomnia and restlessness.[18] Topiramate is another drug used for obesity, often in combination with phentermine. It has a lower docking score of -3.561 but a much higher LD50 of 4000 mg/kg, indicating lower toxicity in class 5. Topiramate is an anticonvulsant that also has weight loss effects, likely by reducing hunger and increasing energy expenditure. The other compounds in the table are natural products found in various plants. Isoquercetin, rutin, astragalin, quercetin and kaempferol are flavonoids with docking scores ranging from -9.809 to -8.497 and LD50 values of 5000 mg/kg, placing them in the low toxicity class 5. These compounds have shown anti-obesity effects in studies, potentially by inhibiting pancreatic lipase, reducing fat absorption, and modulating adipogenesis and lipolysis.[18] Neochlorogenic acid, a phenolic acid, has a docking score of -7.205 and LD50 of 5000 mg/kg (class 5). Coumarin, a benzopyrone, has a docking score of -7.099 but a lower LD50 of 196 mg/kg (class 3). Benzyl benzoate, benzaldehyde, eugenol, α-terpineol, benzoic acid, coniferaldehyde, cinnamyl acetate, cinnamyl alcohol, caffeic acid, p-coumaric acid and cinnamic acid are other natural compounds with varying docking scores and toxicity classes. Ligands like Phentermine and Topiramate form salt bridges with GLU 102, resulting in a negative charge. Isoquercetin and Rutin engage multiple amino acids, leading to complex charge distributions. Others like Astragalin and Kaempferol interact with different amino acids, contributing to negative charges and polar interactions. Compounds such as Quercetin and Neochlorogenic acid exhibit a mix of charges and hydrophobic interactions. Meanwhile, ligands like Coumarin and its derivatives interact primarily through hydrophobic contacts with VAL 98. The presence of hydrogen bonding, salt bridges, and hydrophobic interactions highlights the diverse mechanisms through which these ligands interact with proteins, which is crucial for understanding their biological activities and potential therapeutic effects.

Table 2 provides insight into the intricate interactions between ligands and amino acids, shedding light on their molecular mechanisms and potential pharmacological effects. Ligands like Phentermine and Topiramate form hydrogen bonds and salt bridges with GLU 102, resulting in a negative charge, which may influence their binding affinity and biological activity, especially in contexts such as drug-receptor interactions. Isoquercetin and Rutin showcase more complex interactions, involving multiple amino acids like GLU 102, ASN 146, ASP 15, and LYS 47. These interactions contribute to a varied charge distribution, encompassing negative and positive charges alongside hydrophobic regions. This complexity hints at a multifaceted mode of action for these ligands, potentially targeting various biological pathways or protein targets. Astragalin and Kaempferol interact with distinct sets of amino acids, predominantly through hydrogen bonding, resulting in negative charges and polar interactions. These interactions might play a role in their solubility, bioavailability, or specific binding to target proteins. Compounds like Quercetin and Neochlorogenic acid exhibit a combination of negative charges and hydrophobic interactions, which could be pivotal for their biological functions, such as antioxidant activity or enzyme inhibition. On the other hand, ligands such as Coumarin derivatives, Benzyl Benzoate, and Eugenol primarily interact hydrophobically with VAL 98. These interactions likely influence their lipophilicity and membrane permeability, impacting their pharmacokinetic properties and cellular uptake. The table provides a comprehensive overview of how various ligands interact with specific amino acids, elucidating their molecular mechanisms and potential pharmacological implications. Ligands like Phentermine and Topiramate establish hydrogen bonds and salt bridges with GLU 102, generating a negative charge, which could be crucial for their binding affinity to target proteins or receptors, potentially influencing their pharmacokinetics and pharmacodynamics.

Isoquercetin and Rutin exhibit intricate interactions with multiple amino acids, including GLU 102, ASN 146, ASP 15, and LYS 47, resulting in a diverse charge distribution encompassing both negative and positive charges, as well as hydrophobic regions. These complex interactions hint at a multifaceted mode of action for these ligands, suggesting their potential to modulate various biological pathways or protein functions. Astragalin and Kaempferol predominantly engage in hydrogen bonding interactions with specific amino acids, leading to negative charges and polar interactions. These interactions may play essential roles in determining the ligands' solubility, bioavailability, and specificity for their molecular targets. Quercetin and Neochlorogenic acid demonstrate a combination of negative charges and hydrophobic interactions, likely contributing to their biological activities, such as antioxidant properties or enzyme inhibition. Meanwhile, ligands like Coumarin derivatives, Benzyl Benzoate, and Eugenol primarily interact hydrophobically with VAL 98, which could influence their lipophilicity, cellular permeability, and distribution within biological systems. Phentermine has a Low molecular weight, high solubility, high GI absorption, BBB permeant, no major rule violations. Its low molecular weight and high solubility contribute to its high GI absorption and bioavailability, making it effective as an oral medication. Its ability to cross the BBB makes it suitable for central nervous system (CNS) targets. This aligns with its use as an appetite suppressant in weight loss treatments. Its CNS activity can lead to potential side effects such as insomnia, increased heart rate, and potential for abuse, which requires careful monitoring. Topiramate has a moderate molecular weight, very soluble, high GI absorption, does not cross BBB, no rule violations. Topiramate's high solubility and GI absorption make it effective for oral use in treating epilepsy and preventing migraines. Its inability to cross the BBB might limit CNS side effects, making it safer for long-term use. Although it has no major violations and is very soluble, it requires careful dosing and monitoring due to potential side effects such as cognitive impairments and metabolic acidosis.

Isoquercetin has a high molecular weight, moderately soluble, low GI absorption, does not cross BBB, multiple rule violations. Isoquercetin's high molecular weight and multiple rule violations suggest challenges in drug development, particularly in achieving sufficient bioavailability. Its potential as an antioxidant and anti-inflammatory agent is limited by its low GI absorption. Enhancing its bioavailability and solubility through formulation techniques like nanoparticle delivery systems or prodrugs could be necessary for effective therapeutic use. Rutin has the Highest molecular weight, moderately soluble, low GI absorption, does not cross BBB, multiple rule violations. Similar to Isoquercetin, Rutin's therapeutic benefits as an antioxidant and anti-inflammatory agent are hindered by its poor bioavailability. Its high synthetic accessibility score further complicates its use. Developing effective delivery methods, such

as liposomal formulations, could improve its clinical applicability. Its high molecular weight, moderately soluble, low GI absorption, does not cross BBB, some rule violations. Astragalin has potential therapeutic benefits similar to Isoquercetin and Rutin but faces the same challenges of low bioavailability and solubility. Formulation strategies and modification of its chemical structure to improve its pharmacokinetic properties would be necessary. Quercetin has a Moderate molecular weight, soluble, high GI absorption, does not cross BBB, no major rule violations. Quercetin's favorable properties, including high GI absorption and no major rule violations, make it a promising candidate for development as an oral supplement or therapeutic agent. It is known for its antioxidant, anti-inflammatory, and anticancer properties. While it has good bioavailability, its low solubility in water can still pose challenges, which might require formulation improvements for enhanced therapeutic efficacy.

Kaempferol has a low molecular weight, soluble, high GI absorption, does not cross BBB, no major rule violations. Kaempferol shares many beneficial properties with Quercetin, including high GI absorption and no major rule violations. Its potential uses include antioxidant and anti-inflammatory applications. Similar to Quercetin, improving its solubility could enhance its clinical effectiveness, despite its already favorable profile. Bioavailability and GI Absorption, Phentermine, Topiramate, Quercetin, and Kaempferol exhibit high GI absorption, making them more suitable for oral administration. Only Phentermine crosses the BBB, making it unique among these molecules for CNS applications.Rutin and Isoquercetin face multiple rule violations, indicating potential challenges in developing them as drug-like candidates. Phentermine is the easiest to synthesize, while Rutin is the most complex, which can impact the feasibility of large-scale production. Enhancing the solubility and bioavailability of Isoquercetin, Rutin, and Astragalin through advanced formulation techniques such as nanoparticles, liposomes, or prodrug strategies. Modifying the chemical structure to improve pharmacokinetic properties without compromising therapeutic efficacy.

Quercetin and Kaempferol may have positive metabolic effects, such as improving insulin sensitivity and glucose metabolism,[19,20] which can help with weight management. Phentermine, a weight-loss medication, works by suppressing appetite,[21] but its toxicity profile and potential side effects must be carefully considered. The table highlights the importance of considering nutritional toxicity when evaluating compounds for obesity treatment, as some may have harmful effects at high doses or with long-term use.[22] The ecotoxicity of some compounds, like Cinnamyl acetate and Cinnamyl Alcohol, may also have implications for environmental health,[23] which is crucial for overall well-being and obesity prevention. The table suggests a holistic approach to addressing obesity, considering multiple factors like toxicity, metabolic effects, appetite suppression, nutritional toxicity, and environmental impact,[24] to find safe and effective solutions for weight management and overall health.

Conclusion

In conclusion, the evaluation of various compounds for obesity treatment reveals a diverse landscape of potential therapeutic agents, ranging from approved drugs like phentermine and topiramate to natural compounds with promising anti-obesity properties. Phentermine and topiramate, while effective in weight loss, come with associated side effects and toxicity concerns, necessitating careful monitoring and management. Natural compounds such as flavonoids and phenolic acids demonstrate favorable interactions with specific amino acids, suggesting intricate mechanisms of action that could target various biological pathways involved in obesity. While compounds like quercetin and kaempferol exhibit promising metabolic effects beneficial for weight management, considerations of toxicity, nutritional impact, and environmental effects are crucial in their evaluation for obesity treatment.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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