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Research Article

The Expected Medical Uses of Saudi Arabia Coffee Constituents Through Computer Aided Drug Design

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Abstract

Background: In this research work we have investigated the molecular structure of 17 Arabian coffee flavonoids to identify their potential protein targets using Swiss Target Prediction platform. The obtained results indicated that aldose reductase, carbonic anhydrase II and lymphocyte differentiation antigen CD38 are the primary targets for the tested flavonoids.
Methods: Absorption, distribution, metabolism and excretion predictions were also performed to explore the pharmacokinetic profile of the Arabian coffee flavonoid content. Molecular docking investigations were also performed with aldose reductase, carbonic anhydrase II and lymphocyte differentiation antigen CD38.
Results: It has showed docking scores between -13.07 and -20.20 kcal/-mol for aldose reductase, -11.76 to -18.27 kcal/mol for carbonic anhydrase II and -10.65 to -19.44 kcal/mol for lymphocyte differentiation antigen CD38. Metabolic pathway analysis for Arabian coffee flavonoids predicted potential metabolites of epigallocatechin gallate, delphinidin 3-(6"-malonyl-glucoside), cyanidin-3-O-glucoside and isoquercitrin.
Conclusion: Arabian coffee flavonoids have the potential to be used in the development of medical treatments targeting proteins such as aldose reductase, carbonic anhydrase II and lymphocyte differentiation antigen CD38.

INTRODUCTION

The Arabic coffee contains vitamins and minerals, high level of potassium and low level of sodium that gives good control of blood pressure, additionally the Arabic coffee has a cardamom in its constituents and cardamom is known of its power to detoxify the human body (Jalal et al., 2023). It has also ability in keeping you alert and energized in the morning to be able to do your daily tasks. Arabic coffee can boost the immune system and prevent Parkinson disease. It also acts as mood elevator and can fight against depression (Badkook , 2013; Haque et al., 2013). The Arabic coffee was re-ported to show a neuroprotective role and act against cognitive deficits (Wasim et al., 2020). Saudi Arabia coffee has antioxidant properties due to its content of polyphenols and flavonoids (Alamri et al., 2022). Additionally coffee Arabica oil is well known for many medicinal uses due to its content of biologically active fatty acids (AL- Asmari et al., 2020). Taxonomy of Coffee arabica plant: Kingdom (Plantae), Phylum (Mag- noliophyta), Subphylum (Rosophytina), Class (Rosopsida), Subclass (Asteridae), Order (Rubiales), Family (Rubiaceae), Genus (Coffee), Species (arabica) (Abdulwahab et al., 2022). Figure 1 is illustrating two photos for the Saudi Arabia Coffee plant (https://www.alamy.com/stock-photo/coffee-saudi-arabia.html?sortBy=relevant).

Arabian Coffee main constituents

Saudi Arabia coffee has a very good advantage as it contains not only the coffee Arabica beans but also

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other natural additives that potentiate its healthy benefits as you can find it mixed with Cardamom or Saffron, these additives give the Arabic coffee a specific delicious taste in addition to their detoxifying and healthy properties. Figure 2 illustrates some main constituents in the Arabic coffee [5-8], that can be investigated for their pharmacological profile to let us know how these constituents can affect our human body. Coffee contains many chemical components, including sugar such as sucrose, fructose, arabinos, galactose, glucose, mannose, mannitol, xylose, hydroxymethyl-furfural (Bauer et al., 2018) (Figure 3). Moreover, Arabic coffee contains many types of amino acids such as glutamine, asparagine, histidine, alanine, proline, leu-cine, and phenylalanine, additionally, it has fatty acids and lipid, for example palmitic, stearic, linolenic, and oleic acids (Wei et al., 2012)(Figure 4).

Figure 1: Saudi Arabia Coffee plant photo retrieved from [https://www.alamy.com/stock-photo/coffee-saudi-arabia.html?sortBy=relevant last accessed 7 Feb 2023].

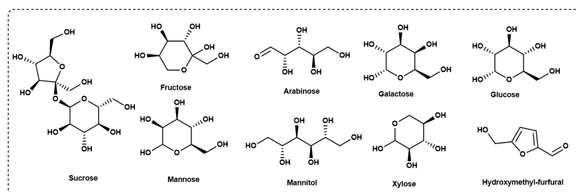

Figure 2: Some Sugar in Arabian coffee.

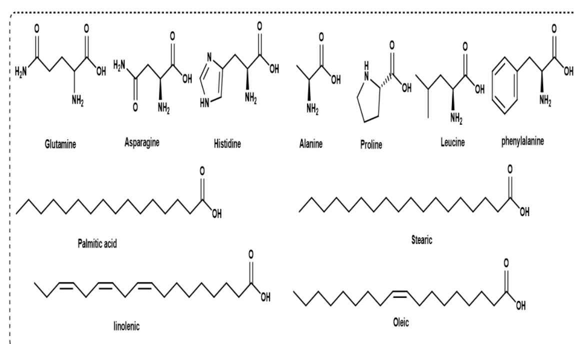

Figure 3: Some amino acids and fatty acids in Arabian coffee

Moreover, Arabian coffee has many types of essential useful substances as, terpenoids, alkaloid, saponins, carotenoids and coumarins, sterols, phenolic acids and flavonoids.

Terpenoids: cafestol , kahweol, ursolic acid, tricalysiolide , and mascaroside (Abdulwahab et al., 2022). Alkaloid as caffeine, theobromine, theophylline, trigonel l ine and nicotinic acid , saponins: oleanolic acid and ursolic acid (Abdulwahab et al., 2022), Figure 5.

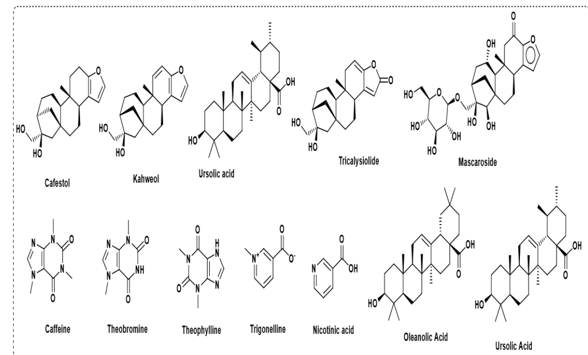

Figure 4: The chemical structures of some terpenoids, alkaloid, saponins in Arabian coffee

Carotenoids and coumarins: Violaxanthin, Neoxanthin, Lutein, β-Carotene and mangiferin , scopoletin , antheraxanthin and zeaxanthin. Sterols as β-sitosterol, stigmasterol, campesterol , cholesterol, 5-avenasterol, and 7-avenasterol (Acidri et al., 2020; Chen, 2019), Figure 6.

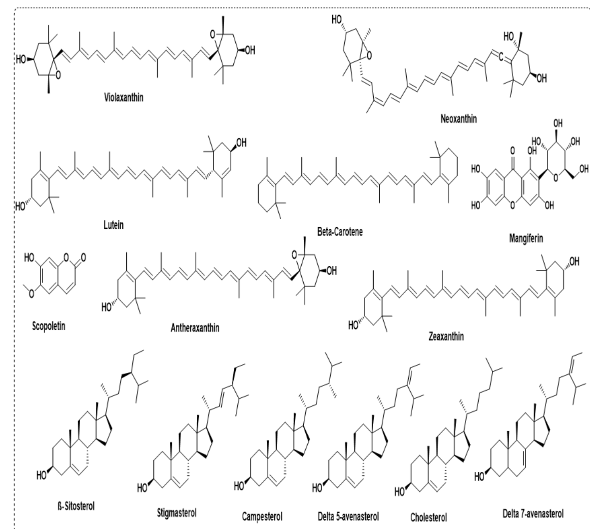

Figure 5: The chemical structures of some Carotenoids, couma-rins, and Sterols in Arabian coffee.

Phenolic acids: vanillic acid, 3-hydroxybenzoic acid, protocatechuic acid, caffeic acid, sinapic acid, caftaric acid, 3,4-di-O-caffeoylquinic acid, 4-O-pcoumaroylquinic acid, p-coumaric acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid methyl ester, 4-O-feruloylquinic acid, 4-O-feruloyl-5-O-caffeoylquinic acid, 1-caffeoylquinic acid, and 4,5-Dicaffeoylquinic acid (Asamenew et al., 2019), Figure 7.

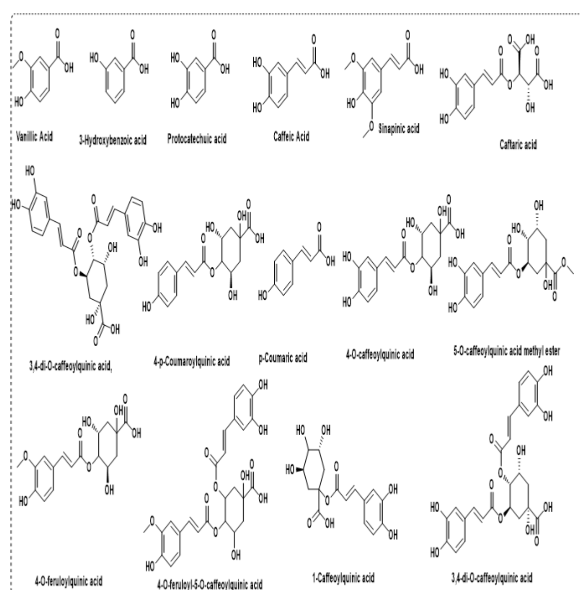

Figure 6: The chemical structures of some Phenolic acid.

Flavonoids: epicatechin, catechin, gallate, epigallo - catechin gallate, delphinidin 3-(6-̈malonyl-glucoside), kaempferol, cyanidin-3-glucoside, cya-nidin-3-O- rutinoside , quercetin, isoquercitrin , rutin, hyperoside , luteolin, patuletin , fisetin, myricetin, and apigenin (Ratanamarno & Surbkar , 2017), Figure 8.

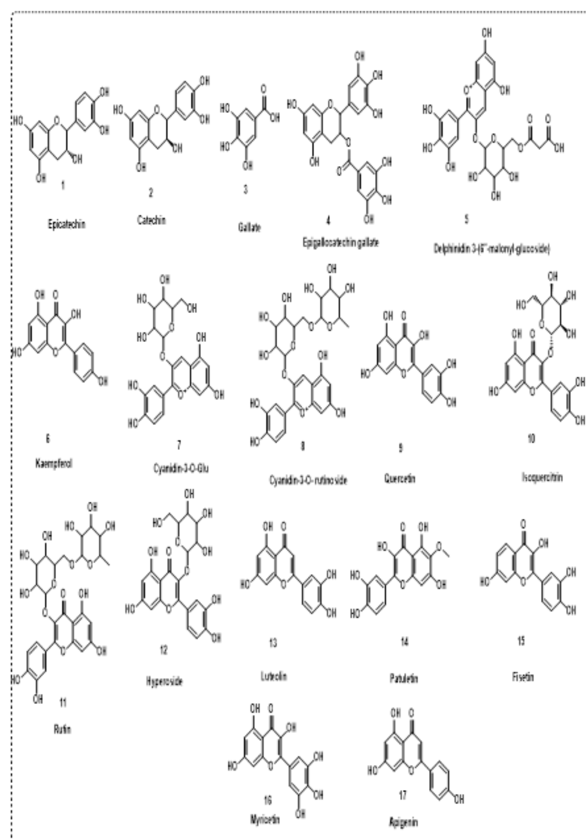

Figure 7: The chemical structures of the flavonoid compounds.

Flavonoids are secondary metabolites mostly composed of a benzopyrone ring. Flavonoids exhibit several therapeutic advantages, encompassing anticancer, antioxidant, anti-inflammatory, and antiviral effects. Computational pharmacology, an interdisciplinary field, ex-amines the effects of drugs within the body. It employs physics, biology, chemistry, pharmacology, and computer science to elucidate intricate drug-receptor interactions (Barakat et al., 2024). Computational pharmacology provides pharmacological research with unparalleled precision and intricacy. It has been utilized to discover novel pharmaceuticals, anticipates drug–drug interactions, and examine pharmacological processes. Researchers employ mathematical and computational models to mimic drug efficacy and molecular interactions in computational pharmacology. It can forecast and evaluate the safety and efficacy of medications prior to clinical trials (Gautam et al., 2023). This study aims to anticipate the targets of certain Arabian coffee flavonoids and examine their pharmacokinetics. Additionally, we conduct a molecular docking research to ascertain the target binding affinity. Ultimately, we forecast the metabolic pathways for the most promising compounds.

MATERIALS AND METHODS

Target Prediction

Swiss Target Prediction (http://www.swisstargetprediction.ch) is a widely utilized database for forecasting compound targets and is employed to anticipate the potential targets of flavonoid compounds (Daina et al., 2019).

Absorption, Distribution, Metabolism, Excretion prediction

The ADMET properties of flavonoids, including water solubility, blood-brain barrier penetration, human intestinal absorption (HIA), and plasma protein binding, were computed using the SwissADME website (http://www.swissadme.ch/) (Daina et al., 2017).

Molecular docking study

The docking investigation was performed utilizing AutoDock Vina 4.2. The structures of all flavonoid compounds were acquired from the PubChem website (https://pubchem.ncbi.nlm.nih.gov). The Protein Data Bank (PDB) was employed to obtain the molecular codes for carbonic anhydrase, lymphocyte differentiation antigen CD38, and aldose reductase, identified by the PDB IDs: 1bn1 (Boriack-Sjodin et al., 1998), 3rop (Kwong et al., 2012a), and 2ine (Brownlee et al., 2006), respectively The proteins and ligands must be in PDBQT format for docking to occur. The enzyme and the co-crystallized molecule required preparation with M.G.L tools prior to the docking process (Trott & Olson, 2009). The visualizer in Discovery Studio 4.5 was employed to present the docking results.

Metabolism pathway

The metabolic pathways and expected metabolites of the substances epigallocatechin gallate, delphinidin 3-(6-̈malonyl-glucoside), cyanidin-3-O-glucoside, and isoquercitrin were forecasted utilizing Biotransformer (http://biotransformer.ca) (Djoumbou-Feunang et al., 2019). The chosen compounds were submitted to the server.

RESULTS AND DISCUSSION

Target Prediction

Utilizing the molecular structure of 17 Arabian coffee flavonoids (Figure 8), 100 potential flavonoid targets were identified via the Swiss Target Prediction platform (Supplementary data, Table S1). The Swiss Target Prediction website indicates that epicatechin and its isomer catechin have no target predictions. Aldose reductase, carbonic anhydrase II, and lymphocyte differentiation antigen CD38 were the primary targets among the 15 flavonoids.

Absorption, Distribution, Metabolism, Excretion prediction

In accordance with Lipinski's rule of five, this study conducted a computational analysis to determine the quantity of rotatable bonds, topological polar surface area (TPSA), and other physicochemical characteristics of the evaluated candidates. Table 1 indicates that eight out of seventeen flavonoid compounds (Epigallocate -chin gallate, delphinidin 3-(6-̈malonyl-glucoside), cyanidin-3-glucoside, cyanidin-3-O-rutinoside, isoquercitrin , rutin, hyperoside , and myricetin) violate Lipinski's rule due to possessing more than five hydro-gen bond donors and/or more than ten hydrogen bond acceptors. The molecular weights of cyanidin-3-O-rutinoside and rutin surpass 500, as indicated in Table 1. Conversely, epicatechin, catechin, gallate, kaempferol, quercetin, luteolin, patuletin , fisetin, and apigenin adhere to Lipinski's rule, suggesting their potential for pharmacological use. They have hydrogen bond acceptors (HBA) ranging from 5 to 8, which is below the threshold of 10 necessary to satisfy the first criterion of Lipinski's rule. Moreover, regarding the quantity of hydrogen bond donors (HBD), the remaining nine flavonoid compounds exhibit HBD values between 3 and 5 (i.e., fewer than 5), so satisfying the second criterion of Lipinski's rule. The third component of Lipinski's rule is corroborated by the observation that all nine molecules possess a molecular weight under 500. The logP values of the compounds exhibited considerable variation, ranging from -1.08 to 0.24. The results align with the fourth parameter of Lipinski's rule, which posits that logP values under 5 signify potential pharmaceutical candidates. The molecular flexibility and oral bioavailability of the therapeutic candidates were assessed by quantifying the number of rotatable bonds. The research indicated that molecules have between 1 and 8 rotatable bonds. Moreover, the TPSA (a physicochemical attribute indicating molecular polarity) of epicatechin, catechin, gallate, kaempferol, quercetin, luteolin, fisetin, and apigenin is below 140 Å², falling within the permissible range (0 to 104.2 Å²) (Table 1).

The penetrability of all substances across the blood-brain barrier (BBB), their intestinal absorption, and plasma protein binding (PPB) properties were assessed. According to Table 2, any substances that do not breach the blood-brain barrier are thus anticipated to be safe for the central nervous system. Nine flavonoid compounds have significant intestinal absorption.

Additionally, the absorption percentage (%ABS) was estimated using the formula %ABS = 109 − (0.345 × TPSA) [15], with the compounds exhibiting a range from 16.04% to 77.63% (Table 2). Bioavailability, an index of the drug content in plasma, is the primary factor affecting absorption. The bioavailability of 10 flavonoid compounds was found to be significant.

Because 14 of the compounds are not substrates of the Pgp protein. Epicatechin, catechin, and rutin are substrates of P-glycoprotein, exhibiting a little danger of cellular efflux, so achieving maximal efficacy.

Molecular docking study

Docking experiments evaluate the model's validity and elucidate the binding interactions of medicines with their biological targets in terms of affinity. The docking simulation was conducted between 17 flavonoid compounds and aldose reductase (Pdb ID: 2ine), carbonic anhydrase II (Pdb ID: 1bn1), and lymphocyte differentiation antigen CD38 (Pdb ID: 3rop), based on the target prediction study. The enzymes underwent re-docking with the co-crystallized ligands to verify their binding affinity and conformation. The effectiveness of the docking techniques was demonstrated by the presentation of a Root Mean Square Deviation (RMSD) value of 0.26 A for aldose reductase (Figure 9A), 0.38 A for carbonic anhydrase II (Figure 9B), and 0.43 A for lymphocyte differentiation antigen CD38 (Figure 9C).

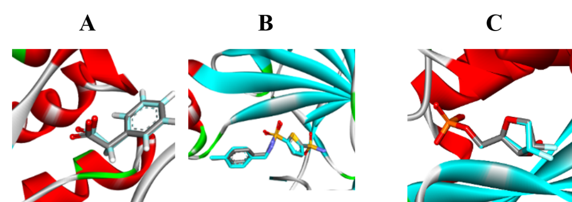

Figure 8: The root mean square deviation (RMSD) between the original and docked poses of the co-crystal ligands: (A) aldose reductase was 0.26 Å, (B) carbonic anhydrase II was 0.38 Å, and (C) lymphocyte differentiation antigen CD38 was 0.43 Å

The analyzed compounds exhibited docking scores be-tween -13.07 and -20.20 kcal/mol when evaluated against aldose reductase. The cocrystal ligand had a docking value of -5.34 kcal/mol. The docking scores

Table 1: Physicochemical properties of 17 flavonoids

Compound	HBD	HBA	M logP	MWt	No. ofRot. bonds	Lipinski´s Violations	TPSA
Epicatechin	5	6	0.24	290.27	1	0	110.38
Catechin	5	6	0.24	290.27	1	0	110.38
Gallate	4	5	-0.16	170.12	1	0	97.99
Epigallocatechin gallate	8	11	-0.44	458.37	4	2	197.37
Delphinidin 3-(6"-malonyl-glucoside)	9	15	-2.36	551.43	8	3	257.04
Kaempferol	4	6	-0.03	286.24	1	0	111.13
Cyanidin-3-glucoside	8	11	-1.76	449.38	4	2	193.44
Cyanidin-3-O-rutinoside	10	15	-3.08	595.53	6	3	252.36
Quercetin	5	7	-0.56	302.24	1	0	131.36
Isoquercitrin	8	12	-2.59	464.38	4	2	210.51
Rutin	10	16	-3.89	610.52	6	3	269.43
Hyperoside	8	12	-2.59	464.38	4	2	210.51
Luteolin	4	6	-0.03	286.24	1	0	111.13
Patuletin	5	8	-0.83	332.26	2	0	140.59
Fisetin	4	6	-0.03	286.24	1	0	111.13
Myricetin	6	8	-1.08	318.24	1	1	151.59
Apigenin	3	5	0.52	270.24	1	0	90.9

Table 2: Pharmacokinetic properties parameters

Compounds	GIAbsorption	BBBPermeation	P-gpsubstrate	BioavailabilityScore	% ABS
Epicatechin	High	No	Yes	0.55	70.91
Catechin	High	No	Yes	0.55	70.91
Gallate	High	No	No	0.56	75.19
Epigallocatechin gallate	Low	No	No	0.17	40.69
Delphinidin 3-(6"-malonyl-glucoside)	Low	No	No	0.17	20.32
Kaempferol	High	No	No	0.55	70.66
Cyanidin-3-glucoside	Low	No	No	0.17	42.26
Cyanidin-3-O-rutinoside	Low	No	No	0.17	21.93
Quercetin	High	No	No	0.55	63.68
Isoquercitrin	Low	No	No	0.17	36.37
Rutin	Low	No	Yes	0.17	16.04
Hyperoside	Low	No	No	0.17	36.37
Luteolin	High	No	No	0.55	70.66
Patuletin	Low	No	No	0.55	60.49
Fisetin	High	No	No	0.55	70.66
Myricetin	Low	No	No	0.55	56.70
Apigenin	High	No	No	0.55	77.63

of the evaluated flavonoids against carbonic anhydrase II varied from -11.76 to -18.27 kcal/mol, in contrast to the co-crystal ligand, which had a docking score of -8.47. The binding energy of compounds associated with lymphocyte differentiation antigen CD38 varied from -10.65 to -19.44 kcal/mol (Table 3).

Docking into aldose reductase

Aldo-Keto-Reductases (AKRs) are multifunctional enzymes that metabolize carbonyl-containing substrates, including sugars, lipid aldehydes, and ketosteroids. Aldose reductase is a prevalent enzyme of the aldo -keto reductase superfamily, exhibiting extensive substrate selectivity. Members of this superfamily facilitate the

Table 3: Docking energy scores in kcal/mol of 17 flavonoid compounds against Aldose reductase, carbonic anhy-drase II, Lymphocyte differentiation antigen CD38 en-zymes.

Compounds	**Docking energy scores in kcal/mol**		
	Aldose reductase	Carbonic anhydrase II	Lymphocyte differentiation antigen CD38
Co-crystal ligand	-5.34	-8.47	-6.50
Epicatechin	-14.16	-12.49	-13.69
Catechin	-16.62	-12.96	-14.17
Gallate	-13.07	-12.25	-10.65
Epigallocatechin gallate	-20.20	-15.28	-19.44
Delphinidin 3-(6"-malonyl-glucoside)	-16.17	-16.66	-18.70
Kaempferol	-13.64	-14.07	-12.87
Cyanidin-3-glucoside	-16.27	-17.16	-16.67
Cyanidin-3-O-rutinoside	-17.33	-18.27	-17.10
Quercetin	-15.30	-14.13	-13.71
Isoquercitrin	-20.10	-16.88	-18.12
Rutin	-13.29	-15.81	-15.78
Hyperoside	-15.92	-15.55	-14.63
Luteolin	-15.92	-11.44	-14.51
Patuletin	-17.03	-13.77	-14.30
Fisetin	-16.15	-12.19	-12.19
Myricetin	-17.95	-14.71	-14.99
Apigenin	-13.48	-11.76	-12.00

NADPH-dependent reduction of various aldehydes and short-chain ketones to their respective alcohols. Aldose reductase catalyzes the conversion of glucose to sorbitol and has been associated with diabetic problems in persons with poorly regulated glucose levels; hence, this enzyme has been regarded as a therapeutic target and has been a focal point of research for several decades. Aldose reductase (AR) is a significant target in the creation of therapies for hyperglycemia-related health issues, including retinopathy (Penning, 2015; Ruiz et al., 2012).

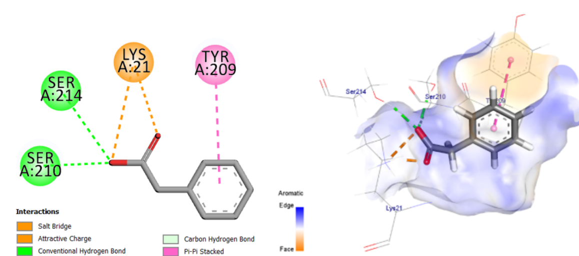

Figure 9: 2D and 3D illustrate the anticipated binding confor-mation of co-crystal ligand (phenyl acetic acid) in the active site of aldose reductase enzyme

The key amino acids in the active site of aldose reductase included Tyr209, Cys298, Phe122, Trp219, Ala299, Trp20, Val297, Leu300, and Ser302. The binding pocket is partitioned by Trp 111 into the catalytic subpocket and the specificity pocket. The catalytic pocket, which is situated deeply, consists of residues Tyr 48, Lys 77, and His 110 (Shahab et al., 2023; Steuber et al., 2007). Seventeen flavonoid compounds were docked in the active site of the aldose reductase enzyme, yielding docking scores between -13.07 and -20.20 kcal/mol, in contrast to phenyl acetic acid (co-crystal ligand) at -5.34 kcal/mol (Table 3). The compounds epigallocate -chin gallate and isoquercitrin demonstrated optimal stability during docking, indicated by docking scores of -20.20 and -20.10 kcal/-mol, respectively (Table 3). Phenyl acetic acid formed three hydrogen bonds with Ser210 and Ser214, along with two favorable interactions with Lys21 and Pi-Pi stacking with Tyr209 (Supp. Data (Table S1), Figure 10). The hydroxyl groups of epigallocatechin gallate formed 12 hydrogen bonds with Thr19, Trp20, Lys21, Trp111, Ser214, Asp216, Lys262, Asp43, Gln183, and the catalytic amino acid Tyr48. Additionally, epigallocatechin gallate formed hydrophobic contacts with Tyr209, Trp20, Pro211, Lys262, Ile260, and Cys298 (Table S1, Figure 11). The principal interactions of isoquercitrin with the aldore-ductase protein were recorded at -20.10 kcal/mol, in-volving Thr19, Trp20, the catalytic pocket (Lys77, His110, Tyr48), Ser214, Cys298, Lys262, and Asp43 through conventional hydrogen bonds, and Gly18, Ser214, Ser210, and Gln183 via carbon-hydrogen bonds (Table S1), Figure 12). It additionally established a Pi-sigma bond with Tyr209

and an alkyl bond with Pro211, Lys262, Leu212, and Lys262.

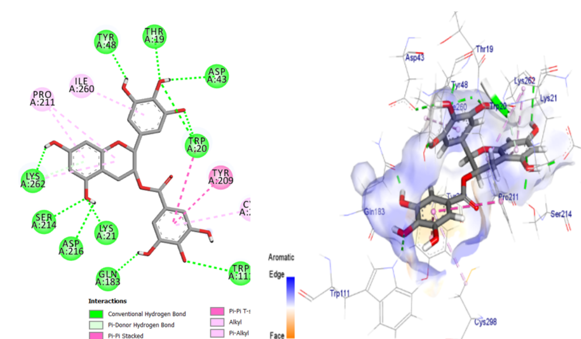

Figure 10: 2D and 3D illustrate the anticipated binding confor-mation of Epigallocatechin gallate in the active site of aldose reductase enzyme.

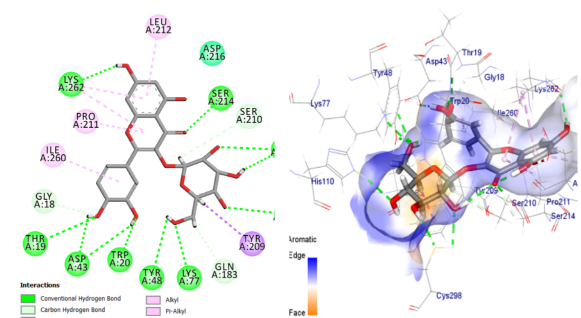

Figure 11: 2D and 3D illustrate the anticipated binding confor-mation of Isoquercitrin in the active site of aldose reductase enzyme.

Docking into carbonic anhydrase II

Carbonic anhydrases (CAs) participate in numerous physiological processes, such as respiration, the transfer of carbon dioxide and bicarbonate, pH and carbon dioxide homeostasis, ureagenesis, adipogenesis, gluconeogenesis, and calcification (Denner et al., 2024; Nocentini et al., 2021). Inhibitors of carbonic anhydrase II, namely, have lately increased in significance. This can be elucidated, on one hand, by their effective application in the management of ocular disorders (e.g., glaucoma) (Scozzafava & Supuran , 2014).

The residues His64, Asn62, Asn67, His94, Asp72, Phe131, Gly132, Thr200, and Pro201 are predominanly situated on the hydrophilic surface of the protein. Notably, the binding of inhibitors dislodged a water molecule known as ̈deep water,̈which is controlled by the amide nitrogen of Thr199, revealing a potential placeholder frequently observed in CA II crystal structures (Iyer et al., 2006). Furthermore, prior spectroscopic investigations have demonstrated that the binding of CO2 does not necessitate any inner-sphere coordination by the zinc ion. The results indicate that CO2 would bind in a manner that temporarily interacts with the hydrophobic portion of the active site. The hydrophilic portion was also proposed to contribute to the orientation of CO2 (Domsic & McKenna, 2010). A docking study of 17 flavonoids and a co-crystal ligand was conducted against CA II, with the docking scores presented in Table 1. The minimum energy binding values were -17.16 and -18.27 Kcal/mol for cyanidin-3-glucoside and cyanidin-3-O-rutinoside, respectively. Figure 13 depicts the binding mode of the co-crystal ligand within the active site of CAII, exhibiting four hydrogen bonds with Gln92, Thr199, and Leu198. Furthermore, the co-crystal ligand demonstrated many interactions, including Pi-anion, Pi-sigma, Pi-sulfur, Pi-Pi T-shaped, alkyl, Pi-alkyl, and metal acceptor bonds, with a docking score of -8.47 kcal/mol. Cya-nidin-3-glucoside and cyanidin-3-O-rutinoside bind identically as co-crystal ligands in the active site of carbonic anhydrase II (CAII). Both compounds engaged in the binding mode via interactions with His94 through attractive charge formation, Asn62 and Thr199 via hydrogen bond formation, Val121 and Leu198 through Pi-alkyl bonding, and His94 through Pi-anion and Pi-Pi T-shaped interactions. Furthermore , cyanidin-3-O-rutinoside established metal-acceptor and Pi-cation interactions with the zinc atom (Figure 14 and 15, Table S2).

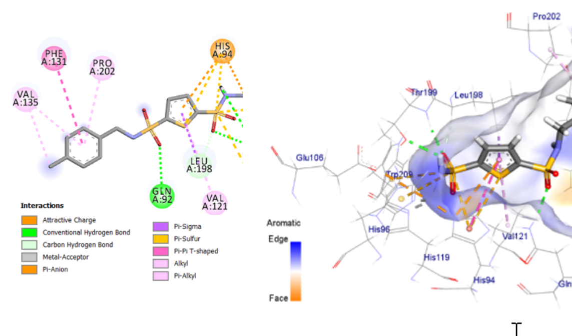

Figure 12: 2D and 3D illustrate the anticipated binding conformation of co-crystal ligand in the active site of aldose carbonic anhydrase II enzyme.

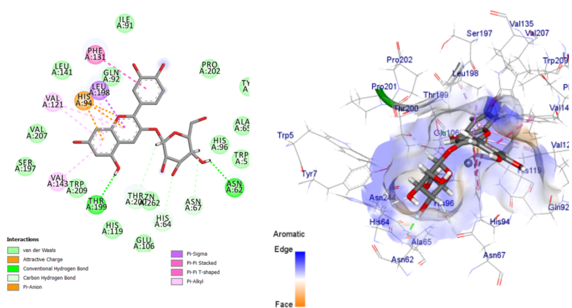

Figure 13: 2D and 3D illustrate the anticipated binding conformation of Cyanidin-3-glucoside in the active site of aldose carbonic anhydrase II enzyme.

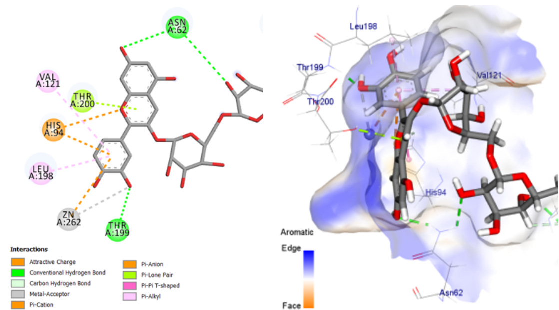

Figure 14: 2D and 3D illustrate the anticipated binding confor-mation of Cyanidin-3-O- rutinoside in the active site of aldose carbonic anhydrase II enzyme

Docking into Lymphocyte differentiation antigen CD38

CD38 was initially identified in lymphocytes using antibody typing, however it has now been recognized as an enzyme that is universally expressed in nearly all mammalian tissues. It has been proven that it is a signaling enzyme that catalyzes the synthesis of two Ca2+ messengers: cyclic ADP ribose (cADPR) from NAD and nicotinic acid adenine dinucleotide phosphate (NAADP) from NADP. Both messenger molecules have demonstrated the ability to regulate a broad spectrum of physiological functions, including abscisic acid signaling in plants and sponges, as well as insulin release in mammalian β-cells. The catalytic mechanism by which CD38 facilitates numerous processes resulting in the synthesis of two physically and functionally different messenger molecules has been thoroughly elucidated by crystallography and site-directed mutagenesis (Kwong et al., 2012b; Piedra-Quintero et al., 2020). Gene knockout experiments have demonstrated that CD38 is essential for various physiological activities, including insulin secretion, susceptibility to bacterial infections, and the social behavior of mice, by control-ling neuronal oxytocin production. Consequently, it is highly vital to devise particular and broadly applicable inhibitors of CD38. The inhibition is dependent on catalysis and results in the formation of a covalent inter-mediate with the catalytic residue of CD38. The critical amino acid residues in the active site of CD38 were Arg127, Ser126, Glu226, and Trp189 (Benton et al., 2021; Kwong et al., 2012b; Li et al., 2022; Piedra-Quintero et al., 2020). The 17 compounds exhibited favorable interactions inside the binding region of the CD38 protein, with docking scores ranging from -10.65 to -19.44 kcal/mol, in contrast to the co-crystal ligand score of -6.5 kcal/-mol (Table 3). Epigallocatechin gal-late and delphinidin 3-(6-̈malonyl-glucoside) have the lowest energies of -19.44 and -18.70 kcal/mole, respectively. The co-crystal ligand exhibited five hydrogen connections with Trp125, Phe222, and Glu226, along with a Pi-Pi stacking interaction with the Trp125 residue (Figure 16). The hydroxyl phenolic group of epigallocatechin gallate formed 10 hydrogen bonds with the amino acids Arg127, Asp156, Glu226, Ser126, Ser220, Glu146, Thr221, and Trp125, whereas delphinidin 3-(6-̈malonyl-glucoside) established 9 hydro-gen bonds with the residues Arg127, Asp156, Glu226, Ser126, Ser220, Glu146, Thr221, Trp189, and Trp125. Trp189 and Leu145 established over five hydrophobic interactions with both substances (Figure 17 and 18, Table S3).

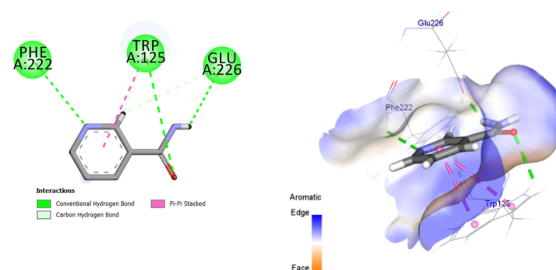

Figure 15: 2D and 3D illustrate the anticipated binding confor-mation of co-crystal ligand in the active site of CD38 enzyme.

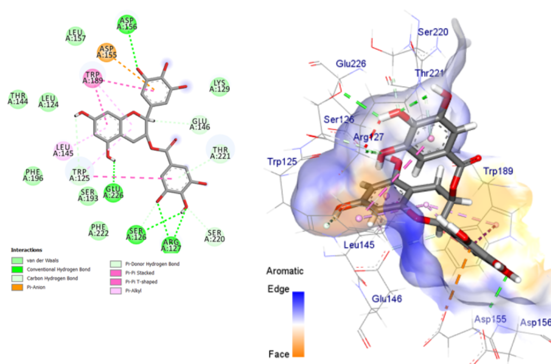

Figure 16: 2D and 3D illustrate the anticipated binding confor-mation of Epigallocatechin gallate in the active site of CD38 enzyme.

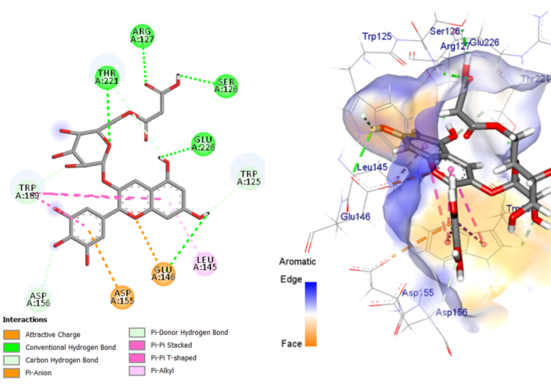

Figure 17: 2D and 3D illustrate the anticipated binding confor-mation of Delphinidin 3-(6"-malonyl-glucoside) in the active site of CD38 enzyme.

Metabolism pathway

The lowest energy conformations in docking studies were chosen for the prediction of metabolic pathways. The compounds epigallocatechin gallate, delphinidin 3-(6-̈malonyl-glucoside), cyanidin-3-O-glucoside, and isoquercitrin were forecasted utilizing Biotransformer (http://biotransformer.ca) (Djoumbou-Feunang et al., 2019). The chosen compounds were submitted to the server. Subsequently, metabolic transformations in phase I and II were selected. The Phase I metabolite prediction yielded no results. The resultant data was categorized into metabolic pathways, detailing the anticipated metabolites and the phase II enzymes that may facilitate this activity in humans. The findings are contained in Figures 19-22.

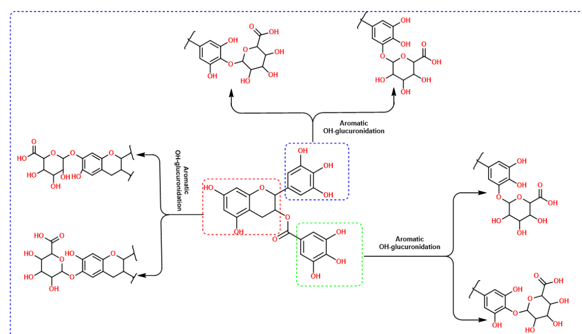

Figure 18: Anticipated phase II metabolic pathways and metabolites of compound epigallocatechin gallate in humans.

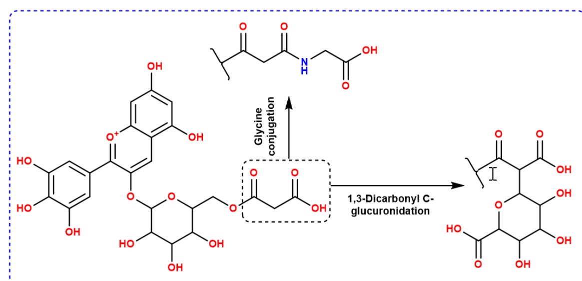

Figure 19: Anticipated phase II metabolic pathways and metabo-lites of compound delphinidin 3-(6"-malonyl-glucoside) in humans.

One likely metabolic route and six expected metabolites were identified in the metabolic analysis of the chemical epigallocatechin gallate. Figure 19 depicts the metabolic pathways of epigallocatechin gallate, characterized by aromatic OH-glucuronidation mediated by the UDP glucosyltransferase enzyme. The metabolic pathways for delphinidin 3-(6-̈malonyl-glucoside) encompass 1,3-dicarbonyl C-glucuronidation mediated by the UDP glucosyltransferase enzyme and glycine conjugation facilitated by the glycine N-acetyltransferase enzyme (Figure 20). The anticipated phase II metabolites of cyanidin-3-O-glucoside involve catechol O-methylation by O-methyltransferase (Figure 21). Moreover, the primary anticipated routes for the molecule isoquercitrin include the demethylation of 14-alpha-methylsterol by the enzyme alcohol sulfotransferase and the O-methylation of catechol by O-methyltransferase (Figure 22).

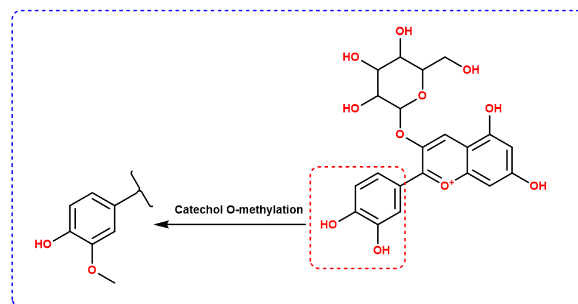

Figure 20: Anticipated phase II metabolic pathways and metabo-lites of compound cyanidin-3-O-glucoside in humans.

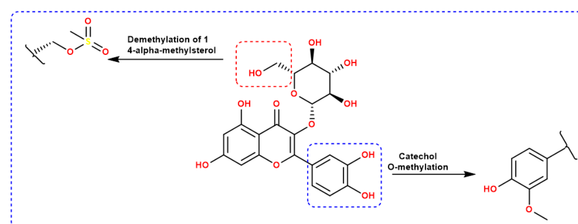

Figure 21: Anticipated phase II metabolic pathways and metabolites of compound isoquercitrin in humans.

CONCLUSION AND RECOMMENDATION

Finally we can say that this research work has successfully identified potential flavonoid targets using the Swiss Target Prediction platform and conducted a comprehensive analysis of pharmacokinetic properties of 17 Arabian coffee flavonoids. The results highlighted the importance of adhering to Lipinski's rule of five, with several compounds that have showed promising pharmacological potential based on their physicochemical characteristics. Molecular docking studies provided valuable insights into the binding interactions of the flavonoid compounds in the Arabian coffee with aldose reductase, carbonic anhydrase II and lymphocyte differentiation antigen CD38. The docking scores indicated strong affinity between the Arabian coffee flavonoid content and their protein targets indicating therapeutic potential for these flavonoids. Additionally, the metabolic pathway analysis predicted potential metabolites of the investigated compounds, shedding light on their potential biotransformation pathways in humans. This research work will help to understand the pharmacological properties of Arabian coffee flavonoids, putting the groundwork for future research on their therapeutic applications.

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DECLARATIONS

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose. The authors declare no conflict of interest.

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