

Targeting insulin signaling and TRAF2/JNK pathway: a comprehensive in silico study of Uncaria tomentosa compounds

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Abstract

Type 2 diabetes (T2D) is a metabolic syndrome frequently associated with obesity and endoplasmic reticulum stress-mediated inflammation, which can lead to unfolded protein response (UPR), impaired insulin signaling, and apoptosis. In an attempt to identify potential natural therapeutic candidates, this study investigated the mechanisms of action of fourteen compounds present in *Uncaria tomentosa* (UT), a medicinal plant from the Amazon rainforest, using *in silico* modeling. The study focused on UPR, TRAF2/JNK pro-inflammatory and insulin signaling pathways, which play key roles in T2D. The UT compounds were docked against several human proteins involved in these pathways, and molecular dynamics simulations confirmed stable interactions between the target proteins (PERK, TRAF2, JNK, TNF- α , IRS-1, PI3K, AKT, GSK3 β , and PPAR γ) and four of the UT compounds, *5-Carboxystrictosidine*, *Cinchonain*, *Epicatchin* and *Mitraphylline*. Additionally, ADMET property analyses were conducted for the four promising compounds, revealing favorable pharmacokinetic properties. These findings suggest that specific UT compounds may offer therapeutic potential in managing T2D by modulating signaling pathways related to the conditions UPR, inflammation, and insulin resistance.

1. INTRODUCTION

Diabetes is a non-communicable disease with a large increase in cases in the last years [1]. The number of diagnosed cases of diabetes rose from 108 million in 1980, to 422 million in 2014, with more rapid prevalence increase in low- and middle-income countries than in high-income countries [1; 2]. More than 95% of the diabetes cases are type 2 diabetes mellitus (T2D), a metabolic disorder with high mortality rates and significant healthcare expenses worldwide [3; 1; 4].

According to some authors, the global mortality rate caused by T2D and its complications was 6.7 million in 2021 as it is estimated that in 2045 there will be a significant increase to 700 million cases of T2D in the world [2; 5; 6]. Furthermore, the International Diabetes Federation published in 2021 that 3 in 4 adults in developing or non-developed countries have T2D. In total, USD 966 billion has been spent worldwide on health treatments for T2D in the last 15 years [2]. According to Parker *et al.* (2023), 1 in every 4 dollars spent in health care in the United States in 2022, was used for treatment of patients with T2D [7].

T2D is a chronic condition characterized by hyperglycemia and metabolic disturbances involving carbohydrates, lipids, and proteins, resulting from changes in insulin production, secretion and/or its mechanism of action [3; 8; 9]. Insulin resistance, defined as an attenuated biological response to circulating insulin, is a defect observed in both obesity and T2D [10].

Several molecular events contribute to insulin resistance, most of which are associated with oxidative stress, inflammation, or ER stress [9; 11; 12;]. Under oxidative stress, ER stress is triggered and initiates the Unfolded Protein Response (UPR) [12; 13; 14; 15].

The UPR relies on three protein sensors, of which the inositol requiring enzyme 1 (IRE1) is the most conserved. IRE1 consists of a luminal domain, a transmembrane helix, and cytosolic kinase and RNase domains. In its inactive form, the luminal domain binds the chaperone BIP, blocking its ability to dimerize [12; 16]. During the UPR, BIP dissociates, which enables dimerization, trans-autophosphorylation and activation.

Once IRE1 is activated, TNF receptor-associated factor 2 (TRAF2) is recruited to bind to this stressor sensor, mediating the activation of N-terminal c-Jun kinase (JNK) [16; 17]. Particularly under the accumulation of ROS and misfolded proteins, several pathways are activated to protect cells from damage [12; 16; 18]. However, if the stress condition cannot be mitigated, the ER also signals molecular events involved in the expression of pro-inflammatory cytokines, such as tumoral necrosis factor alpha (TNF- α) [16; 19]. This cytokine leads to the expression of TRAF2 and JNK, which regulate pro-apoptotic pathways to eliminate damaged cells [16; 19].

JNK also induces the phosphorylation of Ser312 (human numbering) in insulin receptor substrate 1 (IRS-1), inhibiting its activity [20; 21; 22]. This reduces the insulin-binding capability, further worsening insulin resistance [12; 21; 23].

Therapies that include drugs targeting lipid metabolism has been suggested for the treatment of individuals with various diseases, including obesity and T2D. Indeed, the World Health Organization (WHO) has proposed strategies to incorporate complementary and alternative therapies, such as phytotherapy, into the development of new technologies and innovations as global public health tools [1].

Uncaria tomentosa (UT), popularly known as “cat's claw”, is a species of the Rubiaceae family, recognized as an herbal medicinal plant native to the Amazon rainforest [24]. It has already been demonstrated that UT extract can attenuate oxidative stress and the expression of proteins during ER stress, and that it exhibits antioxidant and anti-inflammatory properties [9; 25; 26; 27]. However, which specific compounds from the plant extract that might interact with proteins involved in the UPR or insulin signaling pathways have not yet been identified.

In this study, we used *in silico* modeling to explore the potential interactions of fourteen UT compounds with key target proteins, including PERK, TNF- α , TRAF2, JNK, IRS-1, PI3K, AKT, GSK3 β and PPAR γ .

2. MATERIAL AND METHODS

2.1 Selection of compounds and target proteins

The crystal structures of 13 proteins, corresponding to those involved in the UPR, ISR or insulin signaling pathway in *Homo sapiens*, were downloaded from the *Protein Data Bank* (www.rcsb.org) (Table 1). For HRI kinase, due to the lack of a crystal structure, a homology model previously developed in the group using the Yasara software, was utilized. In addition, the structures of fourteen compounds found in UT [28], were obtained from the PubChem database (<http://www.pubchem.ncbi.nlm.nih.gov>) (Table 2). The chemical structures of the fourteen compounds are shown in **Supplementary Fig. S1**.

Subsequently, the structures were transferred to Maestro software [29] for further preparation, docking, simulations and analysis.

Table 1

Selected proteins and their respective codes in Protein Data Bank (PDB), used in the in silico modelling.
 Group 1 involves proteins of the ISR and UPR receptor pathways; Group 2 involves proteins related to the inflammation and cell survival pathway; Group 3 involves proteins of the insulin signaling pathway.

	Target proteins	PDB code	Resolution (Å)
Group 1	Protein Kinase RNA-Like ER Kinase (PERK)	4M7I	2.34
	Inositol-requiring enzyme 1 (IRE1)	3P23	2.70
	Heme-regulated eIF2- α kinase (HRI)	Homology protein	-
	General control nonderepressible 2 (GCN2)	7QQ6	2.80
	Eukaryotic translation initiation factor 2 alpha and gamma (eIF2 α)	8QZZ	3.35
Group 2	TNF Receptor Associated Factor 2 (TRAF2)	1D0A	2.0
	c-Jun N-terminal kinases (JNK)	4HYS	2.42
	Tumor necrosis factor alpha (TNF- α)	2AZ5	2.10
Group 3	Insulin receptor substrate (IRS-1)	2Z8C	3.25
	Phosphoinositide 3-kinase (PI3K)	4UWH	1.93
	Protein kinase B (PKB/AKT)	1O6L	1.60
	Glycogen synthase kinase 3 beta (GSK3 β)	3F88	2.60
	Peroxisome proliferator-activated receptor gamma (PPAR γ)	1I7I	2.35

Table 2
Selected compounds present in the UT plant, and their respective codes in the Pubchem databank.

	UT compounds	PubChem code
1	<i>5-Carboxystrictosidine</i>	CID: 44593370
2	<i>7-Deoxyloganin acid</i>	CID: 443322
3	<i>Cinchonin</i>	CID: 442675
4	<i>Epicatechin</i>	CID: 72276
5	<i>Hirsutine</i>	CID: 3037151
6	<i>Hirsutine</i>	CID: 3037884
7	<i>Isomitraphylline</i>	CID: 11726520
8	<i>Isorhynchophylline</i>	CID: 3037048
9	<i>Mitraphylline</i>	CID: 94160
10	<i>Rhynchophylline</i>	CID: 5281408
11	<i>Strictosamide</i>	CID: 10345799
12	<i>Uncarine C (Pteropodine)</i>	CID: 10429112
13	<i>Uncarine D (Speciophylline)</i>	CID: 168985
14	<i>Uncarine E (Isopteropodine)</i>	CID: 9885603

2.2 Protein structure preparation

All downloaded structures were prepared using the Protein Preparation Wizard tool in Maestro [29]. During the preprocessing stage, hydrogen atoms and disulfide bonds were added to the initial coordinates. All water molecules located at a distance greater than 5.0 angstroms (Å) were deleted. To determine the likely protonation states of the side chains and the energy penalties associated with alternate protonation states, a pH of 7.0 ± 0.2 was applied.

The protein hydrogen bond assignments were then optimized in the H-bond Refine Tab using sample water orientations and PROPKA at pH = 7.0 [30]. For the initial restrained minimizations, the root-mean-square deviation (RMSD) for heavy atom convergence was set to 0.3 Å. The optimized potential for liquid simulations (OPLS4) force field was employed, and hydrogen atoms were minimized while allowing sufficient heavy atom movements to relax strained bonds, angles and clashes [31].

2.3 Compound preparation and ligand docking

The structures of the compounds were prepared using the LigPrep module in Maestro. The Epik module [32] was used to evaluate possible ionization states at physiological pH 7.0 ± 0.2 , and the OPLS4 force field was selected for the optimization.

To perform molecular docking and predict the interactions of the protein–ligand complexes (Fig. 1), the Induced Fit Docking (IFD) methodology in Glide was used [33]. The cubic grid box for the docking was defined at the centroid of the bound co-crystallized ligand in the active binding site, with a side length of 20 Å. All fourteen ligands were docked into the active sites of the target proteins. During the initial docking procedure, the van der Waals scaling factor was set at 0.5 for both receptors and ligands. The Prime refinement step was applied to the side chains of residues within 5.0 Å of the ligand [29].

2.4 Molecular dynamics (MD) simulations

The stabilities of the protein-ligand complexes were investigated through MD simulations, using the Desmond engine in Schrödinger [29], in NPT ensemble for 200–300 ns, when the complexes reached a relatively stable binding conformation and dynamic behavior. The TIP3P force field was used to model water molecules and periodic boundary conditions were applied with a 10 Å water buffer surrounding the protein within a cubic simulation box [29]. Na⁺ and Cl[−] ions were added to neutralize the system and achieve a final NaCl concentration of 150 mM. Temperature and pressure were set to 300 K and 1 bar, using the Nose-Hoover thermostat and Martyna-Tobias-Klein barostat, respectively [35; 36].

The OPLS4 force field was employed for the proteins and ligands [31]. As a measure of protein mobility, the Root Mean Square Deviation (RMSD) of the α -carbons of the protein was calculated throughout the simulation, and the RMSD of the ligand heavy atoms during the trajectory of the simulation was also calculated, as a measure of ligand mobility [37]. The RMSD relates to the deviation of the ligand and protein α -carbon atoms, from their initial suggested docking pose during the simulations. All data analyses, including the calculation of RMSD and protein–ligand contacts, were performed using the Simulation Interaction Diagram (SID) tool in Maestro software [29].

2.5 ADMET profiling

To predict pharmacokinetic properties, SMILES (Simplified Molecular Input Line Entry Specification) codes of the selected compounds present in the UT plant were obtained and used to calculate the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, using the SwissADME and ProTox III servers.

The SwissADME platform enables the submission of SMILES files for ligands, detecting the structural fragments present in the compound. Descriptors corresponding to ADMET properties are calculated using internally implemented and validated models within the SwissADME tool. This platform incorporates several model libraries that analyze various ADMET property characteristics based on the physicochemical space of the molecule's structural groups and the database information [38]. The results are provided as graphical outputs with legends indicating compliance or non-compliance with ADMET properties [38].

For toxic substructure analysis, the ProTox III server was used. This tool evaluates structural alerts related to hepatotoxicity, mutagenicity, genotoxicity, carcinogenicity, cytotoxicity, cytochrome P450 interaction, and acute oral toxicity. The server's libraries compile toxicological safety data (both *in vitro* and *in vivo*) from public databases and literature, with a total of 174 datasets/models. These models detect structural alerts in ligands by comparing the molecular information to known toxic groups and substructures of documented substances [39].

3. RESULTS

3.1 Ligand docking of the UT compounds

Fourteen compounds present in the UT plant were preliminarily tested to evaluate their potential affinities with proteins involved in the ISR and TRAF2/JNK pathways, as shown in Figs. 2, 3 and 4.

In the first group of proteins, the kinase eIF2 α and the stress response receptors GCN2, HRI, IRE1 and PERK were analyzed (Fig. 2A, 2B, 2C, 2D and 2E). Among the fourteen tested compounds, none exhibited higher affinity for the eIF2 α than the substrate GTP, or higher affinity for GCN2, HRI or IRE1 kinases than the substrate ATP. However, in the first group of proteins, *Epicatechin* (4) showed a significant interaction with PERK, exhibiting a binding energy around -9.13 kcal/mol, significantly higher than ATP, as shown in Fig. 2E.

In the second group of proteins, relating to inflammation and cell survival pathway, TRAF2, JNK and TNF- α were analyzed (Fig. 3A, 3B and 3C). For TRAF2 (Fig. 3A), ATP was bound at the inhibition site and showed an affinity of -5.53 kcal/mol. *Epicatechin* (4) showed affinity for the inhibition site of the protein, with a binding energy of -5.73 kcal/mol. In addition, in the JNK protein complex (Fig. 3B), *Epicatechin* (4) also demonstrated strong interaction with the protein, with an affinity of -7.23 kcal/mol, in comparison to ATP binding with an affinity of -7.66 kcal/mol.

Finally, for the TNF- α cytokine (Fig. 3C), the co-crystallized inhibitor 307, bound at the active site of the cytokine, displayed an affinity of -5.13 kcal/mol. For this system, *5-Carboxystrictosidine* (1), *Epicatechin* (4) and *Uncarine D* (13) demonstrated relative affinity for the residues of the same inhibition site, with binding energies of -4.68, -4.69, and -4.65 kcal/mol, respectively.

In the third group of proteins, relating to the insulin signaling pathway, IRS-1, PI3K, AKT, GSK3 β and PPAR γ were analyzed (Fig. 4A, 4B, 4C, 4D and 4E). It was found that the insulin-like growth factor 2 (IGF-2), bound in the phosphorylation complex of IR-IRS1 proteins which activates insulin signaling (Fig. 4A), exhibited an affinity of -6.87 kcal/mol. The UT compounds *5-Carboxystrictosidine* (1), *7-Deoxyloganic acid* (2) and *Epicatechin* (4) showed affinities with residues at the same phosphorylation site of the complex, with binding energies of -6.86, -6.80 and -7.75 kcal/mol, respectively.

For the kinase PI3K (Fig. 4B), the substrate ATP bound at the catalytic activity site, with an affinity of -9.13 kcal/mol, while *Epicatechin* (4) exhibited a relative affinity of -8.99 kcal/mol at the catalytic site of PI3K.

None of the compounds exhibited higher affinity for the kinases AKT and GSK3 β than the substrate ATP (Fig. 4C and 4D). For the PPAR γ protein (Fig. 4E), the prostaglandin J2 (PGJ2) bound at the protein active site, which activates PPAR γ expression, showed an affinity of -8.88 kcal/mol. For this protein, only four of the 14 compounds were able to dock to the active site. In this case, *5-Carboxystrictosidine* (1) exhibited a strong affinity for the active site of PPAR γ , with a binding energy of -10.05 kcal/mol (Fig. 4E).

4.2 MD simulations

The stability of the binding between the UT compounds and target proteins was evaluated, along with the types of interactions established. For the molecular dynamics analysis of the first group, only PERK had

adequate stability in interactions with *Epicatechin* (4) in the kinase binding site, with average RMSD of 1.5 Å (**Supplementary Fig. S2**), in agreement with the docking study, showing that the complexes maintained RMSD values within 3.0 Å, indicating stable and consistent ligand-protein interactions.

In the second group of proteins, molecular dynamics of UT compounds with TNF-α revealed that *Mitraphylline* (9) (**Supplementary Fig. S3**) displayed stable interactions with the cytokine, with an RMSD of 3.0 Å. Furthermore, *Mitraphylline* (9) also displayed stable interactions with the inhibition site of TRAF2, with an RMSD of 2.7 Å (**Supplementary Fig. S4**), compared to the results observed in the ligand docking (Fig. 3A).

On the other hand, TRAF2 and JNK exhibited binding affinity with *Epicatechin* (4) and molecular dynamics confirmed the interaction remained stable (**Supplementary Fig. S5 and S6**), with RMSD of 3.0 and 3.5 Å, respectively.

For the third group of proteins, it was demonstrated in the molecular dynamics analysis that *5-Carboxystrictosidine* (1) remained stable in the binding site of IRS-1 (**Supplementary Fig. S7**), with RMSD value of 2.5 Å. Additionally, the interaction between PI3K and *Epicatechin* (4) exhibited high stability with an RMSD of 1.5 Å (**Supplementary Fig. S8**). On the other hand, the molecular dynamics of UT compounds with AKT and GSK3β revealed that *Cinchonain* (3) demonstrated partial stability in its interactions with the catalytic site of AKT (**Supplementary Fig. S9**) and greater stability with the phosphorylation inhibition site of GSK3β (**Supplementary Fig. S10**), with RMSD of 5.5 and 2.5 Å, respectively, compared to the results observed in the ligand docking (Fig. 4C and 4D).

Finally, the interaction of *5-Carboxystrictosidine* (1) with the active binding site of PPARγ was assessed (Fig. 4E), given its role in enhancing insulin sensitivity in adipose tissue, skeletal muscle, and liver [40; 41]. The compound was found to interact stably with PPARγ, presenting RMSD of 2.0 Å (**Supplementary Fig. S11**), which is again in agreement with the docking studies.

4.3 ADMET profiling

Understanding the pharmacokinetics and safety profiles of the compounds is crucial for determining their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, particularly when assessing their suitability as drugs.

ADMET analyses were conducted during the virtual screening stage for the four compounds, *5-Carboxystrictosidine*, *Cinchonain*, *Epicatechin* and *Mitraphylline*, that showed the strongest interactions with target proteins of the stress response, TRAF2/JNK or insulin signaling pathway, following the molecular dynamics tests.

The oral bioavailability graphs shown in Fig. 5 illustrate the adjustments required to optimize the behavior of each ligand as drug candidate (pink region of the radar plots). For *5-Carboxystrictosidine* (Fig. 5A), adjustments in polarity and to some extent molecular size were indicated. In the case of *Cinchonain* (Fig. 5B), improvement in polarity was also highlighted, plus in the unsaturation aspect, as suggested for *Epicatechin* (Fig. 5C). Conversely, the radar plot for *Mitraphylline* (Fig. 5D) demonstrated that it is structurally suitable, requiring only minor flexibility adjustments.

In addition, some of the pharmacochemical ADMET properties were analyzed for the four selected compounds (Table 3). It was found that *5-Carboxystrictosidine* has strong hydrophilic characteristics, mainly caused by the sugar moiety, leading to low absorption in the gastrointestinal tract (GIT). On the other hand, the compounds *Cinchonain*, *Epicatechin* and *Mitraphylline* have more lipophilic characteristics, but *Cinchonain* presents low absorption by the GIT, while *Epicatechin* and *Mitraphylline* have high absorption by the GIT.

Most of the compounds with exception of *Cinchonain* showed probabilities for affinity towards P-glycoproteins (P-gp), but all of them present no significant risk of inhibiting the activity of the cytochrome P450 and isoenzymes CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP2E1. In addition, the four compounds did not present any predicted risk of toxicity to hepatocytes or other cells, unless the cardiotoxicity risk, in which *5-Carboxystrictosidine* presented 56% of potential stimulation.

Table 3

Pharmacochemical properties and toxicity profiles. Predicted ADMET properties of the four compounds 5-*Carboxystrictosidine*, *Epicatechin*, *Mitraphylline* and *Cinchonain* obtained through the SwissADME and Pro-Tox III servers, to indicate the physicochemical characteristics, lipophilicity, water solubility, pharmacokinetic aspects, similarity to other drugs (drug-likeness) and toxicity risk.

ADMET properties		UT compounds			
		5- Carboxystrictosidine	Epicatechin	Mitraphylline	Cinchonain
Physicochemical characteristics	MW (g/mol)	574,58 g/mol	290,27 g/mol	368,43 g/mol	452,41 g/mol
	Heavy atoms	41	21	27	33
	H + acceptors	12	6	5	9
	H + donors	7	5	1	6
Lipophilicity	Log P (-3 to 5)	-2.05	0.36	1.62	1.52
Solubility in water	Log S (ESOL, -4 to 0)	Very soluble (-1.68)	Soluble (-2.22)	Soluble (-3.18)	Moderately soluble (-4.33)
Pharmacokinetics	GTI absorption	Low	High	High	Low
	BBB permeability	No	No	No	No
	P-gp substrate	Yes	Yes	Yes	No
	CYP450 inhibitor and isoenzymes	No	No	No	No
Drug-likeness	Lipinski	No	Yes	Yes	Yes
Toxicity risk	Hepatotoxicity	No = 69%	No = 72%	No = 75%	No = 73%
	Cardiotoxicity	Yes = 56%	No = 99%	No = 58%	No = 79%
	Mutagenicity	No = 54%	No = 55%	No = 62%	No = 73%
	Cytotoxicity	No = 65%	No = 84%	No = 65%	No = 80%

5. DISCUSSION

This study aimed to identify compounds from *Uncaria tomentosa* [24; 28] that interact with key proteins involved in UPR and insulin signaling pathways, such as PERK, IRS-1, PI3K, AKT, GSK3 β , TNF- α , TRAF2, JNK or PPAR γ , using an *in silico* modeling.

From the ligand docking, the compounds with higher affinity for the proteins than the natural substrates or co-crystallized ligands were identified by comparing the obtained docking scores (in kcal/mol).

In the first group of proteins, some of the transmembrane proteins involved in UPR, such as PERK and IRE1, and some that trigger ISR, such as HRI and GCN2, were evaluated [42]. No inhibitory effects were predicted between HRI, IRE1, or GCN2 and the 14 compounds. On the other hand, it was observed that the compound *Epicatechin* strongly binds to PERK kinase. This result suggests that the compound might interact with the binding site of the kinase enough to be stable [42]. Once PERK is activated, eIF2 α is phosphorylated, which attenuates proteins synthesis under ER stress conditions [43].

For eIF2 α , no affinity was observed with the compounds, suggesting that the compounds present in UT do not directly attenuate protein synthesis [42]. This is further supported by the finding that PERK could also be inhibited by *Epicatechin*.

In the second group of proteins, the interactions of the UT compounds with the cytokine TNF- α , TRAF2 or JNK, expressed in one of the autophagy pathways were evaluated [44; 45].

During the ligand docking modelling, it was verified that the pro-inflammatory cytokine TNF- α exhibited affinity for three compounds: *5-Carboxystrictosidine*, *Epicatechin*, and *Uncarine D*. However, when evaluating the molecular dynamics of these compounds with the cytokine, no stable interactions with the binding site were found. This occurrence can be attributed by the fact that during molecular dynamic simulations, the ligand and protein can adopt different conformations, which may disrupt interactions initially predicted by docking. The dynamic behavior can reveal that some docking poses are not stable or energetically favorable under physiological conditions, leading to weaker or lost interactions during MD [39, 42].

However, in a second assessment by molecular dynamics it was observed that *Mitraphylline* interacts stably with TNF- α , suggesting that *Mitraphylline*, as an anti-inflammatory compound, could interfere with the activity of the pro-inflammatory cytokine TNF- α and subsequently modulate inflammatory responses [25].

Regarding the TRAF2 protein, while the flavonoid *Epicatechin*, known for its antioxidant action [46; 47], demonstrated higher affinity with the binding site of TRAF2 than the natural substrate, *Mitraphylline* demonstrated the opposite (Fig. 5A). However, after evaluating the dynamics between *Epicatechin* or *Mitraphylline* and TRAF2, stable interactions were observed between both compounds and the protein's binding site.

From the docking, JNK showed strong interaction with *Epicatechin*. When evaluating the dynamics between *Epicatechin* and the kinase, the interaction was also confirmed to be stable. These results suggest that *Epicatechin* and *Mitraphylline* can interact stably and potentially block the activity of TNF- α , TRAF2 and JNK regulating oxidative stress and pro-inflammatory pathways [46; 47].

To relate the results obtained for the UT compounds and to evaluate the potential for treating insulin resistance, the stability of the fourteen UT compounds was also assessed through molecular dynamics, with the binding sites of target proteins involved in the insulin signaling pathway.

The compound *5-Carboxystrictosidine* showed stable binding towards IRS-1, from the docking and the MD simulations. The dynamics between PI3K and *Epicatechin* were also stable, even the small difference presented in the docking studies between *Epicatechin* (-8.99 kcal/mol) and ATP (-9.13 kcal/mol). This difference of affinity could be explained by the additional interactions and conformational adjustments that can be revealed in the molecular dynamic simulations, which may compensate for differences in binding affinity suggested by limitations in the docking scores [42, 69].

Finally, when evaluating the interactions of the kinases AKT or GSK3 β with the compounds, it was found that *Cinchonain* displayed stable binding towards the kinases in the MD simulations.

Little is known about the relationship and interaction between *5-Carboxystrictosidine*, *Epicatechin* and *Cinchonain* with the proteins of the insulin signaling pathway. However, according to some authors [24; 25; 28; 46; 48], these compounds cited, isolated from the plants *Uncaria tomentosa* or *Psychotria nuda*, have antioxidant characteristics and promote attenuation of ROS production in human erythrocytes, macrophages and skeletal muscle tissue. This may be related to the attenuation of ER stress and the modulation of insulin receptor signaling [12; 49].

Furthermore, the possible interaction of the transcription factor PPAR γ with the compounds was evaluated. PPAR γ antagonizes the metabolic syndrome of type 2 diabetes (T2D) through the negative regulation of peripheral inflammatory processes, including the suppression of pro-inflammatory cytokines and increased insulin sensitivity in adipose tissue, skeletal muscle, and liver [40; 41; 50; 51]. When evaluating the affinity and binding stability between the UT compounds and PPAR γ , it is suggested that this compound may act as a potential PPAR γ agonist, enhancing insulin sensitivity through the regulation of glucose and lipid metabolism [41, 51], regarding *5-Carboxystrictosidine* also showed stable binding towards IRS-1 protein, a key mediator in the insulin signaling pathway, indicating its possible role in improving insulin receptor signaling and downstream metabolic effects [40, 50, 51].

The interactions of the four selected compounds with the residues of the target proteins were further analyzed based on the MD simulations (Table 4).

Table 4
Characterization of the different protein interactions with the UT compounds during the molecular dynamic simulations

UT compounds	Protein	Hydrogen bond interactions	Hydrophobic interactions
		Amino acids (interactions $\geq 30\%$)	
<i>Epicatechin</i>	PERK	Val651; Lys621; Gln888; Arg891; Phe955; Gly956	--
	PI3K	Tyr670; Asp761; Ile685; Gln683; Ser687; Glu692	Tyr670
	TRAF2	Ala48; Glu60; Leu73; Asp160; Phe161	--
	JNK	Glu109; Met111	--
<i>Mitraphylline</i>	TNF- α	--	Tyr59; Tyr119
	TRAF2	Met97; Asp160	--
<i>5-Carboxystrictosidine</i>	PPAR γ	His323; Ser289; Arg288	Leu340
	IRS-1	Gln1004; Glu1047; Glu1077; Met1079; Asp1083;	--
<i>Cinchonain</i>	GSK3 β	Asp133; Lys85; Gln185; Asn186	--
	AKT	Leu158; Lys160; Ala232, Glu236; Glu279; Asp293; Thr436	Phe439

The interactions found between *Epicatechin* and PERK residues Val651, Gln888, Phe955, Gly956 located in the DFG-*motif* and ATP binding site, correspond to 4 out of the 10 key residues found in the activation site (Leu598, Arg600, Gln888, Cys890, Lys938, Ser940, Asp954, Phe955, Gly956, Thr986) [52; 53], which suggests that *Epicatechin* might impair the activation of the kinase and inhibit the expression under the UPR and stress responses.

The interactions of the same compound *Epicatechin*, a polyphenol known for its antioxidant role, and the JNK residues Glu109 and Met111 located in the inhibition site of the kinase, correspond to 2 out of 3 residues that mediate the suppression of JNK phosphorylation (Glu109, Leu110, Met111) [54; 55; 56], which suggests that *Epicatechin* might inhibit the activation of JNK, which plays a significant role in responses to oxidative stress [55].

Regarding the anti-inflammatory response of *Mitraphylline*, thus was found to bind strongly to the residues Tyr59 and Tyr119, located in the inhibitory binding site of the pro-inflammatory cytokine TNF- α [57; 58]. The binding of one or more compounds to this region alters the trimmer symmetry and destabilize the cytokine, thus acting as TNF- α inhibitors [57; 58].

In relation to the insulin signaling pathway, Peasari *et al.* (2018) reported that IRS-1 residues Glu1077, Met1079, and Asp1083, which interacted strongly with *5-Carboxystrictosidine*, are located in the active site of this tyrosine kinase and modulate its insulin receptor activity [59]. Moreover, some authors [60; 61] described that the residues Tyr670, Ile685, and Ser687, which are involved in the affinity between *Epicatechin* and the protein kinase PI3K, are located in the catalytic phosphorylation site and may contribute to the activation of the protein.

In addition, some authors [62; 63; 64] indicated that residues Leu158, Lys160, Glu236, Glu279, Thr436, and Phe439 in the AKT protein kinase which exhibited affinity for *Cinchonain*, are located in the catalytic site of the kinase. For GSK3 β , the residues Asp133, Gln185 and Asn186 which also interacted with the compound *Cinchonain*, are located in the active site of the protein kinase [65; 66], suggesting that this compound may act as a modulator of GSK3 β activity.

To verify whether UT compounds could also be considered as therapeutics targeting lipotoxicity-induced insulin resistance, their affinity for PPAR γ was evaluated. Both His323 and Ser289 are among the residues that stabilize *5-Carboxystrictosidine* binding to the protein. According to some authors [67; 68], interactions with the residues His323 and Ser289 are characteristic of PPAR γ agonists and contribute to the activation of the transcription factor, which is considered as a target against hyperglycemia associated with T2D.

Despite the valuable predictions presented in this study, it is not possible to fully replicate the complexity of biological systems by the computational methods. Therefore, this study serves as base for conducting complementary experimental assays to validate and confirm the therapeutic potential of the predicted interactions, as well as to achieve a comprehensive understanding of the mechanism of action of the UT compounds.

4. CONCLUSIONS

In summary, the results presented in this study contribute to a better understanding of the mechanisms of action of the compounds present in the *Uncaria tomentosa* plant, within the molecular context of UPR, ER stress, insulin signaling regulation, insulin resistance and cell death. *5-Carboxystrictosidine*, *Cinchonain*, *Epicatechin* and *Mitraphylline* were found to exhibit the strongest affinities with the proteins involved with UPR and insulin resistance conditions, demonstrating significant interactions with key residues during the *in silico* modelling. This further supports the possible therapeutic benefits of the plant, although future experimental validations remain necessary.

Declarations

AUTHOR CONTRIBUTIONS

Bruna L. F. Marchi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Software; Visualization; Writing - original draft. *Shraddha Parate*: Investigation; Methodology; Validation; Writing - original draft. *Vibhu Jha*: Investigation; Methodology; Validation; Writing - original draft. *Felipe S C Alcalde*: Investigation; Writing - original draft. *Leif A. Eriksson*: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision;

Validation; Visualization; Writing – review & editing. *Viviane A Nunes*: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing - review & editing.

DATA AVAILABILITY STATEMENT

Protein structures after preparation, docked structures of the target proteins and UT compounds, plus the MD simulations, are freely available for download at zenodo.org (<https://zenodo.org/records/17458126> and <https://zenodo.org/records/17458126>).

CONFLICT OF INTEREST

We declare that there is no financial or other potential conflict of interest.

FUNDING DECLARATION

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Figures

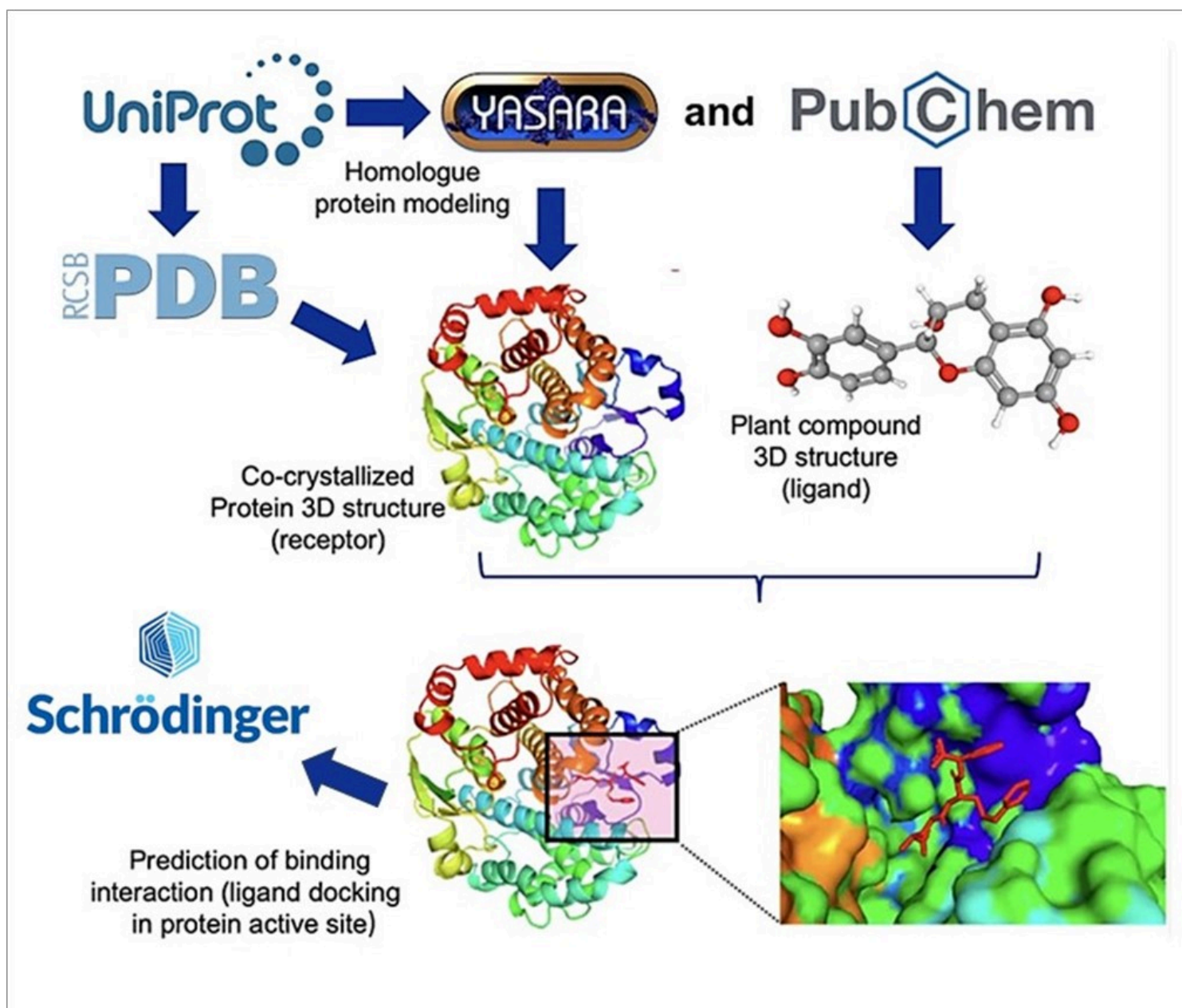


Figure 1

Schematic computational method of ligand docking, used to predict the binding affinity between the plant compounds and target proteins. Uniprot and PubChem databank were used to get the PDB of co-crystallized proteins (receptor) and UT compounds (ligands), respectively. Yasara software was used for homology protein modeling when needed [34]. After the preparation of each receptor and ligand, the docking was done using Glide in Schrodinger to predict the binding interaction.

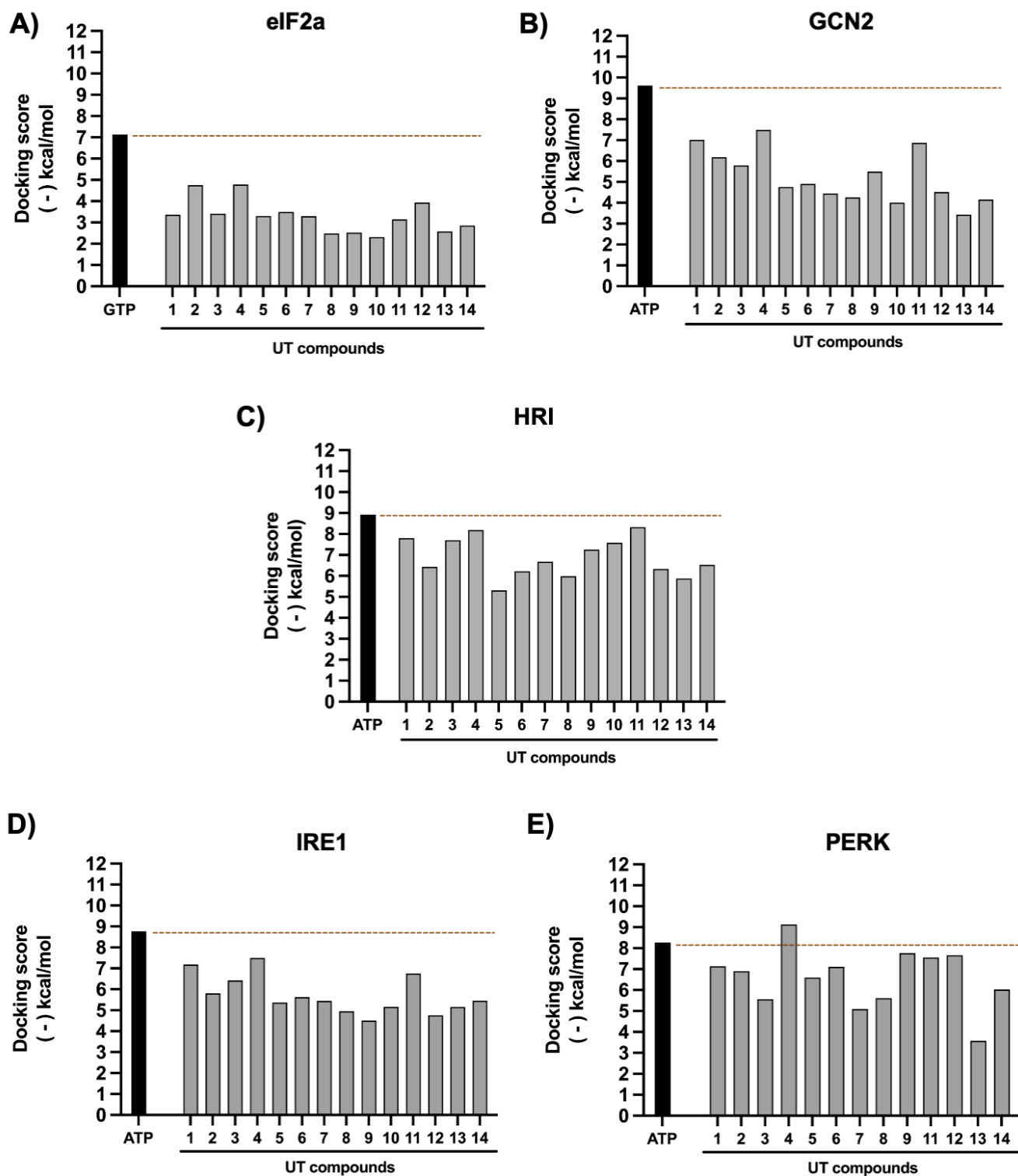


Figure 2

Affinity between the proteins A) eIF2a, B) GCN2, C) HRI, D) IRE1 and E) PERK, and the compounds present in UT plant. Molecular docking scores between the fourteen UT compounds and the kinase binding site of the selected proteins, represented by the negative values, in kcal/mol. Compounds numbering is shown in **Table 2**.

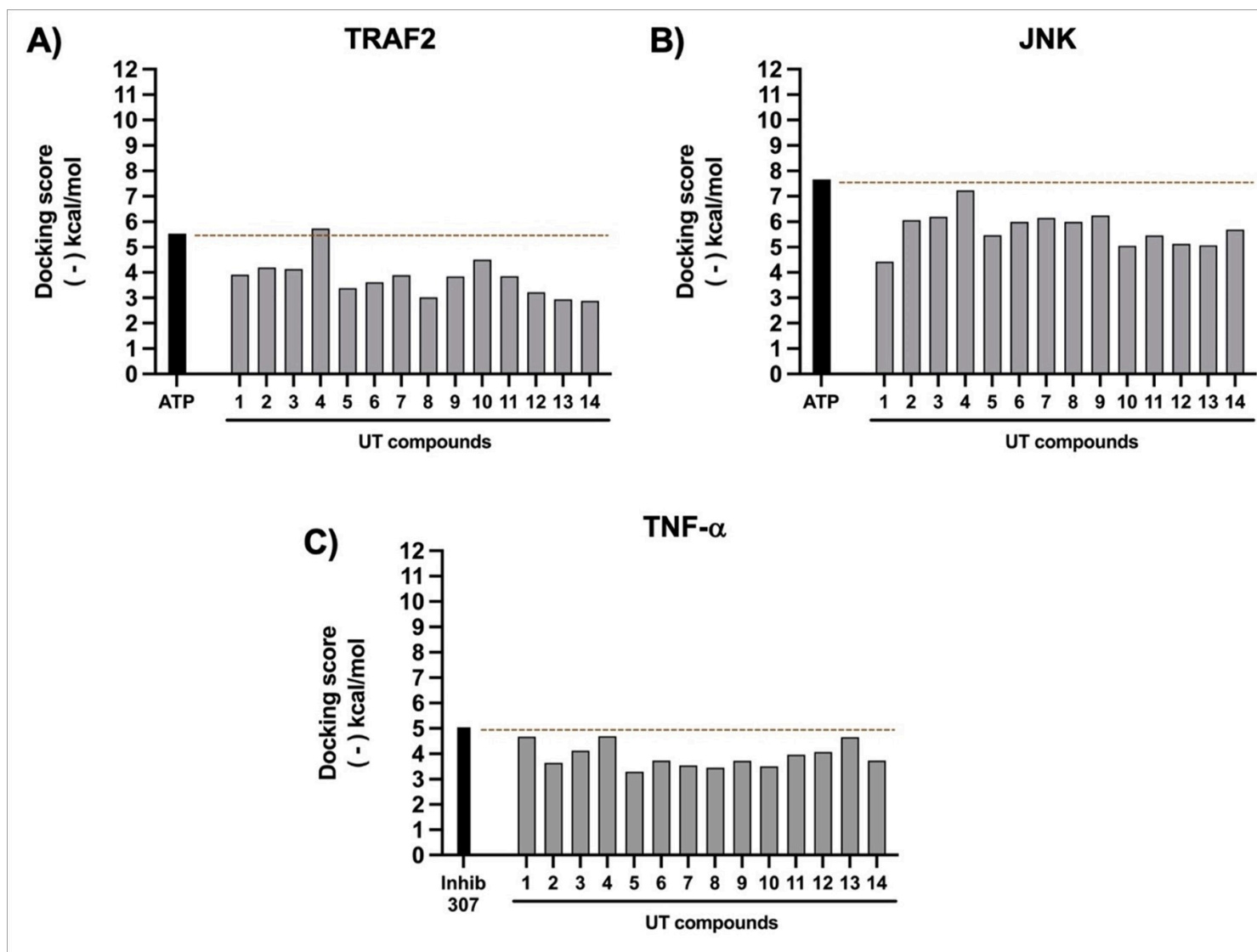


Figure 3

Affinity between the proteins A) TRAF2, B) JNK, C) TNF- α and the UT compounds. Molecular docking score between the fourteen compounds and the binding site of the selected proteins, represented by negative values, in kcal/mol. Compounds numbering is shown in **Table 2**.

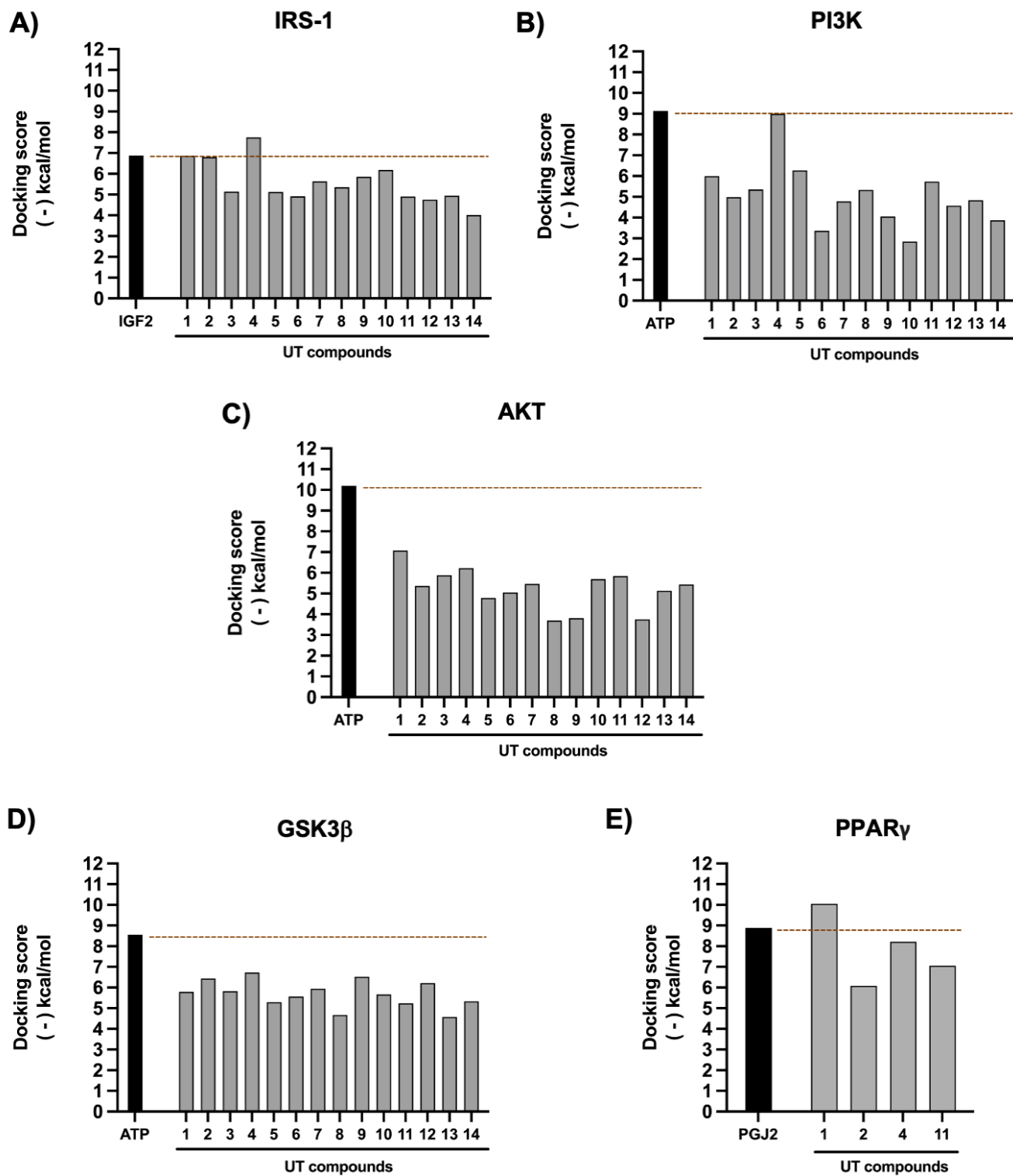
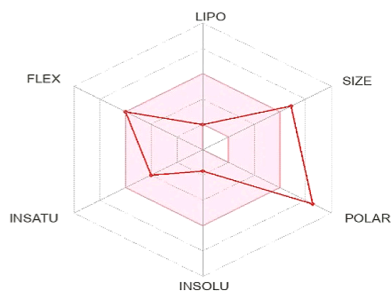
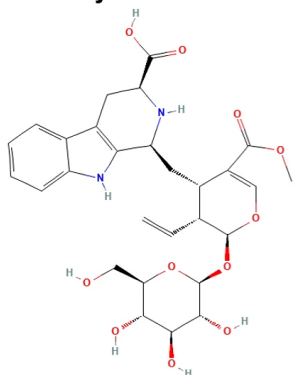


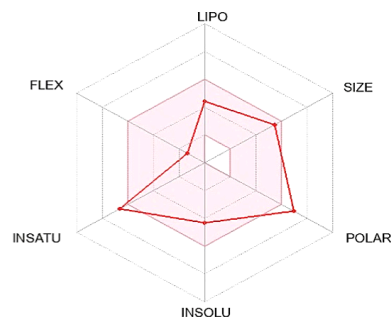
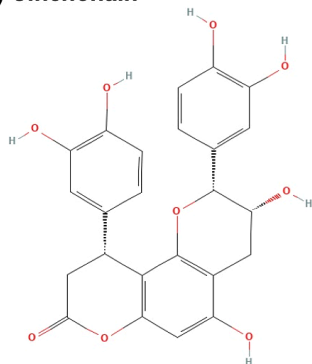
Figure 4

Affinity between the proteins A) IRS-1, B) PI3K, C) AKT, D) GSK3 β , E) PPAR γ and UT compounds. Molecular docking score between the fourteen compounds and the binding sites of the selected proteins, represented by negative values, in kcal/mol. Compounds numbering is shown in **Table 2**.

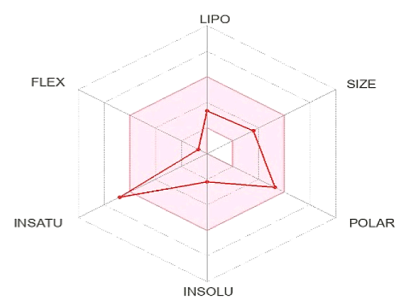
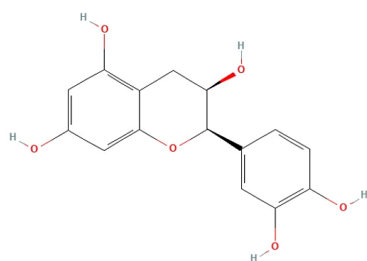
A) 5-Carboxystrictosidine



B) Cinchonain



C) Epicatechin



D) Mitraphylline

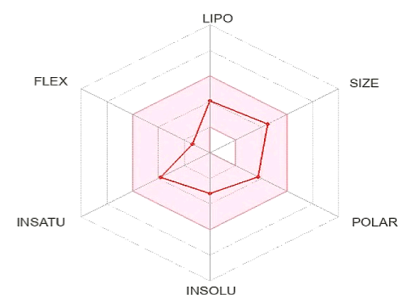
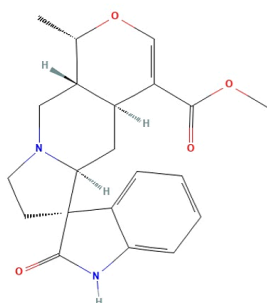


Figure 5

Chemical structures and main characteristics related to the oral bioavailability. The four most promising compounds, **A) 5-Carboxystrictosidine**; **B) Cinchonain**; **C) Epicatechin**; **D) Mitraphylline**, were evaluated using bioavailability radar plots, represented by six physicochemical properties: lipophilicity (LIPO), molecular weight (SIZE), polar surface area (POLAR), solubility (INSOLU), saturation (INSATU), flexibility (FLEX)

Supplementary Files

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