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Predicted Immunomodulatory and Anti-Inflammatory Potential of *Ficus carica* Phytochemicals Targeting NF-kB and TNF-α Signaling Pathways: An In-Silico Investigation

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Abstract: Chronic inflammation and immune dysregulation are key contributors to the development and progression of metabolic diseases, including type 2 diabetes mellitus (T2DM). Natural phytochemicals capable of modulating inflammatory signaling pathways have attracted increasing interest as potential multi-target therapeutic agents. This study investigated the predicted immunomodulatory and antidiabetic potential of major *Ficus carica* leaf phytochemicals using an integrated in silico approach combining molecular docking, physicochemical characterization, pharmacokinetic analysis, and toxicity prediction. Six bioactive compounds (quercetin, kaempferol, chlorogenic acid, caffeic acid, rutin, and gallic acid) were evaluated against four key inflammatory and metabolic targets: NF-κB p50, TNF-α, DPP-4, and α-glucosidase. Molecular docking demonstrated that quercetin and kaempferol exhibited the strongest binding affinities toward both inflammatory and metabolic targets. Quercetin showed the highest affinity for NF-κB p50 (−7.39 kcal/mol) and DPP-4 (−7.00 kcal/mol), forming stable complexes through hydrogen bonds, hydrophobic interactions, π−π stacking, and electrostatic contacts. Physicochemical and pharmacokinetic analyses indicated favorable drug-likeness and acceptable aqueous solubility for most compounds. Toxicity prediction suggested low acute toxicity (classes 4–5) but indicated potential cardiotoxicity, cytotoxicity, and immunotoxicity, emphasizing the need for cautious interpretation. Overall, the predicted interactions with NF-κB and TNF-α support the potential immunomodulatory properties of *Ficus carica* phytochemicals, particularly quercetin and kaempferol, as promising multi-target candidates for inflammation-associated metabolic disorders. However, these computational findings remain hypothesis-generating and require validation through *in vitro* and *in vivo* studies to confirm their biological activity, safety, and therapeutic potential.

Keywords: *Ficus carica*; Immunomodulation; Chronic Inflammation; NF-kB; TNF-α; Flavonoids; Molecular Docking; Inflammatory Signaling Pathways

1. Introduction

Chronic inflammation and immune dysregulation are increasingly recognized as central mechanisms involved in the development and progression of several metabolic and inflammatory disorders [1,2]. Persistent activation of inflammatory signaling pathways contributes to tissue damage, oxidative stress, and metabolic dysfunction [3]. Among the major inflammatory mediators, Nuclear Factor-kappa B (NF-kB) and Tumor Necrosis Factor-alpha (TNF-α) play essential roles in the regulation of cytokine production, immune responses, and chronic inflammatory processes [4]. The abnormal activation of these pathways has been strongly associated with immune-mediated inflammation, insulin resistance, and the progression of chronic metabolic diseases [5]. Consequently, targeting inflammatory and immune signaling pathways has emerged as an important therapeutic strategy for the management of inflammation-associated disorders [6].

Type 2 diabetes (T2D) is a complex disease that affects the body's metabolism by causing high blood sugar levels to persist because the body does not use insulin properly (insulin resistance), and the cells in the pancreas that make insulin do not work properly (progressive β-cell dysfunction). The first step leading to the development of T2D is insulin resistance, which often occurs along with compensatory hyperinsulinaemia. Hyperinsulinaemia can prevent insulin from accomplishing its normal function (insulin signaling), while allowing pathways that produce fat (lipids) to continue (lipid synthesis) [7,8]. T2D is a worldwide epidemic, affecting approximately 300 million people and increasing due to the impact of lifestyle and environmental factors resulting in a significant public health issue [8]. Concurrently, the economic burden of managing this disease is substantial, with annual global healthcare expenditures related to diabetes treatment exceeding USD 1 trillion [9]. Management of type 2 diabetes mellitus (T2DM) is challenging due to the multifaceted and heterogeneous nature of T2DM (i.e., it has many factors contributing to its development), which include genetic, metabolic, and environmental factors. As such, there is an urgent need for improved therapeutic strategies. Good glycemic control is paramount to preventing the progression of the disease and minimizing complications in the long term; however, obtaining and sustaining adequate glycemic control requires a thorough understanding of the mechanisms that govern T2DM [10–12].

In addition to its classic metabolic profile, type 2 diabetes mellitus has also become increasingly recognized as a disease of chronic low-grade inflammation [13]. There is a growing body of evidence indicating a central role for the immune system in the pathophysiology of type 2 diabetes mellitus [14]. Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are instrumental in creating insulin resistance by impeding insulin signaling pathways [15]. Concurrently, the activation of nuclear factor-κB (NF-κB), which is a master regulator of inflammatory responses, contributes to an increase in cytokine production as well as oxidative stress [16]. Overall, the interactions of these processes create a strong connection among metabolic derangements, chronic inflammation, and oxidative stress, thereby further complicating the progression of type 2 diabetes mellitus and its treatment [17].

Multiple studies now demonstrate that there is a tight association between chronic inflammation, activation of our immune system, and metabolic disorders. Based on this, the idea of immunometabolism has been established. This means that in addition to their roles regulating immune responses, inflammatory cytokines and transcription factors also modulate how we metabolize glucose and the way in which insulin signals and the processes involved in oxidative stress. Therefore, compounds capable of modulating inflammatory mediators such as NF-kB and TNF-α may provide promising therapeutic benefits by simultaneously targeting immune dysfunction and metabolic abnormalities.

The most common methods used to treat patients with Diabetes Mellitus (Type 2) are pharmacological treatments, such as Dipeptidyl Peptidase-4 inhibitors; Alpha-glucosidase Inhibitors and keeping blood glucose levels stable by working through different mechanisms of action. However, while these drugs can work well for patients, they also carry the risk of negative side effects, insufficient long-term results and associated costs [18,19]. Furthermore, due to the fact that many of these medications only work on one pathway (the target of action of the drug), and the condition of Type 2 Diabetes is considered a Multi-Factorial Disease because it has multiple molecular target sites, this highlights an urgent need for a greater variety of better and safer means of treating Type 2 diabetes that will provide patients with a method of safely treating T2DM using multiple routes of action [11,20,21].

Due to their ability to provide potential natural resources for developing new forms of treatment for complicated illnesses like diabetes, research into plants for medicinal purposes has increased. Natural materials are also

advantageous to researchers because they provide access to many different structures; therefore, they would be multi-targeted; and generally, they come with low toxicity [22]. For example, polyphenols and flavonoids have been intensely researched because of their antioxidant, anti-inflammatory and anti-diabetic actions. Both polyphenols and flavonoids have multiple mechanisms of modulating different signal pathways, and thus they can serve as an attractive target for developing Novel therapeutic agents [23]. Polyphenols and flavonoids are also known for their immunomodulatory properties through the regulation of inflammatory signaling pathways, cytokine secretion, and immune cell activation. Several natural flavonoids have demonstrated the ability to suppress NF-kB activation, inhibit pro-inflammatory cytokine production, and reduce oxidative stress. These biological properties make plant-derived phytochemicals attractive candidates for the development of multi-target therapeutic agents against chronic inflammatory and immune-related disorders.

Various cultures around the world including those from Mediterranean countries, Asia and parts of Africa have long used the common fig (*Ficus carica*, belonging to the Moraceae family) for medicinal purposes due to its many different uses as a traditional medicine [24]. Each part of the tree has therapeutic uses particularly the leaves and fruits of the fig tree. Phytochemical analysis of the medicinal properties of this plant has shown that it contains a variety of bioactive compounds including flavonoids, phenolic acids, and coumarins, which have all been shown to have multiple physiological effects and thus could be beneficial in treating multiple metabolic diseases based upon studies showing that they possess antidiabetic and antioxidant properties, and anti-inflammatory effects [25].

Despite these promising findings, the molecular mechanisms that underlie the biological activity of *Ficus carica* are not adequately understood [26]. A lack of integrated studies exists that combine phytochemical information with molecular analyses of important target proteins involved in diabetes and inflammation [27]. Molecular docking has developed as an effective method of predicting interactions between bioactive compounds and target proteins. Docking studies help develop multiple target strategies by determining molecular binding affinity, method(s) of interaction, and possible mechanisms of action for each target. Multi-target strategies will be particularly important for complex diseases, such as Type 2 Diabetes Mellitus, which involve multiple interconnected metabolic and inflammatory pathways [28,29]. Beyond their role in metabolic disorders, NF-κB and TNF-α are central regulators of innate and adaptive immune responses. Persistent activation of the NF-κB signaling pathway promotes the transcription of numerous pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and various chemokines, thereby sustaining chronic inflammation and immune dysregulation. Likewise, TNF-α is a key cytokine involved in leukocyte recruitment, macrophage activation, and the amplification of inflammatory cascades. Consequently, compounds capable of modulating these signaling pathways are increasingly considered promising candidates for immunomodulatory therapies aimed at restoring immune homeostasis in chronic inflammatory diseases.

This study investigates the immune-modulating effects against inflammation from the phytochemicals of the fig tree (*Ficus carica*) by measuring their targets for the inflammatory/metabolic pathway, specifically NF-kB p50, TNF-α, DPP-4, and α-glucosidase, using in-silico pharmacokinetic modeling and molecular docking studies. This study will evaluate if the potential therapeutics of *Ficus carica* phytochemicals can act to modulate multiple inflammatory signaling pathways that are associated with chronic metabolic and immune dysregulation through the use of molecular interaction analysis and toxicity/drug-likeness prediction.

2. Materials and Methods

2.1. Preparation of Ligands

Ligands belonging to *Ficus carica* leaves' primary phenolic and flavonoid components from prior phytochemically published studies [30], were retrieved as SDF 3D files from the PubChem dataset and converted into PDB files via PyMOL. Subsequently, all files were downloaded from AutoDock individually and converted into a pdbqt file format (**Figure 1**).

The phytochemical compounds selected for this study were identified from previously published reports on *Ficus carica* L. phenolic constituents. According to the literature, these compounds have been reported in different plant parts, including leaves, fruits (peel and pulp), and pericarp (**Table 1**). The selected compounds were chosen based on their abundance, biological relevance, and reported pharmacological activities.

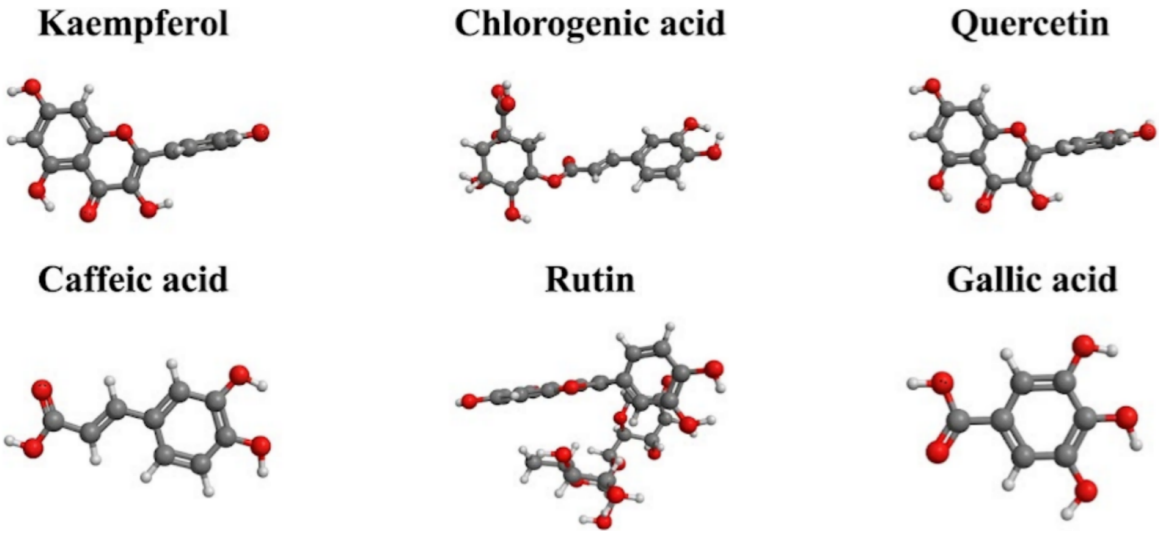

Figure 1. 3D structure of the ligands.

Table 1. Selected phytochemical compounds of *Ficus carica* L. and their reported plant parts.

Phytochemicals Compounds	Plant Part Reported in the Literature
Kaempferol	Leaves and fruits
Chlorogenic acid	Leaves, peel and pulp
Quercetin	Leaves and fruits
Caffeic acid	Leaves and fruits
Rutin	Leaves, pulp and pericarp
Gallic acid	Leaves, pulp and pericarp

2.2. Toxicity Analysis

The toxicity profile was assessed using the ProTox-III tool, and this *in silico* assessment of the toxicity of the biomolecules provided an overall evaluation of many toxicity parameters.

2.3. ADMET Studies

ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) analysis is an essential requirement for pharmacodynamic characterization of the molecules. Therefore, for this study, we used the SWISSADME web-based platform [31] for fast and accurate estimates of the various properties of the biomolecules that we are interested in determining. The Smiles of the ligands were downloaded from the PubChem database.

2.4. Preparation of Proteins

The following crystallographic information was obtained from the Protein Data Bank: TNF-α with PDB ID: 2AZ5; Human Dipeptidyl Peptidase (DPP-4) with PDB ID 1R9M; α-glucosidase with PDB ID: 3LAV; and NFKB P50/P65 with PDB ID: 1VKX (**Figure 2**). The proteins were prepared for use in AutoDock by removing all co-crystallized ligands found at their active sites as well as any water molecules in accordance with the procedure reported by Aouji et al. [32] and Desai et al. [33] and utilized Biovia Discovery Studio 2025 software (Accelrys, San Diego, CA, USA) for this purpose. AutoDockTools (v.1.5.7, 4.2.6) was then used to add the necessary missing hydrogen atoms, assign the Kollman-type partial charges, and finally convert the protein structures into pdbqt format for use in the docking study.

2.5. Molecular Docking Analysis

Using an automated script, AutoDock Vina was used to analyze how bioactive compounds interact with enzymes through their molecular interactions. All docking parameters were recorded within the config file.txt for each docking job. The simulations utilized a local search approach (LGA) with a genetic algorithm [32,33]. The active

regions of the various enzymes were defined by using AutoGrid and centering the grid around the co-crystallized ligands on a cube measuring 60 Å per side and separated from each grid point by 0.500 Å. Each probed protein's active site box grid was specified (the coordinates used were: TNF-α (−13.687, 71.606, 27.002), DPP-4 (16.754, 0.633, 14.913), α-glucosidase (54.393, 100.327, 19.852), NFKB P50/P65 (10.802, 15.740, 34.898). To confirm that the docking method was accurate, we redocked the ligand that was co-crystallized to it and measured that the RMSD was less than 2.0 Å in relation to the native structure. We were able to determine the specific amino acid residues that were able to bind to the target and we were able to visualise the complex created using the Biovia Discovery Studio 2025 program. The docking method was validated using established inhibitors as positive controls. Sitagliptin, for DPP-4; miglitol for α-glucosidase; SPD304 for TNF-α; parthenolide for NF-κB are well established references for their respective targets through multiple publications.

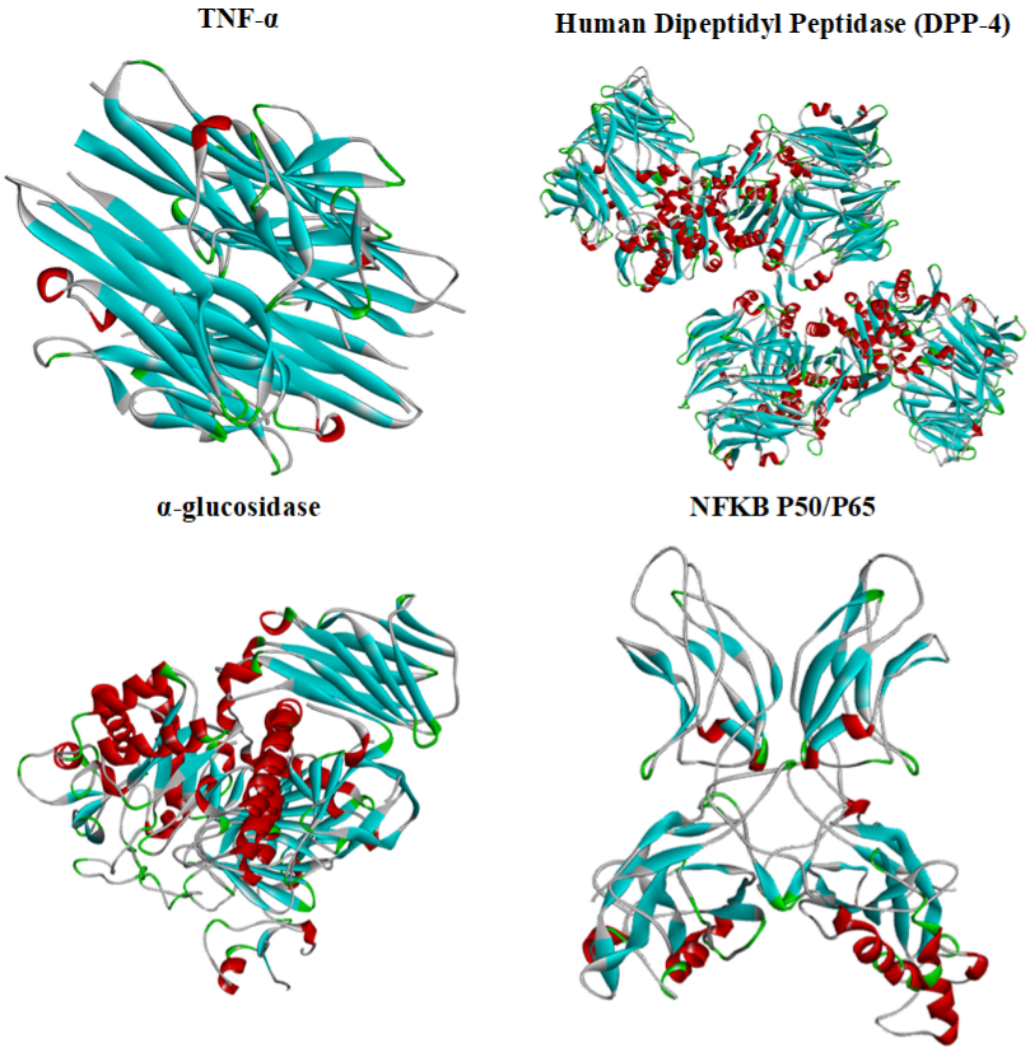

Figure 2. 3D structure of the proteins.

3. Results and Discussion

The toxicity characteristics of the phytochemical compounds selected were evaluated and shown in **Table 2** and **Figure 3** using ProTox-III. The results demonstrate that each compound, i.e., Kaempferol, chlorogenic acid, Quercetin, caffeic acid, Rutin, and gallic acid showed different but generally non-harmful toxicities.

The predicted LD_{50} values ranged from 159 to 5,000 mg/kg, which indicates a low acute toxicity of most compounds. More precisely, Kaempferol, Chlorogenic acid, Caffeic acid, Rutin and Gallic Acid fall into toxicity classes 4–5, suggesting a relatively safe profile, while quercetin is classified in 3, indicating moderate toxicity. These results

are consistent with previous reports noting that plant-based polyphenols generally have low systemic toxicity and a broad therapeutic index [34,35].

Table 2. Toxicity analysis of biocompounds.

L	LD_{50}/ToxC	Neph	Hepa	Carc	Card	Muta	Cyto	Neur	Resp	Nutr	Imm
L_1	3,919/5	0.62	0.68	0.72	0.91	0.52	0.98	0.89	0.83	0.66	0.96
L_2	5,000/5	0.56	0.72	0.68	0.99	0.93	0.80	0.89	0.57	0.64	0.99
L_3	159/3	0.62	0.69	0.68	0.99	0.51	0.99	0.89	0.83	0.63	0.87
L_4	2,980/5	0.59	0.57	0.78	0.97	0.98	0.86	0.83	0.59	0.77	0.50
L_5	5,000/5	0.77	0.80	0.91	0.98	0.88	0.64	0.89	0.63	0.54	0.98
L_6	2,000/4	0.69	0.61	0.56	0.89	0.94	0.91	0.88	0.52	0.83	0.99

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid; LD_{50}: Lethal dose 50 (mg/kg); ToxC: Toxicity class; Hepat: Hepatotoxicity; Carcin: Carcinogenicity; Neur: Neurotoxicity; Imm: Immunotoxicity; Cytot: Cytotoxicity; Nephr: Nephrotoxicity; Resp: Respiratory toxicity; Card: Cardiotoxicity; Muta: Mutagenicity; Nutr: Nutritional toxicity.

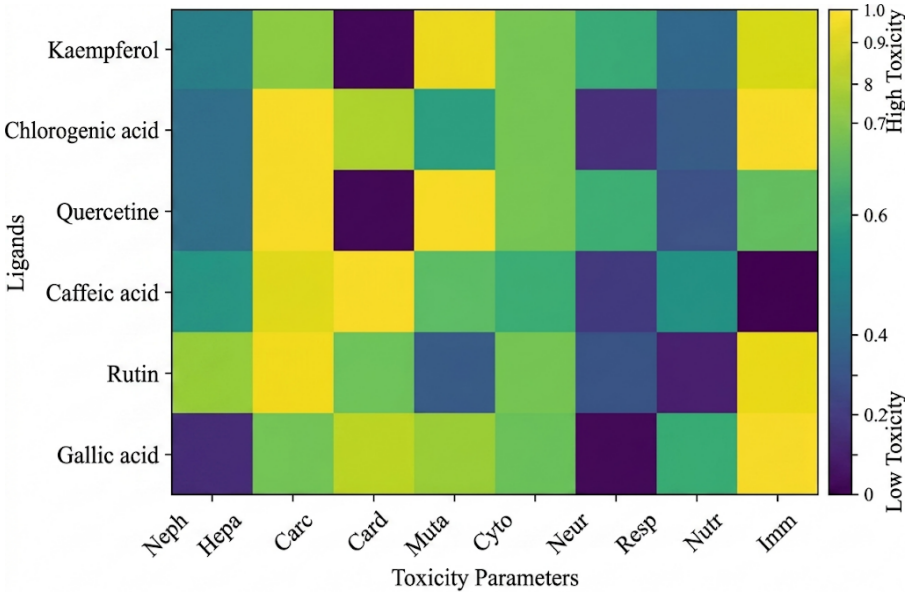

Figure 3. Evaluation *in silico* de la toxicité multidimensionnelle des ligands.

The toxicity parameters for the predicted organs define moderate to high probabilities for hepatotoxicity (0.57–0.80), cytotoxicity (0.64–0.99), and nephrotoxicity (0.56–0.77) for all ligands. Thus, according to these simulations and despite the biological activities of the compounds, the results were presented in the form of in silico predictions that should only be interpreted with caution and questioned by experimental validation. However, relatively high scores were noted for cardiotoxicity (0.89–0.99), revealing important interactions with the cellular and cardiovascular systems.

Such results are hardly surprising, since flavonoids and phenolic acids do exhibit dose-dependent biological effects, in the same way as oxidative stress and modulation of apoptosis. Quercetin and kaempferol have thus been reported as exhibiting cytotoxic effects at high concentrations, which is usually associated with their antioxidant and anticancer properties [34].

For the compounds studied, the mutagenic prediction had a variable amplitude, oscillating from moderate (0.51) to high (0.98) and the carcinogenic prediction revealed moderate scores (from 0.56 to 0.91). These results in any case suggest a risky potential at high doses or for prolonged periods, but the risky nature must be understood with caution. Polyphenolic compounds are often reported to have a dual behavior, namely that as antioxidants they would act at the physiological level and that at higher concentrations they would be likely to exert pro-oxidant effects [36]. This hypothesis can explain the genotoxic signals predicted virtually, but which remain variable notoriety.

The high probability levels observed for neurotoxic effects (0.83–0.89) and moderate to high for immunotoxic effects (0.50–0.99) and intermediate respiratory toxicity values (0.52–0.83) seem to be related more to the ability of the compounds to interact at the level of signaling pathways than to the induction of toxic effects. Thus, flavonoids are known to modulate immune and inflammatory responses via the regulatory pathways of NF-kB and cytokines. The observed predictions may thus correspond to a pharmacological activity rather than to a rather worrying toxicity in terms of immunomodulation [37].

Chlorogenic acid and rutin also showed a better safety profile with regard to their high LD_{50} values associated with fairly moderate and balanced toxicity parameters. On the other hand, although quercetin has a slightly higher toxicological behavior profile, it remains sufficiently accepted for pharmacological applications and could therefore be considered reliable. In a good balance between biological activity and proven safety, gallic acid is also a good candidate for further studies.

The overall toxicity evaluated shows that the compounds show potential safety profiles, but not established and requiring additional toxicological studies. With moderate biological reactivity, the compounds are presented as candidates for validation *in vitro*, then *in vivo*. The low acute toxicity associated with an important biological activity constitutes an asset for the development of multi-target drugs in the context of complex diseases such as type 2 diabetes and chronic inflammation.

In short, the *in silico* toxicity analysis indicates that the compounds studied have low to medium toxicity levels and important biological interactions, compatible with the known pharmacological activities of polyphenols of plant origin and confirm the relevance of these molecules for molecular docking studies and their potential role as antidiabetic and potentially immunomodulatory agents.

3.1. Physicochemical Parameters

Table 3 shows the physicochemical properties of the selected phytochemical compounds of *Ficus carica*. The compounds were analyzed using key descriptors such as molecular weight (MW), lipophilicity (Log P), hydrogen bond donors and acceptors, the number of rotating bonds, violations of the Lipinski rule and molar refractivity.

Table 3. Dependent variables of chemical compounds.

	PubChem ID	MW	LogP	nOH	nOHNH	Nb	Nb Viol	Mol Ref
L_1	5280863	286.24	1.70	6	4	1	0	76.01
L_2	1794427	354.31	0.87	9	6	5	1	83.50
L_3	5280343	302.23	1.63	7	5	1	0	78.03
L_4	689043	180.16	0.97	4	3	2	0	47.16
L_5	5280805	610.5	0.46	16	10	6	3	141.38
L_6	370	170.12	0.21	5	4	1	0	39.47

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid; Mol Wt: molecular weight (g/mol), LogP: lipophilicity, nOH: no. of H bond acceptors, nOHNH: no. of H bond donors, Nb: no. of rotatabe bonds, Nb viol: no of violations, Mol ref: molecular refractivity.

The molecular weights of the substances vary between 170.12 and 610.5 g/mol. Kaempferol, quercetin, caffeic acid and gallic acid were all found in the acceptable range (<500 g/mol) proposed by Lipinski's rule of five which could indicate a favorable oral bioavailability. On the other hand, rutin had a rather high weight (610.5 g/mol), above the Lipinski threshold and would then be more difficult to permeate and absorb.

All the compounds displayed relatively low Log *p* values (0.21–1.70), which means that their hydrophilic character is dominant. This choice is an asset to ensure good solubility in water and promote interactions with polar biological targets. However, low lipophilicity can lead to a deficit in membrane permeability, the usual counterpart of polyphenolic compounds. Quercetin and kaempferol nevertheless displayed somewhat elevated Log *p* values (1.6–1.7) suggesting a better solubility/permeability compromise in comparison with the most hydrophilic compounds such as gallic acid.

The concentration of hydrogen bond donors (nOHNH) and acceptors (nOH) was relatively high in each compound, which is probably due to the presence of several hydroxyl groups. While this favors the establishment of stable interactions with the protein targets that are sought for molecular docking, it can however disadvantage passive diffusion through biological membranes. It should be noted that rutin was the one that had the highest number of hydrogen bond donors (10) and acceptors (16), which gives it its high binding potential, but which also

contributes to its small pharmacokinetic properties.

The number rotatable bonds varied between 1 and 6, which corresponds to low to moderate flexibility. A low degree of flexibility is often synonymous with stable ligand-protein interactions, which is an asset for the search for the best mooring pose.

The molar refractive values varied between 39.47 and 141.38, reflecting the differences in size and polarizability. The higher refractive values observed for rutin show a better potential for intermolecular interactions, but can also be correlated with a greater molecular complexity.

Overall, it was noticed that kaempferol, quercetin, caffeic acid and gallic acid had the most favorable drug profiles, both in terms of correspondence with Lipinski's rules and physico-chemical properties, while chlorogenic acid showed acceptable characteristics, with only one violation, and that rutin seems to be the least drug-like compound, as because of it too high molecular weight, its excessive ability to interact by hydrogen bonding and multiple non-conformities to the rules.

In sum, the molecules evaluated have moderately favorable drug similarity properties, the majority of compounds at least in accordance with Lipinski's rule of five, kaempferol and quercetin appearing to be the most promising, because they have both an adequate size, a good partition coefficient and decisive hydrogen bonding capabilities, while rutin had very problematic defects for drug development.

The physico-chemical analysis revealed that for most compounds, Lipinski's rule of five can be respected, crediting a favorable resemblance to the drug. On the contrary, rutin has numerous violations due to an excessively high molecular weight and a polarity indicating a probably decreased membrane permeability. The quercetin and kaempferol compounds assign each other the optimal lipophilicity because in the end, they achieve solubility and permeability in balance. This parameter is indeed necessary to ensure oral bioavailability, proving to be in agreement with previous investigations observing a good structural similarity with regard to flavonoids from a pharmacological point of view [38,39].

3.2. In Silico Pharmacokinetic Profile (SwissADME)

SwissADME was used to assess how fast selected phytochemicals from *Ficus carica* are absorbed through various processes (**Table 4**). The compounds tested, including kaempferol, chlorogenic acid, quercetin, caffeic acid, rutin and gallic acid, showed differences in their absorption/distribution/metabolism profile; thus, showing that these compounds have different structures.

Table 4. In-silico pharmacokinetics of ligands using SwissADME.

L. No	ESOL (Log S)	GIads	BBB	P-gp	Cytochromes				
					3A4	1A2	2C19	2C9	2D6
L_1	−3.31	High	No	No	Yes	Yes	No	No	Yes
L_2	−1.62	Low	No	No	No	No	No	No	No
L_3	−3.16	High	No	No	Yes	Yes	No	No	Yes
L_4	−1.89	High	No	No	No	No	No	No	No
L_5	−3.30	Low	No	Yes	No	No	No	No	No
L_6	−1.64	High	No	No	Yes	No	No	No	No

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid.

All the compounds displayed an adequately favorable aqueous solubility, according to the ESOL model, with Log S values ranging from −3.31 to −1.62, which corresponds to the good classification of their solubility. It should be noted that this property is crucial at the level of oral drug candidates to facilitate dissolution in gastrointestinal fluids. Kaempferol, Quercetin, Caffeic acid and Gallic Acid should have a good level of gastrointestinal absorption in accordance with their good potential for oral bioavailability. On the other hand, Chlorogenic Acid and Rutin have shown a low level of absorption, perhaps due to their polarity and their increased molecular heaviness.

None of the compounds studied crosses the blood-brain barrier (BBB), which indicates a low probability of effects in the central nervous system and therefore a possible reduction in potential neurotoxicity as well as off-target effects. Regarding the interaction with P-glycoprotein (P-gp), only rutin is intended as a compatible substrate, whose active evacuation by transporters localized on intestinal cells can further reduce its bioavailability. The other compounds that do not interact with P-gp may have better absorption and retention properties.

Regarding the analysis of the metabolic inhibition of cytochrome P450 (CYP), the variability observed concerning the interactions with the ligands tested is quite marked. Indeed, kaempferol and quercetin have shown inhibitory effects on several isoforms, in particular CYP3A4, CYP1A2 and CYP2D6, thus showing their potential for drug interactions, while gallic acid has shown for its part a very limited inhibition with only CYP3A4 as the target. Chlorogenic acid, caffeic acid and rutin have proven to be non-inhibitors for the CYP isoforms tested and would make it possible to invoke a lower risk of metabolic interactions. This variability of the observed interactions reflects intrinsic differences in the structure of flavonoids and phenolic acids, and is in agreement with the literature, flavonoids having a greater propensity to modulate the activity of CYP compared to simpler phenolic acids.

Kaempferol, quercetin, caffeic acid and gallic acid are distinguished by favorable pharmacokinetic profiles, combining good solubility and good gastrointestinal absorption. However, the possible inhibition of the CYP isoenzymes by kaempferol and quercetin constitutes a factor to be considered in the development of new drugs. On the other hand and in contrast, chlorogenic acid and rutin present probable obstacles to absorption, which could be attributable to their polarity and to their excessive molecular weight constituting a brake on absorption. Moreover, and as a supplement, the interaction of rutin with P-gp further compromises its pharmacokinetic opportunity.

An evaluation of the pharmacokinetics of ligands revealed that solubility is only one factor that contributes to their pharmacokinetic characteristics. For example, though all ligands were assessed to be soluble, specific ligands may exhibit differing degrees of bioavailability that could potentially alter the therapeutic efficacy of the ligands. Quercetin and kaempferol were also noted to have significant potential due to the relative favorable absorption characteristics exhibited by these compounds. However, further evaluation of the interaction of quercetin and kaempferol with CYP enzyme systems is required to demonstrate and ensure therapeutic efficacy. On the other hand, the bioavailability of both chlorogenic acid and rutin may require additional formulation or other modifications to maximize the bioavailability of these ligands. The results of the pharmacokinetics show that almost all of the tested compounds were found to have a high degree of water and fat solubility as well as being largely non-toxic. However, they exhibited some diversity in their absorption behavior from the various groups of compounds tested (i.e., the non-polar flavonoids displayed much better absorption than the more polar phenolic acids). The absorption profile is limited by the inability of any substances to penetrate the blood-brain barrier and therefore, the compounds will have limited CNS activity. The potential for interactions with cytochrome P450 due to the flavonoids has implications on metabolic stability and there is a concern for possible drug interactions [31].

3.3. Bioavailability Radar Analysis

Presented below are radar graphs showing physicochemical/drug-like characteristics for some *Ficus carica* molecules (e.g., kaempferol, chlorogenic acid, quercetin, caffeic acid, rutin and gallic acid) (**Figure 4**). Specifically, these graphs present a visual representation of various key physicochemical/drug-like properties such as lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), insolubility (INSOLUBLE), flexibility (FLEX) and unsaturation (INSATU).

In general, the majority of the compounds are partially localized in the optimal space of said drug, which denotes pharmacokinetic characteristics of acceptability. Nevertheless, deviations from the desirable zone have been identified for several descriptors, testifying to the natural origin and the structural diversity of these phytochemicals. The various compounds presented are characterized by moderate lipophilicity associated with a rather strong polarity, which is a characteristic of polyphenolic compounds due to the large number of hydroxyl groups. Thus, although a high polarity can sometimes adversely affect a certain passive permeability of the membrane, it is beneficial for solubility and the establishment of hydrogen bond interactions with biological targets. It can be noted in particular that quercetin and kaempferol present a good compromise between lipophilicity and polarity, suggesting satisfactory absorption and interaction with the enzymatic active sites, whereas chlorogenic acid and gallic acid, which are more polar, may see their membrane permeability decrease in favor of increased bioavailability in aqueous medium.

The plots obtained by radar show that the majority of the compounds have rather suitable molecular sizes, within or close to the optimal range for the similarity of the drugs. Rutin, on the other hand, is of a higher molecular size and it is characterized by a lower flexibility which could compromise its bioavailability and its eventual permeability. A certain structural rigidity, as involved in the expansion of flexibility, displayed by a majority of ligands, could be a good asset for a specific and very stable approach to target proteins in particular as has often been

perceived in molecular docking interactions.

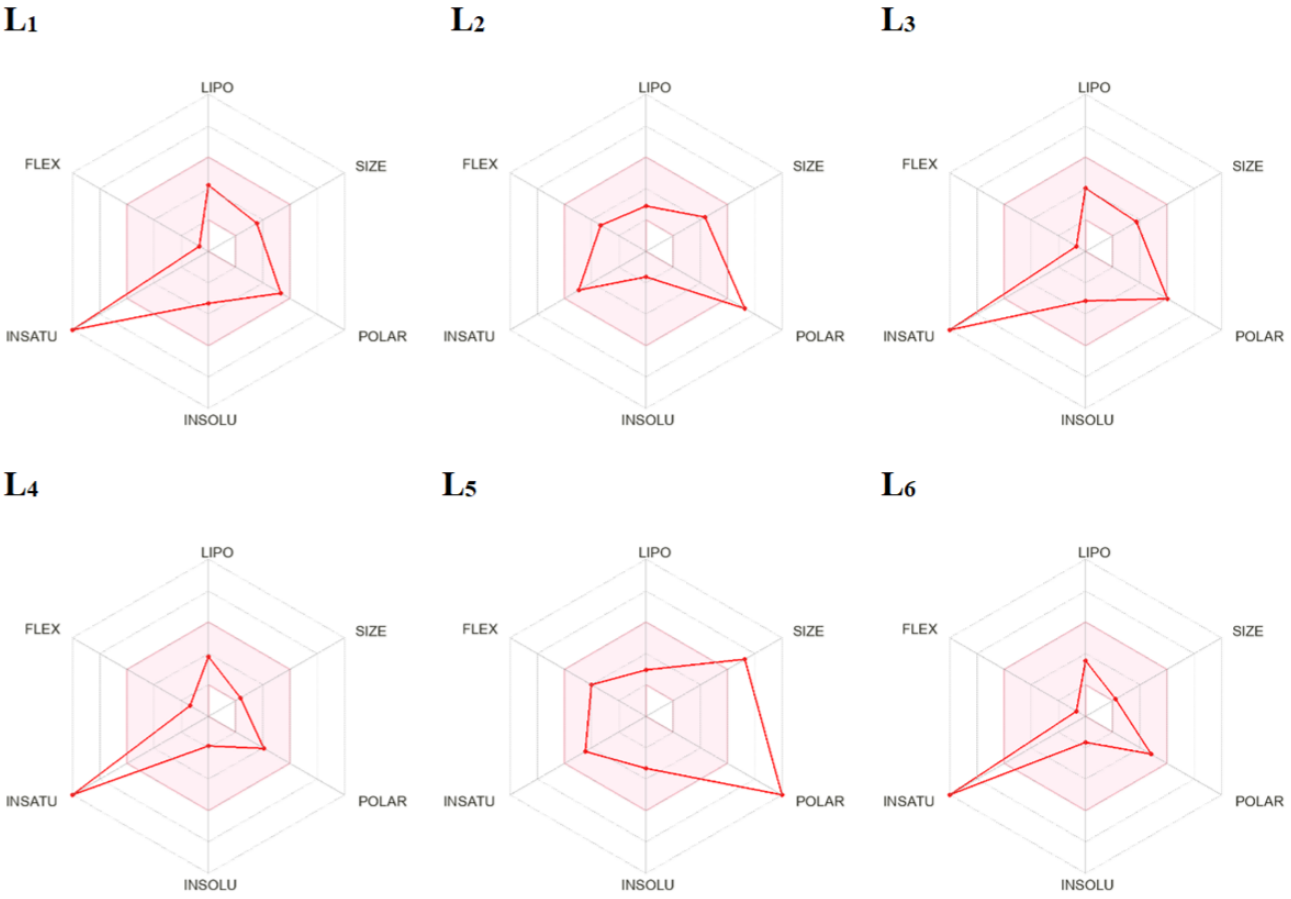

Figure 4. Bioavailability Radar Analysis.

All the compounds have positive solubility profiles, in particular phenolic acids (caffeic acid, gallic acid): good solubility is a favorable property facilitating the absorption of the drug and its systemic distribution. However, the saturation level appears high for most ligands, indicating a high level of unsaturated bonds, which is in line with flavonoids and also constitutes a favorable effect for the antioxidant effect but which can also play a role in metabolic stability.

Among the compounds studied, kaempferol and quercetin have the most balanced drug similarity profiles since most of their parameters display acceptable values. Chlorogenic acid and gallic acid have a very high polarity and solubility, which can make them compatible with aqueous biological environments while possibly harming their membrane permeability. Rutin (610.5 g/mol, high number of hydrogen bond donors and acceptors, low lipophilicity) is also located far beyond the optimal drug like space for all parameters. Rutin's deviation from Lipinski's rule of five and the bioavailability radar suggests that it does not demonstrate good oral bioavailability because of its low membrane permeability and tendency to be actively effluxes (i.e., it's a P-glycoprotein substrate). While rutin displays good biological activity *in vitro*, its physicochemical properties present a significant pharmacokinetic barrier to developing as a therapeutic agent. Structural optimization (e.g., via glycoside removal or prodrugs) will be required to induce drug-like properties. The analysis of the radar highlights the fact that it is a compromise between solubility, permeability and molecular size of natural compounds. The compounds have a very strong biological capacity but their physicochemical properties mean that their bioavailability will perhaps be a major handicap, especially for even larger and even more polar molecules.

In total, according to the results of the physico-chemical analysis, the phytoconstituents of *Ficus carica* possess moderately favorable drug similarity properties, due in particular to the polarity and the size of the molecule, among which kaempferol and quercetin are the most promising pharmacokinetically, justifying their further functional

exploration in pharmaceutical development.

3.4. Molecular Docking

The docking results against TNF-α revealed that caffeic acid presented the strongest interaction (−6.11 kcal/mol; Ic = 33.25 μM), closely followed by kaempferol and quercetin (**Table 5**). These results suggest that these compounds may contribute to anti-inflammatory activity by inhibiting TNF-α. All the compounds had moderate binding energies, indicating a potential but a lower specificity compared to SPD304.

Table 5. Interaction scores between bioactive compounds and proteins.

	TNF-α		Human Dipeptidyl Peptidase (DPP-4)		α-Glucosidase		NFKB P50/P65	
	Be	Ic	Be	Ic	Be	Ic	Be	Ic
L_1	−6.04	37.47 μM	−5.82	54.54 μM	−6.52	16.66 μM	−5.32	126.49 μM
L_2	−5.60	78.56 μM	−4.14	930.91 μM	−3.75	1.77 mM	−6.07	35.80 μM
L_3	−5.73	62.62 μM	−7.00	7.45 μM	−6.43	19.23 μM	−7.39	3.86 μM
L_4	−6.11	33.25 μM	−6.05	36.77 μM	−4.25	763.29 μM	−5.81	55.39 μM
L_5	−5.46	99.96 μM	−5.25	142.92 μM	−3.52	1.94 mM	−4.27	743.28 μM
L_6	−5.26	138.30 μM	−5.69	67.78 μM	−4.25	765.67 μM	−5.02	208.65 μM
Stds	−7.21	5.20 μM	−7.44	3.51 μM	−6.02	38.37 μM	−7.41	3.72 μM

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid; Stds: Control positive; Be: Binding energy (Kcal/mol); Ic: Inhibition constant.

The binding modes of the *Ficus carica* phytochemicals selected in the active site of the tumor necrosis factor alpha are illustrated in **Figure 5**. The docking poses reveal that all the ligands are well housed in the binding pocket, forming a network of stabilizing interactions including hydrogen bonds, hydrophobic contacts and π-based interactions. A predominant feature observed in most ligands is the formation of conventional hydrogen bonds with residues of key amino acids such as Ser, Gly, Lys and Asp. The interactions mentioned above are important for stabilizing the ligand in the active site and increasing binding affinity. Based on the frequency of involvement of residue types (Ser60, Gly121, and Lys11) during ligand recognition and bonding stabilization, these residues have been found to be important for stabilizing hydrogen bonds between ligands and the active site. Hydrogen bonding is enhanced by π–π stacking and π–alkyl interactions between flavonoids' aromatic rings and residues such as Tyr and Leu, which enhance the stability of the bond by enhancing the hydrophobic contacts within the active pocket. Due to their presence and the strong binding interactions resulting from them, it is not surprising that quercetin and kaempferol have multiple π interactions during docking. This likely results in their higher binding affinities during docking than previously observed.

Caffeic and gallic acids are phenolic acids that have lower hydrophobic interaction yet are still able to form stable hydrogen bonded interactions throughout their entire binding interface. Therefore, it can be concluded that the binding is primarily driven by polarity rather than being driven by hydrophobic complementarity. Additionally, there are instances of adverse ligand-residue interactions which may decrease the overall stabilization of the bond to a small degree, but these adverse ligand-residue interactions do not seem to be significant enough to disrupt the binding of the ligand as a whole within the binding pocket. The structural analysis performed also highlights the effect ligand conformations and functional group orientations have on these interactions. The most efficient ligands for communication as a result of either π interactions or hydrogen bonding with other ligands or in solution are ligand complexes which contain planar-like aromatic rings containing a large number of –OH functional groups. The conformational structure of these ligands is flavonoid in nature, and the biological activity of flavonoids is related to the increase in biological activity of ligands containing a planar-like aromatic system and a large number of –OH functional groups.

Of all the ligands tested against DPP-4, quercetin had the highest reported binding affinity as determined by a binding free energy of −7.00 (kcal/mol) and an inhibition constant (Ki) of 7.45 μM—indicating that it could inhibit DPP-4 more effectively than any of the other tested ligands, but still less than the reference Doddington. Both caffeic acid and kaempferol also displayed advantageous interactions, exhibiting moderate binding energies and inhibition constants. In contrast, chlorogenic acid demonstrated the least binding strength (−4.14 kcal/mol), implying it has the least ability to inhibit the action of DPP-4 (**Table 5**).

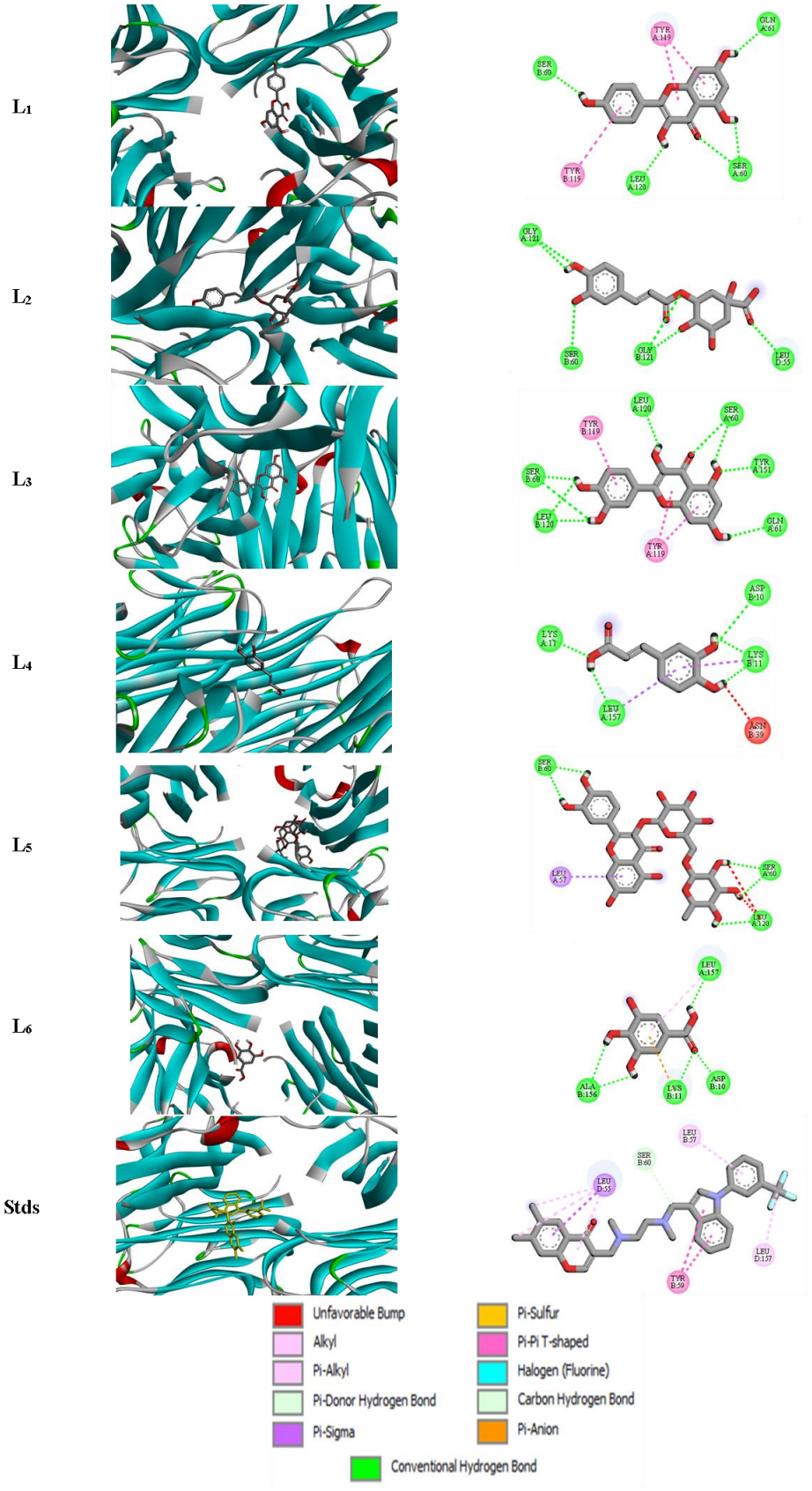

Figure 5. Mode of association of the compounds with the TNF-α Receptor, illustrated in 3D (left) and in 2D (right).
Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid.

The binding modes for the phytochemical compounds derived from *Ficus carica* are within the Dipeptidyl Peptidase-4's active site as shown in **Figure 5**. All ligands were successfully accommodated into the catalytically active site of the protein demonstrating as noted stable bond orientation. Upon analyzing the interaction profile of the ligands suggests an abundance of conventional hydrogen bonds (formed with the key residues (Ser/Glu/Tyr/Gly) that have been widely recognized to participate in substrate recognition and catalysis. The presence of these hydrogen bonds contributes greatly to stabilizing the ligand within the active site. In addition to polar interactions, several of the ligands formed π−π stacking or π−alkyl stacking along with hydrophobic interactions to residues Tyr/Phe/Leu which, in turn, contribute to enhancing overall binding affinity. The presence of aromatic rings on the flavonoids likely contributes to the additional hydrophobic interactions that result from the more deeply inserted binding pocket. The number of interactions created by two of the compounds (quercetin and kaempferol) was higher due to the combination of hydrogen bonds with hydrophobic contacts. Alternatively, chlorogenic acid and gallic acid formed a reduced number of hydrophobic interactions and primarily depended upon hydrogen bonding. For the compound rutin, there were many hydrogen bonding interactions present; however, there was very limited penetration of the active site because of the large size of the compound.

The data show that the phytochemicals from *Ficus carica* interact with Dipeptidyl Peptidase-4 via a combination of hydrogen bonding and hydrophobic interactions and these interactions are critical for effective inhibition of Dipeptidyl Peptidase-4 enzymatic activity (**Figure 6**). A systematic examination of the residues of the key amino acids (Tyr, Ser, Glu and Leu) in this case confirms their involvement in stabilizing the ligand molecules observed based on earlier analyzed crystal structures [40] where these residues play an important role in how the substrate is recognized and how it catalytically functions.

Quercetin and kaempferol flavonoids had the best interaction characteristics (many hydrogen bonds plus π−π stacking and π−alkyl interactions), creating large networks of bonds between them. They have planar aromatic structures as well as many hydroxyl groups, which increase both bond stability and selectivity (**Figure 7**). This corresponded to past studies that showed flavonoids work well as potential DPP-4 inhibitors due to the strength of their binding interactions in the active site of DPP-4 [41,42]. Conversely, phenolic acids (chlorogenic acid, caffeic acid, and gallic acid) were shown to interact with DPP-4 primarily through hydrogen bonding, that is, having fewer number of hydrophobic contacts with DPP-4. This behavior may be due to the small size (compared to the size of flavonoids) and higher polarity of these acids as well as how little room they have to fill the hydrophobic parts of the DPP-4 active site [43]. Rutin shows how steric effects impact bonding performance, even though rutin has multiple hydrogen bonds, its large glycosides make it difficult to fit correctly into the catalytic cavity and therefore lower its binding affinity compared to smaller polyphenols. Several studies have included glucose-regulating phytochemicals by identifying patterns of their activities that emulate DPP-4 inhibitors by blocking the enzyme's active site so that they cannot react with substrate and can thereby become more active and improve glucose regulation. As such, they represent an important class of compounds being used as pharmacological therapies for patients with type 2 diabetes and are extremely popular due to their large benefit-to-cost ratio.

For α-glucosidase, kaempferol showed the best binding affinity (−6.52 kcal/mol; Ic = 16.66 μM), followed by quercetin (−6.43 kcal/mol), which are higher than the positive control. These results indicate a strong inhibitory potential, supporting their role in the control of postprandial hyperglycemia. Conversely, chlorogenic acid and rutin showed low binding and high inhibition constants, suggesting limited efficacy against this enzyme (**Table 5**).

Figure 7 illustrates the various modes of binding for each of the phytochemical components from *Ficus carica* into the alpha-glucosidase active site. All ligands were successfully docked within the catalytic pocket, demonstrating stable orientations and high geometric complementarity with the active site. Upon interaction analysis, it was revealed that ligands form numerous conventional hydrogen bonds with significant residue components (i.e., Arg 608) at Asp, Glu, Tyr 609, Ala 604, etc., which are known for their role in substrate binding/catalytic activity. These interactions play a key role in the stabilization of the ligand.

Several ligands have established hydrophobic interactions through interactions between π−π stacking, π−alkyl and alkyl contacts with the aromatic side chains of different amino acid residues; for example, Leu 577, Leu 195, Val 358, Pro 194, and Ile 581. Of these identified ligands, both quercetin and kaempferol have the highest number of established interactions by having a combination of hydrophobic contacts and hydrogen bond formations (i.e., quercetin forms a total of 6 hydrophobic and 3 hydrogen bonds, while kaempferol has 5 hydrophobic and 4 hydrogen bond formations). In contrast, both chlorogenic acid and gallic acid form fewer hydrophobic interactions

based solely on their formation of hydrogen bond interactions. Finally, although rutin had a significant number of hydrogen bond interactions, it was not able to penetrate into the active site due to steric hindrance.

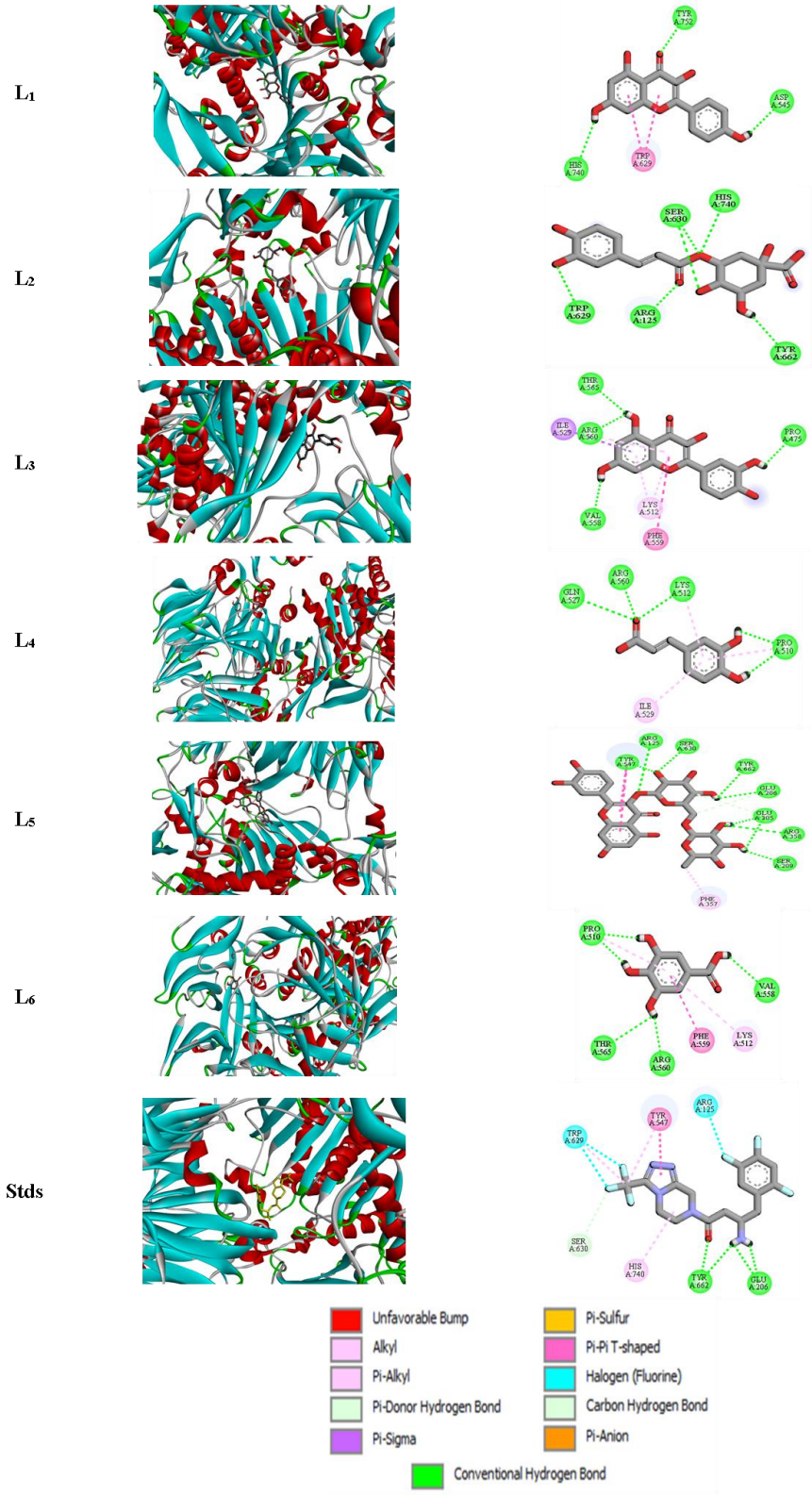

Figure 6. Mode of association of the compounds with the DPP-4 Receptor, illustrated in 3D (left) and in 2D (right).
Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid.

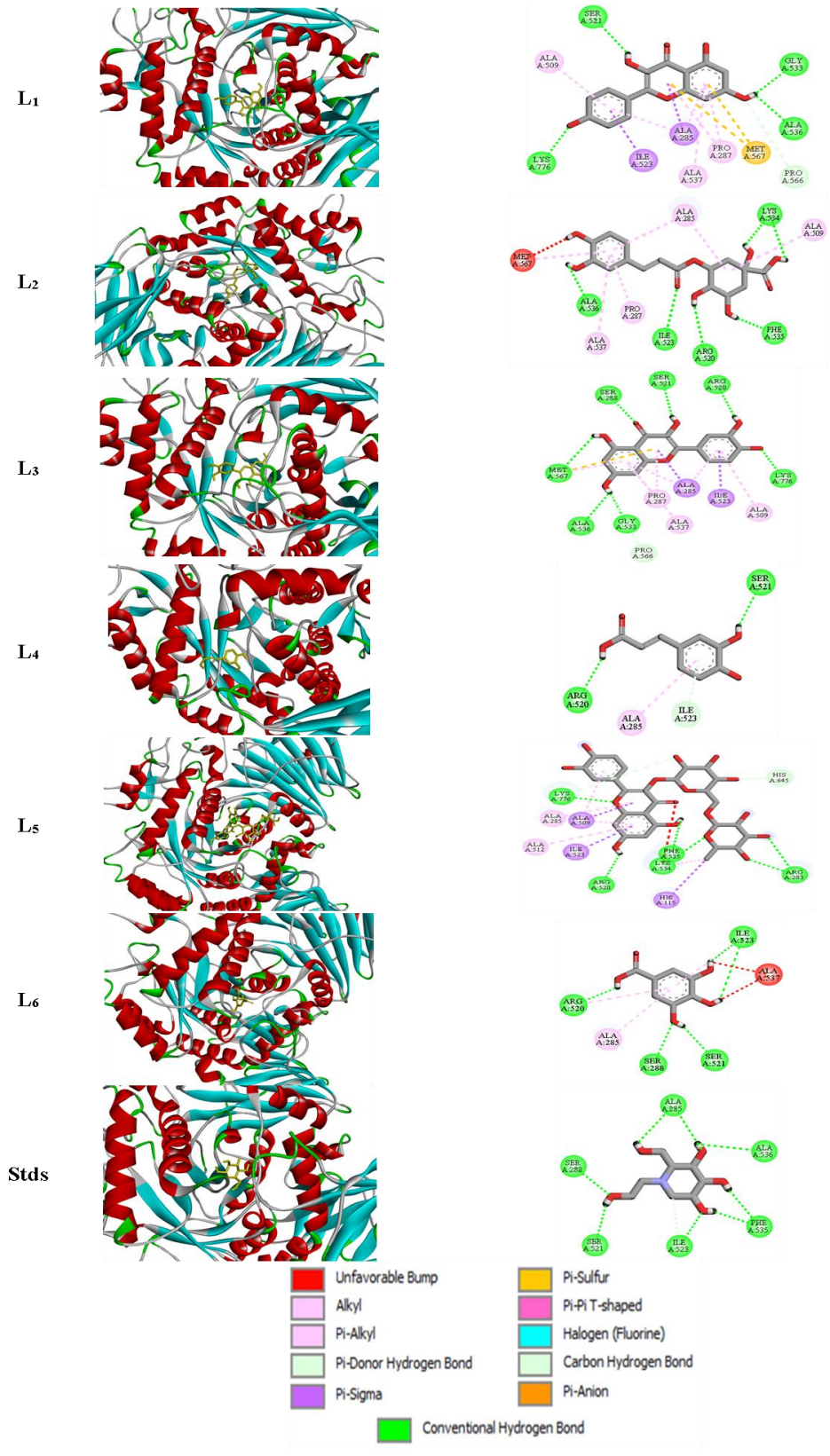

Figure 7. Mode of association of the compounds with the α-glucosidase Receptor, illustrated in 3D (left) and in 2D (right).

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid.

Based on what was found in **Figure 6**, the phytochemical compounds found in *Ficus carica* can inhibit α-glucosidase via a combination of hydrogen bonding and hydrophobicity. Both are important for effective enzymatic inhibition. Residues contributing to the stabilization of the ligands include Arg 608, Tyr 609 and Glu/Asp, which also support their respective roles in the catalytic mechanism [44]. The binding properties of quercetin and kaempferol, two prominent flavonoids, have been shown to exhibit strong binding patterns, forming multiple hydrogen bonds and have π–π and π–alkyl interactions. The structure of these compounds, consisting of planar aromatic rings and several hydroxy groups, allows these two compounds to have a lot of potential interactions with different regions of the soluble α-glucosidase (polar and nonpolar). This data supports findings from previous research where flavonoids were demonstrated to be effective α-glucosidase inhibitors, providing evidence that flavonoids can bind at the active site and prevent access to the substrate [45].

Interactions primarily originate from hydrogen bonding, with less contribution from hydrophobic in the case of phenolic acids (e.g., chlorogenic acid, caffeic acid, and gallic acid). The ability to bind through these types of interactions does not provide a greater degree of stability to inhibit than the phenolic compounds (Flavonoids); this was stated above [46]. The large size of the rutin molecule makes it unable to insert into the catalytic pocket as deeply as it could if there were few hydrogen bonds that could be formed; therefore, the steric limit on how deeply the rutin can insert into the catalytic pocket decreases the degree of binding efficiency that is typically seen with glycosylated flavonoids [46]. Phytochemicals blocking the active site of the enzyme, α-glucosidase, will limit the enzyme's ability to bind to a carbohydrate substrate decreasing glucose being released and absorbed. This mechanism is particularly important for controlling post-meal hyperglycemia in type 2 diabetics who should use α-glucosidase inhibitors to control their blood glucose after eating.

The quercetin ligand displayed the highest binding affinity (−7.39 kcal/mol; Ic = 3.86 μM), slightly lower than that of the reference inhibitor, among the test compounds studied in regard to NF-kB inhibition and, therefore, it may be one of the more effective candidates for further development as an anti-inflammatory compound. Chlorogenic acid also had an acceptable binding affinity (−6.07 kcal/mol) to NF-kB, suggesting that chlorogenic acid could also be useful as an anti-inflammatory compound by modulating these same pathways. The other ligands tested had lower affinities for NF-kB, with rutin and gallic acid showing weak interactions, indicating they would not be as effective as quercetin and chlorogenic acid in targeting NF-kB (**Table 5**).

The binding interactions of the phytochemical compounds of *Ficus carica* with NF-kB p50 are illustrated in **Figure 7**. All the ligands were successfully housed in the binding pocket, showing stable conformations and a favorable spatial orientation. Interaction analysis revealed that the ligands established multiple conventional hydrogen bonds with key amino acid residues, including Arg 246, Asn 186, Gln, Lys 218 and Ser 540, which play an important role in stabilizing ligand binding. These interactions were supplemented by hydrophobic contacts, such as π–alkyl and alkyl interactions involving residues such as Val, Pro, Leu and Ile. In addition, some ligands have formed π–π and π–cation stacking interactions, in particular with residues such as Arg and Lys, improving the binding affinity by electrostatic stabilization. The presence of aromatic rings in flavonoids contributed significantly to these interactions. Quercetin and kaempferol had the most extensive interaction networks of compounds examined as they were able to make hydrogen bonds and also develop hydrophobic contacts. In contrast, chlorogenic acid and gallic acid demonstrated much less extensive interaction networks as they were dominated by hydrogen bonding alone. In comparison, rutin had many hydrogen bonds; however, because of the bulkiness of that molecule, it could only develop limited hydrophobic bonding with other compounds. The patterns of interaction seen in **Figure 8** indicate that the phytochemical compounds (from *Ficus carica*) are likely inhibiting NF-kB through hydrogen bonds and electrostatic interactions; these interactions are assisted by hydrophobic contacts. Next, the residues Arg, Lys, Asn, and Ser stabilise the ligands, which aligns with their role in DNA-binding and transcriptional activity of NF-kB [47].

Particularly quercetin and kaempferol) have been shown to create the optimal binding properties and form large networks of hydrogen bonds and π–π and π–cation interactions between them. Overall these flavonoid compounds have many structural features (multiple hydroxyl groups and quite a number of planar aromatic rings) that contribute to their binding capabilities with polar or charged residues. Furthermore, these findings align with prior studies showing that flavonoids can inhibit the activation of NF-kB by interfering with the binding of this transcription factor to DNA [48,49]. Despite forming numerous hydrogen bonds, the large size of rutin appears to impede its ideal place in the binding site. This finding emphasizes the role that flexibility and molecular dimensions play in determining how efficiently a compound will bind to its receptor, as shown in previous studies on glycosylated

flavonoids [46].

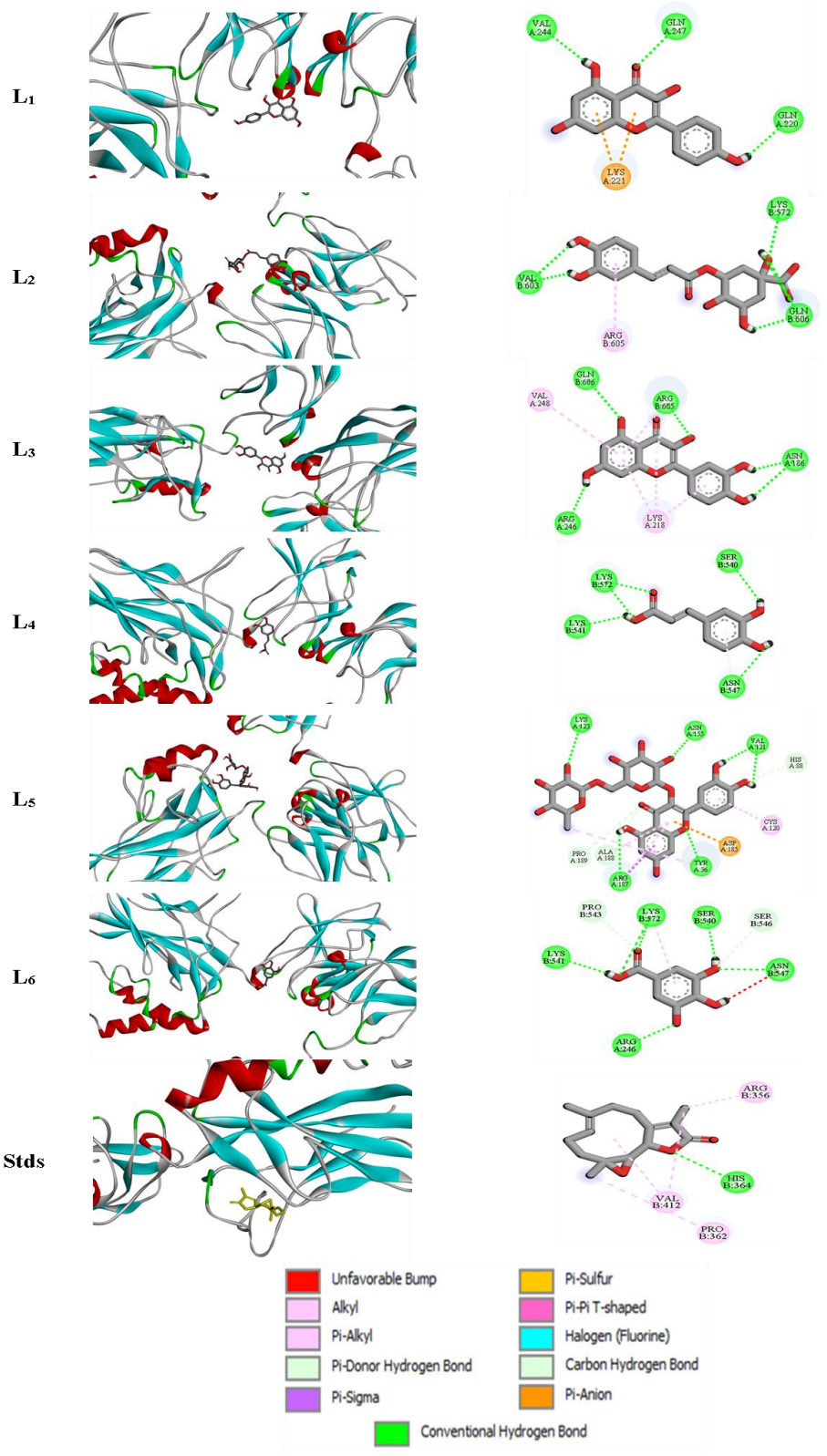

Figure 8. Mode of association of the compounds with the NF-KB P50 Receptor, illustrated in 3D (left) and in 2D (right).

Note: L_1: Kaempferol; L_2: Chlorogenic acid; L_3: Quercetin; L_4: Caffeic acid; L_5: Rutin; L_6: Gallic acid.

The observed interactions imply that the various phytochemicals found in *Ficus carica* L (e.g., leaf, fruit (peel and pulp) and pericarp) were able to decrease NF-kB activity via the stabilization of the NF-kB protein such that it prevents binding to DNA or protein-protein interactions. The important role that NF-kB plays in inflammation makes this data particularly relevant to diseases characterized by chronic inflammation such as type II diabetes and other inflammatory diseases.

Quercetin exhibited superior affinity on multiple targets, most notably DPP-4 and NF-kB, demonstrating exceptionally low inhibition constants. These findings are consistent with other studies that have demonstrated that quercetin is a potent inhibitor of carbohydrate hydrolyzing enzymes and a modulator of the inflammatory response pathway, such as NF-kB activity [50,51]. Similarly, kaempferol has exhibited strong binding interactions with α-glucosidase and TNF-α, which corroborates the supposed role of kaempferol in the management of hyperglycemia and decreasing inflammation [52].

Chlorogenic acid and caffeic acid bind moderately to the enzyme, implying there may be a secondary action of these phenolic acids on enzyme inhibition. This is supported by the literature suggesting that phenolic acid is primarily responsible for antidiabetic action through antioxidant mechanisms, followed by small amounts of enzyme inhibition [43]. Rutin, on the other hand, had relatively low binding to all targets, which could be attributed to both its large molecular weight and also to its structural complexity. It has been documented previously that these two factors contribute to a decrease in binding efficacy and membrane permeation [46].

The enhanced binding activity of flavonoids (e.g., quercetin and kaempferol) can be attributed to their physical properties. These properties are characterized by the presence of many hydroxyl groups that can participate in hydrogen base pairing as well as having a flat, ring-like shape that assists with π–π stacking interactions at the binding site of enzymes. Both of these properties provide better stability and specificity when forming bonds and have been well-documented in numerous studies related to interactions between polyphenols and proteins [53]. These compounds have many ways of acting on different kinds of targets. This makes these drugs very useful when treating complicated conditions like type 2 diabetes, where you need to do multiple things to get the desired effect. The inhibition of Dipeptidyl Peptidase-4 (DPP4) will increase the effects of incretins; inhibition of alpha-Glucosidase will slow down the digestion of carbohydrates and therefore the absorption of glucose; and modulation of NF-kB and TNF-alpha together will enhance the effects of both agents on inflammation, showing that there may be a synergistic effect with this combination of drugs.

3.5. Immunological Relevance of *Ficus carica* Phytochemicals

The current results emphasize that the phytochemicals isolated from the fruit and leaves possess immunomodulatory capabilities by virtue of their interactions with important mediators of inflammation in relation to signaling pathways that regulate the immune response. Their strong binding affinities with NF-kB and TNF-alpha (for quercetin and kaempferol) may also indicate that these compounds could be involved in regulating cytokine production resulting from chronic immune activation. Because NF-kB regulates many gene transcripts that contribute to the production of pro-inflammatory genes, inhibition of its activity by flavonoids (derived from plants) could be an important target for pharmacological treatment of inflammatory diseases.

Additionally, their ability to simultaneously target inflammation and metabolism supports the developing notion of "immunometabolism," in which immune dysregulation occurs in close connection to metabolic dysfunction. The interactions of *Ficus carica* phytochemicals with NF-kB and TNF-α suggest promising therapeutic potential for chronic inflammation that is characterized by prolonged activation of the immune response and oxidative damage. These results support the current interest in developing natural bioactive substances as multi-target immunomodulators for use with inflammatory-related metabolic diseases.

3.6. Immunomodulatory Potential and Therapeutic Implications of *Ficus carica* Phytochemicals

Through the present investigation into phytochemicals present in *Ficus carica*, we have gained valuable evidence on how these compounds might be beneficial as treatment modalities for modulating inflammatory and metabolic pathways that lead to chronic disease. Both quercetin and kaempferol have demonstrated high binding affinities towards NF-kB and TNF-α which could indicate that they are involved in the regulation of cytokine signaling pathways and immune-mediated inflammatory responses. Natural phytochemicals have an opportunity to target inflammatory mediators and metabolic enzymes at the same time, creating a viable multi-target therapy strategy

that could have positive results given the increased awareness of chronic inflammation and immune dysregulation as major contributors to metabolic disorders. NF-kB, or nuclear factor kappa B, is an important transcription factor that regulates pro-inflammatory cytokines and is critical in inducing oxidative stress and the immune system's activation. Prolonged activation of NF-kB has been linked to many chronic inflammatory diseases such as type 2 diabetes mellitus, cardiovascular disease, obesity-related inflammation, and autoimmune diseases. Therefore, *Ficus carica* phytochemicals may have therapeutic benefits as they may inhibit or modulate this signaling pathway in order to help lessen chronic inflammation and restore immune homeostasis. In addition, the interactions observed for TNF-α also lend support to the potential for these compounds to have an anti-inflammatory and immunomodulatory effect. While TNF-α has long been recognized as a key cytokine involved in the pathogenesis of chronic inflammatory disease as well as causing metabolic disorders. Flavonoids such as quercetin and kaempferol may be able to reduce inflammation-mediated insulin resistance and oxidative stress through their interactions with TNFα-associated pathways.

Furthermore, targeting DPP-4 and α-glucosidase together indicates a potential link between metabolic regulation and inflammation mediated by the immune system; thus supporting an understanding of immunometabolism. In terms of being a potential pharmacological advantage compared to typical treatment options that target one specific molecule, this multi-target drug effect may be significant. Even though these results appear very positive, there are a few limitations to identify. The inability of molecular docking and in-silico predictions to accurately represent the complexity of biological systems and immune response *in vivo* is one limitation. As such, we would need to undertake other types of experimental studies (i.e., *in vitro*, *in vivo*, and clinical studies) to determine if these phytochemicals have biological activity, molecular mechanisms, and therapeutic efficacy. Overall, the study provides additional support for the emerging trend of using flavonoids from plant sources to develop immunomodulating compounds that can stimulate specific anti-inflammatory signaling pathways associated with chronic metabolic, autoimmune, and immunological disorders.

The interaction of quercetin, kaempferol, chlorogenic acid, and other phenolic compounds with Dipeptidyl Peptidase-4 (DPP-4), Nuclear Factor KappaB (NF-κB), and Tumour Necrosis Factor-Alpha (TNF-α) indicates their ability to act synergistically with contemporary therapies in managing Type 2 Diabetes Mellitus. By targeting both the glucose metabolism pathway and the inflammatory pathways, these compounds may improve the efficacy of therapy and decrease the incidence of diabetes-related inflammation and complications. Further research needs to be done (via *in vitro*, *in vivo* and clinical studies) to evaluate the potential of phenolic compounds to produce synergism or interaction with currently prescribed medications for Type-2 Diabetes Mellitus.

3.7. Immunological Implications

Chronically active inflammatory processes are being increasingly accepted as one of the most significant pathophysiological mechanisms by which several metabolic disorders, autoimmune diseases, infectious disorders, and degenerative disorders develop and progress [54]. Chronic inflammation differs from acute inflammation in that it involves the prolonged activation of immune cells and the continuous synthesis of pro-inflammatory mediators which ultimately lead to the destruction of body tissues and the impairment of normal organ function [55]. The regulation of chronic inflammatory processes is governed by a complex network of cell signaling pathways; the major pathway which controls chronic inflammatory responses is nuclear factor-kappa B (NF-κB) and its associated cytokine tumor necrosis factor-alpha (TNF-α). The fact that these two molecules represent the central components of these chronic inflammatory processes renders NF-κB and TNF-α attractive targets for the development of potential immunomodulatory approaches to treat numerous chronic inflammatory disorders [56].

NF-kB is one of the main transcription factors responsible for regulating both innate and adaptive immune responses. Under normal physiology, NF-kB is found in an inactivated state in the cytoplasm attached to an IκB family of proteins that inhibit NF-kB. After receiving signals from molecules like microbial products, oxidative stress, inflammatory cytokines, or metabolic changes, IκB proteins are degraded, allowing NF-kB to move into the nucleus to induce the transcription of hundreds of genes involved in inflammation and immunity. Among these are proinflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), interleukin-6 (IL-6), chemokines, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), adhesion molecules and a variety of mediators that activate and migrate immune cells. Therefore, continuous activation of NF-kB results in chronic inflammation, excessive production of cytokines and dysfunction of the immune system, collectively leading to the development of chronic,

inflammatory diseases.

TNF-α is one of the most significant pro-inflammatory cytokines released from activated macrophages, monocytes, dendritic cells and T cells. In addition to initiating inflammatory responses, TNF-α also enhances immune signaling through the stimulation of additional cytokine release, increased recruitment of leukocytes, enhanced activation of endothelial cells, and by enhancing communication between innate and adaptive immune systems. Increased TNF-α production has been linked to many chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, psoriasis, metabolic syndrome, obesity and type 2 diabetes mellitus. As a result, the inhibition/neutralization of TNF-α has been one of the most successful targets of immunotherapy in modern medicine and illustrates the importance of targeting signal pathways involved in inflammation.

A positive feedback loop exists between NF-κB and TNF-α which continues to maintain a state of chronic inflammation, because TNF-α stimulates the activation of the NF-κB signaling pathway and NF-κB stimulates the transcriptional activation of the TNF-α gene and many other inflammatory signaling molecules. This is a reciprocal amplification process that leads to sustained activation of the immune system, increased oxidative stress, and continued damage to tissues. The simultaneous modulation of both pathways is therefore an enticing way to treat excessive inflammatory responses that continue to harm the body but do not interfere with the normal functions of the immune system. The molecular docking results in this study indicate that several of the phytochemicals identified in *Ficus carica*, especially quercetin and kaempferol, have strong binding affinities for both NF-κB and TNF-α. Although in silico (via computer simulations) docking will not provide evidence of biological activity or the direct inhibition of these targets, the predicted ligand-protein interactions indicate that these compounds have the potential to modulate key inflammatory pathways based on their structural properties.

Studies that show a correlation between the two interactions suggest that there is a basis for the proposed mechanism by which these flavonoids mediate their previously described anti-inflammatory and immunomodulating actions. Flavonoids have an increasing body of knowledge regarding their ability to interact with immune system processes in a variety of ways via their many properties. In addition to their ability to scavenge free radicals, some flavonoid compounds have been shown to inhibit the overproduction of several pro-inflammatory cytokines, reduce excessive oxidative stress, modulate macrophage polarization, and modulate both the innate and adaptive arms of the immune system by regulating the activation of nuclear factor kappa gene binding (NF-κB). The flavonoids quercetin and kaempferol have been the subject of the most research, as they are able to provide physiological effects on the immune system by decreasing the quantity of pro-inflammatory mediators produced, while in turn maintaining normal physiological immune response functions. The multiple roles and wide range of potential effects of flavonoids on various aspects of biology makes them ideally suited for developing new multi-target immunomodulatory therapies, particularly for complex diseases that involve an interdependent relationship between inflammatory and metabolic pathways.

The present findings further support the concept of immunometabolism, which recognizes the intimate relationship between metabolic disturbances and immune dysfunction. Chronic metabolic diseases such as obesity and type 2 diabetes are no longer considered purely metabolic disorders but are increasingly viewed as conditions driven by persistent low-grade inflammation involving continuous activation of immune signaling pathways. Therefore, compounds capable of simultaneously interacting with metabolic enzymes (DPP-4 and α-glucosidase) and immune regulators (NF-κB and TNF-α) may provide complementary therapeutic benefits by targeting both metabolic abnormalities and chronic inflammatory processes. This multi-target approach is particularly relevant for diseases in which immune activation and metabolic dysfunction mutually reinforce one another. Finding natural substances that affect many different immune-related targets has a great potential for drug development from an immunotherapeutic standpoint. As opposed to traditional-based drugs aimed at blocking one specific target of interest, many natural plant-derived compounds may exhibit multiple modest simultaneous effects through the activation or inhibition of multiple related signal transduction pathways. The joint modulation of multiple targets may help to restore homeostasis within the immune system, reduce excess inflammation, and avoid many of the negative side effects associated with highly selective immunosuppressive drugs. Consequently, the phytochemicals investigated in the present study deserve further attention as potential lead compounds for the development of novel immunomodulatory agents.

Nevertheless, the present work should be interpreted within the limitations inherent to computational investigations. Molecular docking predicts the likelihood of ligand–protein interactions but cannot establish target in-

hibition, biological efficacy, pharmacological activity, or clinical benefit. Likewise, the predicted immunomodulatory potential reported herein remains hypothetical in the absence of experimental validation. Future investigations should therefore include *in vitro* studies using immune cell models to evaluate cytokine secretion, NF-κB activation, macrophage polarization, and inflammatory mediator production, followed by *in vivo* studies to confirm the immunological relevance of these computational predictions. Such complementary approaches will be essential for determining whether the promising molecular interactions identified in this work can ultimately translate into clinically meaningful immunotherapeutic applications. Overall, the present findings strengthen the hypothesis that *Ficus carica* phytochemicals, particularly quercetin and kaempferol, may constitute promising multi-target immunomodulatory candidates through their predicted interactions with NF-κB and TNF-α signaling pathways. Although these observations remain exploratory, they provide a rational basis for future experimental investigations aimed at developing plant-derived immunotherapeutic agents for chronic inflammatory and metabolic diseases.

4. Conclusion

In this paper, we have provided an integrated in silico approach for the assessment of certain phytochemicals found in *Ficus carica* leaves as potential multi-target modulators of metabolic/inflammatory pathways implicated in type 2 diabetes mellitus. The results of molecular docking analyses showed that the selected compounds were able to bind to several important therapeutic targets related to glucose metabolism and immune system regulation (DPP-4; α-glucosidase; NF-κB; TNF-α), suggesting that they may become an adjunct or alternative form(s) of diabetes therapy. Quercetin and kaempferol had the highest binding affinities and similar interaction profiles, as evidenced by stable hydrogen bonding and hydrophobic interactions with target amino acid residues. The physicochemical and pharmacokinetic properties of the investigated compounds reported generally showed acceptable drug-like characteristics as well as suitable solubility characteristics for the majority of compounds tested. Based upon toxicity predictions, all compounds tested have been predicted as having low acute toxicity; however, multiple compounds have also been associated with potential cardiotoxic, cytotoxic, and immunotoxic potential. Care should be taken when interpreting these computational predictions. The interaction of tested compounds with the NF-κB and TNF-α pathways indicates the potential immunomodulatory effects of *Ficus carica* phytochemicals and support the relevance of these compounds to metabolic disorders resulting from chronic inflammation. Despite being purely computational analysis; they are initial thoughts on discovering new compounds. The molecular docking and in silico ADMET prediction would provide preliminary evidence of what could happen in these biological systems but cannot recreate the complexity of these biological systems. Therefore, more experiments such as *in vitro* enzyme activity, cellular studies and *in vivo* studies need to be done in order to validate the biological activity, safety profile, molecular mechanisms and the therapeutic potential of the compounds described here.

Ficus carica has great potential as a source of bioactive phytochemicals and can lead to the discovery of quercetin and kaempferol as promising initial compounds to study the interactions among metabolic dysfunction, chronic inflammation, and immune dysregulation.

Author Contributions

Conceptualization, M.M., M.A., and Y.M.; methodology, M.A., M.E.B., and Y.M.; software, M.A.; validation, Y.A. and D.H.; formal analysis, M.A., Y.M., and N.B.; investigation, M.A. and Y.M.; data curation, M.A.; writing—original draft preparation, M.A.; writing—review and editing, M.A. and Y.M.; visualization, M.M., M.A., and M.E.B.; supervision, Y.A. and D.H. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

AI Use Statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely for language editing and improvement of grammar, clarity, and scientific writing. No artificial intelligence tools were used for data collection, data analysis, interpretation of results, figure generation, or the development of scientific conclusions. All AI-assisted outputs were critically reviewed, verified, and substantially edited by the authors. The authors take full responsibility for the accuracy, originality, and integrity of the manuscript.

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