**Unveiling the GSK-3β Inhibitory Potential of Ferulic Acid for targeting Neurological Disorder using *in silico* approach**

**ABSTRACT:**

Glycogen synthase kinase-3 (GSK-3) has been known to regulate various cellular and metabolic processes, including neuronal plasticity. Dysregulation of the GSK-3β isoform leads to the development of various neurological disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease. Thus, GSK-3β has gained major attention for therapeutic intervention in various neurological disorders. This study aimed to explore natural derivatives as potential inhibitors of GSK-3β for consideration of therapeutic value in the treatment of neurological disorders. Using an *in silico* approach through virtual screening, molecular docking, and Molecular Dynamic (MD) simulation, we elucidate ferulic acid's binding interaction and affinity with GSK-3β residues. Our study revealed that ferulic acid (out of 545 phytochemicals from Mangifera indica) demonstrated effective inhibitory activity for GSK-3β. Interestingly, an MD-simulation study showed ferulic acid binds with three crucial amino acid residues of GSK-3β for modulating the activity. In addition, ferulic acid passed all ADME/Tox parameters, paving the way for drug design and development targeting neurological disorders. Our findings provide valuable insight into the molecular mechanism underlying Ferulic acid as a potential GSK-3β inhibitor.

**Keywords:**  GSK-3β, Ferulic acid, neurological disorders, Alzheimer’s disease (AD), phytochemicals, bio-informatics, computational biology, molecular docking, molecular dynamic simulation.

**1. INTRODUCTION**

Glycogen synthase kinase-3 (GSK-3) is a versatile enzyme involved in pathways regulating cellular differentiation, glial cell survival, neuronal morphology, neurogenesis, synaptic plasticity, learning, and memory [1, 2]. Dysregulation of GSK-3 leads to the development of neurological disorders [3]. The inhibition of GSK-3 activity prevents hyperphosphorylation of the tau protein essential for linking it to the microtubule network. This hyperphosphorylation leads to the disruption of the cytoskeleton microtubule network in neurons, subsequently disrupting the neuronal network in the brain [4]. The Tau-mediated-microtubule network disruption is a commonly observed characteristic of several neurological disorders. The decline of GSK-3 in the cortex and hippocampus brain regions leads to a marked increase in neuronal polarity, multiple axon formation and abnormal dendritic formation, reduced spine density and a decreased rate of axon elongation. In the case of Alzheimer’s disease, the overexpression of GSK-3 tends to cause neuritic dystrophy, impaired cognition, and decreased neuronal survival. Whereas, in Parkinson’s disease (PD) GSK-3β isoform causes abnormal expression and aggregation of α-synuclein, accompanied by the loss of dopaminergic neurons in the Substantia nigra pars compacta and Lewy bodies of the PD brain. Excess dopamine aggregation is also known to trigger GSK-3β activation in the PD brain. Similarly, the overexpression of GSK-3β-Tyr216 in Huntington’s disease brain is known to trigger tau aggregation in the astrocytes and hippocampus regions as well (Fig. 1summarizes the cellular mechanisms affected by GSK-3β in various neurological disorders) [5] [6]. Consequently, a GSK-3 inhibitor may prove to be a medication for the treatment of Alzheimer’s disease and other neurological disorders [7].

Structurally, GSK-3α and GSK-3β are two GSK-3 isoforms found in all cell types across the animal phylum. The GSK-3β isoform consists of two lobes, namely the β-strand domain (N-terminal stretching from 25 to 25–138 amino acids) and an α-helical domain (C-terminal stretching from 139–343 amino acids). Located between these lobes is an interactive zone comprising an ATP-binding site, loop, and hinge regions (Asp133-Val135) [8]. The activation loop stretches from 200 to 226 amino acids. The β-strand domain is composed of seven antiparallel β-pleated sheets. Inside these sheets is an evolutionarily conserved loop of 4-5 short α- helices (spanning from 96 to 102 amino acids). In this loop, Arg96 and Glu97 play crucial roles in catalytic activity. Glu97 is located in the active site and forms a salt bridge with Lys85[9, 10]. The binding pocket residues Arg96 and Ala204 are unable to establish hydrogen binding when Glu97 and Lys85 fail to form a salt bridge among themselves. This leads to disruption of the phosphate-binding site, allowing the substrate-binding groove to achieve a wider open conformation [11]. We speculate that similar interactions between specific residues and selective phytocompounds may lead to GSK-β inhibition. In the present study, using an *in silico* approach, we screened 545 phytocompounds and identified the interaction between the ferulic acid found in *Mangifera indica* and crucial GSK-3β residues. Ferulic acid passed the necessary *in silico* ADME/Tox parameters to be considered a potential inhibitor for the GSK-3β enzyme.

**2. MATERIALS AND METHODS**

**2.1 Phytochemical and ADME/Tox screening:**

Phytocompounds found in Mangifera indica were screened using the IMPPAT 2.0 (Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0:<https://cb.imsc.res.in/imppat/home>) and PDTDB (Phytochemical and Drug Target DataBase:<https://pdt.biogem.org/search.php>) databases [12, 13]. These phytocompounds were further screened for their drug-likeness and physicochemical properties using the web services ‘SwissADME’ (<http://www.swissadme.ch/>) and admetSAR (<http://lmmd.ecust.edu.cn/admetsar2/>) [14].

**2.3 Target protein selection and structural validation:**

The Research Collaboratory for Structural Bio-Informatics Protein Data Bank (RCSB-PDB) (<https://www.rcsb.org/>) was used to search for an X-ray crystallography structure of GSK-3β [15]. The PDB ID 2JLD was selected as the structure had 2.35 Å resolution, 0.227 and 0.190 R-free and R-working values.

**2.4 Protein and Ligand Preparation:**

The GSK-3β structure, hereto referred to as 2JLD, was prepared using the protein preparation wizard suite of Schrodinger Maestro Suite version 2022-1. The default parameters include assigning bond orders, adding missing heavy atoms, assigning protonation states, and optimizing hydrogen bonds. Similarly, the shortlisted ligands were optimized using the ‘LigPrep’ module [16]. The parameters, such as structure optimization and the addition of any missing atoms or partial charges using the force field OPLS-2005, were set for the ligands. After protein and ligand preparations, the protein grid box was created central to the active site of 2JLD. The active site of the enzyme was determined using the UNIPROT database version 2023-02 (<https://www.uniprot.org/help/uniprotkb>) [17].

**2.5 Molecular docking:**

The Molecular docking analysis was conducted using the Glide suite of Schrodinger Maestro Suite version 2022-1. Firstly, High-Throughput Virtual Screening (HTVS) was used to increase the hit rate and filter the shortlisted phytochemicals [18]. Secondly, these phytochemicals were processed for molecular docking analysis using the Glide SP (standard precision) and XP (extra precision) suites [19] [20]. Thirdly, the top five docking interactions were compared with a negative and positive control.

**2.6 Molecular Dynamic Simulation:** The phytochemical demonstrating the highest binding affinity with GSK-3β was subjected to Molecular Dynamic (MD) simulation using the ‘Desmond’ suite. The simulation was conducted using the isothermal-isobaric ensemble at 300 Kelvin and 1.013 bar pressure for 100 nanoseconds. The OPLS-2005 force field and a predefined TIP3P solvent model were utilized for running the MD simulation [21] Santos [22]. The results of the MD simulation were analyzed using RMSD (Root Mean Square Deviation), RMSF (Root mean square fluctuation), and ligand-receptor interaction (ligand-atom points of contact over time, ligand-receptor point of contact plot at atomic scale).

**3. RESULTS AND DISCUSSION:**

**3.1. Phytochemical screening from *Mangifera indica:***

Few online comprehensive databases provide chemical structures, structure information, and chemical identifiers. These databases provide chemical structures (ligands), which can be downloaded and used for further analysis. Likewise, the present study utilized the IMPPAT and PDTDB databases, which revealed the presence of 545 phytochemicals in *Mangifera indica*. These phytochemicals were shortlisted based on their BBB (blood-brain barrier) crossing capabilities. This yielded 241 compounds; those were subjected to molecular docking with GSK-3β (2JLD).

**3.2. Molecular docking analysis of phytochemicals with GSK-3β:**

The Schrodinger Glide module consists of three sub-modules, viz., HTVS, Glide SP, and Glide XP, designed for refined lead optimization. The sub-module HTVS shortlists compounds based on their binding affinity with protein residues and drug-likeness properties, resulting in lead optimization. We subjected the previously screened 241 phytocompounds to HTVS analysis, which filtered 161 compounds that were lead optimized**.** These compounds were processed using the Glide SP and XP docking suites, which yielded only 13 phytochemicals with higher binding affinities with 2JLD (the top five compounds are shown in Table 1). Among these phytocompounds, only ferulic acid (Fig. 2) demonstrated the highest binding affinity of −7.22 kcal/mol with 2JLD. Upon detailed analysis of the dock poses using the 2D interaction diagram **(**Fig. 3a**),** wefound that the OH groups of ferulic acid formed hydrogen bonds with Lys85 and Val135 residues of 2JLD, thus establishing interaction between the ligand and protein. The hydrogen bond distance between ferulic acid and amino acid residues of 2JLD was measured using the ‘Measure’ tool of Maestro Suite. Results shown in Fig. 3b display the bond distance between the OH group and carboxylic group of ferulic acid with crucial GSK-3β residues Lys85 (2.88Å) and Val135 (2.19Å and 2.15Å), respectively, thus demonstrating a strong binding affinity with the enzyme. This finding prompted us to speculate that such interactions can inhibit enzyme activity *in situ*. However, it requires further validation by comparing it with suitable controls.

The docking results (interactions and bond distances) of ferulic acid with GSK-3β were compared with positive and negative control. A known GSK-3β inhibitor, SAR502250 [(S)-2-(2-(4-flurophenyl)morpholine)-1-methyl-[4,4’-bipyrimidin]-6 (1H)-one] was used as a positive control [23]. It was observed that SAR502250 had a binding energy of −4.4 kcal/mol and formed hydrogen bonds with Val 101 and Asp166 (Fig. 3c). Additionally, the bond distances between Val101 and Asp166 were 2.32 Å and 4.60 Å (Fig. 3d). In the case of the negative control, we docked ferulic acid with hexokinase (a kinase family member involved in glycolysis) [24]. The docked results demonstrated a binding energy of −6.3 kcal/mol and hydrogen bond formation with Asp73 with a bond distance of 3.19Å (Fig. 3e and 3f). Overall, the positive control, SAR502250, was unable to bind with any GSK-3β crucial amino acid residues. This demonstrates the inability of SAR502250 to be an efficient GSK-3β inhibitor. In the case of the negative control, ferulic acid was unable to hinder hexokinase activity *in silico*. Taken together, our results demonstrate that ferulic acid can counteract GSK-3β activity and may allow other cellular enzymes, such as hexokinase, to function effectively. Interestingly, we found that ferulic acid has better efficacy than SAR502250 in inhibiting GSK-3β activity.

For decades, GSK-3 inhibitors such as AZD1080, LY2090314, lithium salt, SB-216763, and tideglusib have been chemically synthesized for treating various neurological disorders. These drugs demonstrate toxicity, lethal side effects, and safety issues during in vivo and clinical trials [31]. Moreover, poor pharmacokinetics and safety issues related to synthetic compounds have been the leading causes of drug rejection in clinical trials [32]. On the other hand, phytochemicals have proven broad safety profiles and efficacy over synthetic compounds [33]. For example, phytochemicals obtained from *Mangifera indica* leaf and root extracts have been studied for their antidiabetic, anticancer, neuroprotective, wound healing, and protection properties against liver injury [34] [35] [36] [37] [38] [39]. However, studies on the therapeutic role of *Mangifera indica*-derived phytochemicals in the treatment of neurodegenerative diseases remain unexplored.

Our *in silico* results revealed the precise interactions between ferulic acid (from Mangifera indica) and crucial GSK-3β residues to have the highest binding affinity of −7.22 kcal/mol as compared to other phytochemicals. In addition, this binding affinity formed hydrogen bonds with crucial GSK-3β residues Lys85 and Val135. In contrast, the positive control SAR502250 formed hydrogen bonds with Val 101 and Asp166 having a binding affinity of −4.40 kcal/mol. The interaction of SAR502250 with non-crucial GSK-3β residues and its low binding affinity as compared to Ferulic acid prompts an argument that Ferulic acid can be a potential GSK-3β inhibitor *in silico*. On the other hand, ferulic acid formed a hydrogen bond with Asp73 with a binding affinity of −6.30 kcal/mol against hexokinase (negative control). We infer that ferulic acid is unable to interfere with the metabolic pathway enzyme (hexokinase) in a cell while effectively inhibiting GSK-3β *in silico*.

It is known that GSK-3β residues Lys85 and Asp200 play crucial roles in GSK-3β regulation. For example, Lys85 is vital for salt-bridge formation with Glu97 (an active site residue) [11]. Consequently, the formation of a hydrogen bond between ferulic acid and Lys85 might restrict GSK-3β chain region movements. Whereas, Val135 is part of the (hinge region) interactive zone—an important residue in the GSK-3β [8]. It can be deduced that the hydrogen bond formed between ferulic acid and Val135 may restrict GSK-3β hinge movement. Thus, ferulic acid demonstrates binding with crucial GSK-3β residues such as Lys85 and Val135. In contrast, the positive and negative controls were unable to bind to crucial GSK-3β residues. We further speculate that ferulic acid might show effective GSK-3β bond formation in vivo experiments, as compared to the positive control SAR502250.

Previous studies have classified the bond distances between a donor and acceptor for inhibition between 2.2 and 4.0 Å. The range between 2.2 and 2.5Å is classified as strong and covalent interactions, 2.5 to 3.5Å for moderate and electrostatic interactions, and 3.2 to 4.0Å is classified as weak and electrostatic interactions [40] [41]. Based on this, the hydrogen bond distances between Ferulic acid and crucial GSK-3β residues are 2.88Å with Lys85 and 2.19Å and 2.15Å with Val135. In contrast, the positive control was able to demonstrate a bond distance of 4.60 Å and 2.32 Å with Asp166 and Val101, respectively. The negative control was able to show a bond distance of 3.19 Å with Asp73. These results point out that the negative and positive controls point towards the possibility of ferulic acid being a GSK-3β inhibitor. The assessment of ligand-protein interaction using molecular docking methods is limited by the absence of entropic and solvation effects occurring in the cellular milieu. This limitation was overcome by MD simulation methods that provide an atomic spectrum of dynamic interaction between target ligand and protein[42].

**3.3 Molecular dynamic simulation of Ferulic acid GSK-3β:**

The MD simulation provides a detailed visualization of ligand-protein interactions on an atomic scale, considering a few physiological parameters such as pressure, temperature, pH, water, ions, and other molecules in the system. These parameters mimic the cellular environment by placing a solvation layer along with a force field around the target ligand protein. Thus, MD simulation approaches are used to assess the overall stability of ligand-protein complexes [21] [22] [25]. Based on this, we conducted the MD simulation between ferulic acid and GSK-3β for 100 ns. The acceptable RMSD values for ligand-protein are usually between 0-3.0Å in a MD simulation with stable and normal conditions [26]. Based on this, our simulation report generated the RMSD (Fig. 4a) values between 1.5 Å and 2.1 Å for GSK-3β and ferulic acid (as shown in Fig. 4b). While the RMSF value denotes conformational changes in target protein chains during the simulation run, Our RMSF values were within the allowed range of 0.6 to 1.8 Å, thereby indicating a normal fluctuation in the RMSF range.

The timeline representation of ligand-protein interaction Fig. 5ahas a top panel showing the total number of specific contacts GSK-3β residues make with OH and carboxylic groups of ferulic acid over the 100 ns simulation. The total points of contact fluctuate between 2 and 9, with an average of 5, thus pointing towards the fluid nature between GSK-3β and ferulic acid. The bottom panel of Fig. 5adisplays which GSK-3β amino acid residues made contact with the OH and carboxylic groups of ferulic acid during the trajectory course. Moreover, the residues that have made more than one specific contact with ferulic acid are represented by a dark orange hue. Our results demonstrate ferulic acid to have persistent interactions with Val135 and Asp200. The darker orange intensity emphasizes that Val135 had more interactions with ferulic acid (more than 90 ns) as compared to Asp200. Fig. 5bshows hydrogen bond (green bar) formation between Ferulic acid and GSK-3β residues during the interactions, along with the significant interaction fractions with residues Val135 and Asp200. The interaction fraction value above 1.0 was due to the multiple contacts made by GSK-3β residues made with ferulic acid. The percent interaction diagram demonstrates the interactions occurring more than 30.0% during the 100 ns simulation trajectory, as shown in Fig. 5c.Our findings display a constant interaction of 91% with the carboxylic group and 98% with the OH group of ferulic acid with the crucial GSK-3β residue Val135. Additionally, 76% of the interaction was observed with another crucial GSK-3β residue, Asp200, during the simulation course.

It is known that the hinge motion in an enzyme structure provides flexibility and allows substrate binding during the reaction. In the case of GSK-3β, the hinge region is found between the β-strand domain and α-helical domain; thereby, obstruction in this region might inhibit the enzyme hinge motion [43]. While the activation loop in an enzyme restricts substrate access, it controls catalysis [44]. Our 100 ns MD simulation results demonstrated interactions with Val135 (hinge region residue) and Asp200 (activation loop residue) with the OH and carboxylic groups of ferulic acid. Such an interaction might inhibit the hinge motion along with preventing substrate access and catalysis of GSK-3β. Additionally, our results display hydrogen bond formation for 90 ns with the aforementioned crucial GSK-3β residues. Overall, these actions are predicted to inhibit GSK-3β, according to the MD simulation results.

**3.4. ADME/Tox Analysis of Ferulic Acid:**

Bioinformatics-based web services aid in the generation of drug-likeness, pharmacokinetics, and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME/Tox) capability/profiles of any given compound. Such properties aid in drug discovery, drug development, and preventing drug rejection during *in vivo* studies [27] Daina [14]. In the current study, we utilized SwissADME and admetSAR web-services that provide drug-likeness, compound physicochemical and medical chemistry properties of any given compound. Further, these web services were used to explore the above-mentioned drug properties of Ferulic acid. Based on this, we found that ferulic acid had a molecular weight of 194.19 g/mol. This compound also showed a bioavailability score of 0.85 and has BBB permeability, along with being highly permeable to the gastrointestinal (GI) tract. Except for the Pfizer 3/75 rule, this compound passed other drug-likeness properties such as Lipinski’s rule of 5, Ghose rule, Veber rule, Egan rule, and GSK 4/400 rule (Table 2).

The BOILED EGG model graphically represents TPSA and WLOGP (lipophilicity) values, along with BBB or GI,and thepossibility of a compound being a P-glycoprotein (P-gp) substrate. Additionally, in this model, the red dot indicates the compound to be a P-gp non-substrate, while the blue dot indicates the compound to be a P-gp substrate [28]. The BOILED EGG model of ferulic acid (Fig. 6a) shows that this compound has a TPSA value of 66.76 Å² and a WLOGP value of 1.39. Additionally, the position of the red dot indicates the compound to be both BBB and GI tract permeable and a P-gp non-substrate.

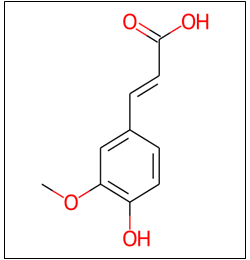
The bioavailability radar represents physicochemical and oral bioavailability properties such as flexibility (number of rotatable bonds), instauration (Fraction Csp3), insolubility (LogS [ESOL]), lipophilicity (XLOGP3), polarity (TPSA), and size (molecular weight) of compounds [29]. In the case of ferulic acid (Fig. 6b and Table 3), the number of rotatable bonds was three: instauration of 0.10, LogS [ESOL] value of -2.11, TPSA value of 66.76 Å², and molecular weight of 194.18 g/mol.

The toxicity assessment of ferulic acid revealed negative probabilities for the Ames mutagenesis test, biodegradation, carcinogenicity, hepatotoxicity, and nephrotoxicity. In addition, acute oral toxicity fell under class IV (non-toxic and non-irritant) [30] (Table 4). Thus, justifying our *in silico* results of ferulic acid being a possible GSK-3β inhibitor.

According to the ADME/Tox criterion, an ideal therapeutic drug must be able to cross the gastrointestinal and blood-brain barrier, apart from having a low polar surface area, reduced molecular flexibility, and passing other drug-likeness parameters [45]. Our ADME/Tox analysis reveals that ferulic acid is able to pass these criteria. Thereby suggesting ferulic acid as a possible GSK-3β inhibitor.

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**Fig. 1:** An overview of GSK-3β affecting various cellular mechanisms of neurons in the cortex and hippocampus brain regions of neurological disorders.



**Fig. 2:** Ferulic acid (2D chemical structure) has two exposed OH groups that allow hydrogen bond formation with the ‘R’ group of crucial GSK-3β amino acids.

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**Fig. 3: Comparative 2D and 3D Molecular docking results showing interaction along with the bond distances of Ferulic acid, positive control and negative control with GSK-3β: a.** The 2D interaction diagram shows two OH and carboxylic groups of ferulic acid forming hydrogen bonds (violet arrows) with crucial GSK-3β residues Lys85 and Val135. **b.** The bond distance between the OH and carboxylic groups of ferulic acid with crucial GSK-3β residues Lys85 (2.88Å) and Val135 (2.19Å and 2.15Å) signifies the strong binding affinity required for inhibition. **c.** The positive control SAR502250 interacts with two non-crucial GSK-3β residues, Val 101 (-NH group) and Asp166 (-OH group). **d.** While the positive control SAR502250 and GSK-3β residues Val101 and Asp166 demonstrate a bond distance of 2.32Å and 4.60Å, respectively **e.** The negative control, Ferulic acid, interacts with the Asp73 (OH group) residue of hexokinase. These results indicate effective *in silico* GSK-3β inhibition. **f.** The negative control Ferulic acid and hexokinase residue Asp73 have a bond distance of 3.19Å. Altogether, the bond distance of ferulic acid with SAR502250 and hexokinase shows weak interactions with GSK-3β residues. As opposed to these results, our finding is that ferulic acid was able to form strong hydrogen bindings with crucial GSK-3β residues.

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**Fig. 4: RMSD and RMSF graphs denoting the similarity and fluctuations between Ferulic acid-GSK-3β coordinates in MD simulation:** **a.** The RMSD graph represents the quantitative measure of ferulic acid and GSK-3β for 100 ns. This graph also demonstrates a difference of 1.5 Å to 2.1 Å between ferulic acid and GSK-3β **b.** The RMSF plot represents the average deviation of ferulic acid and GSK-3β residues for 100 ns. The plot shows a fluctuation between ferulic acid and GSK-3β between 0.6 and 1.8 Å.

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**Fig. 5: Detailed MD simulation representation of Ferulic acid interactive groups with crucial GSK-3β residues:** Additional MD simulation results further affirm the RMSD and RMSF results. **a.** The top panel of the diagram represents the points of contact for GSK-3β made with ferulic acid. The bottom panel shows residue interactions of GSK-3β with ferulic acid. GSK-3β residues Val135 (dark orange) and Asp200 (orange) bonded for 90 ns with ferulic acid during the 100 ns MD simulation. **b.** The interaction diagram shows Ferulic acid OH and carboxylic groups interaction fractions of above 1.0 with Val 135 and Asp200 (GSK-3β residues), respectively, during the 100 ns simulation. **c.** A detailed schematic diagram of ligand-atom interactions with the GSK-3β residues describes that the two OH and carboxylic groups of ferulic acid formed 91% and 98% of hydrogen bonds with Val135 and 76% with Asp200, respectively, during the 100 ns simulation run.

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**Fig. 6: Pharmacokinetic and drug-likeness profiles of ferulic acid:** The ADME/Tox properties, drug-likeness, and medical chemistry of ferulic acid were checked using SwissADME and AdmeSAR web services before proceeding with molecular docking and MD simulation. **a.** The BOILED EGG model of ferulic acid (red dot) demonstrates that ferulic acid can cross the blood-brain barrier (yellow area) and is a potential non-P-GP substrate. **b.** Similarly, the bioavailability radar of ferulic acid plots drug-likeness properties shows LIPO (lipophilicity), SIZE (molecular weight), POLAR (polarity), INSOLU (insolubility), INSATU (instauration), and FLEX (flexibility). It was observed that ferulic acid abides by all the bioavailability radar parameters, except instauration. Overall, these ADME/Tox properties qualify ferulic acid as a possible GSK-3β inhibitor.

**Table 1:** The top five binding affinity scores of phytocompounds after docking with GSK-3β (PDB ID: 2JLD) demonstrating Ferulic acid to have the highest binding affinity as compared to the other phytochemicals present in *Mangifera indica*.

|  |  |
| --- | --- |
| **Phytochemical** | **Docking score (kcal/mol)** |
| Ferulic acid | −7.22 |
| Benzoic acid | −6.79 |
| Carvacrol | −6.74 |
| Thymol | −5.98 |
| (+)-delta-Cadinene | −5.43 |

**Table 2:** Table shown different parameters ofFerulic acid. ADME Profile and Drug-likeness Properties.

|  |  |
| --- | --- |
| **Parameters of Ferulic acid** | **Score** |
| Bioavailability score | 0.85 |
| Solubility class [ESOL] | Soluble |
| Solubility class [Silicos-IT] | Soluble |
| Blood Blood-brain barrier permeation | Yes |
| Gastrointestinal absorption | High |
| Log Kp (Skin permeation, cm/s) | -6.41 |
| Number of PAINS structural alerts | 0.0 |
| Number of Brenk structural alerts | 1.0 |
| CYP1A2 inhibitor | No |
| CYP2C19 inhibitor | No |
| CYP2C9 inhibitor | No |
| CYP2D6 inhibitor | No |
| CYP3A4 inhibitor | No |
| P-glycoprotein substrate | No |
| Number of Lipinski’s rule of 5 violations | 0 |
| Lipinski’s rule of 5 | Passed |
| Number of Ghose rule violations | 0 |
| Ghose rule | Passed |
| Veber rule | Good |
| Egan rule | Good |
| GSK 4/400 rule | Good |
| Pfizer 3/75 rule | Bad |
| Weighted quantitative estimate of drug-likeness (QEDw) score | 0.72 |
| Molecular weight (g/mol) | 194.19 |

**Table 3:** Bioavailability radar showing lipophilicity (XLOGP3), size (MW: molecular weight), polarity (TPSA), insolubility (LogS [ESOL]), insaturation (Fraction Csp3) and flexibility (Number of rotatable bonds) the respective value range and values occurring in Ferulic acid.

|  |  |  |
| --- | --- | --- |
| Parameter | Value range | Score |
| Lipophilicity | -0.7< XLOGP3< +5.0 | 1.51 |
| Size | 150g/mol< MW< 500 g/mol | 194.18 g/mol |
| Polar | 20Å2< TPSA< 130Å2 | 66.76 Å² |
| Insolubility | -6< Log S[ESOL]< 0 | -2.11 |
| Insaturation | 0.25< Fraction Csp3< 1 | 0.10 |
| Flexibility | 0< Number of rotatable bonds< 9 | 3 |

**Table 4:** A Few Toxicity properties such as Ames mutagenesis, acute oral toxicity, biodegradation, carcinogenicity, hepatotoxicity and nephrotoxicity of Ferulic acid.

|  |  |
| --- | --- |
| **Property** | **Ferulic acid** |
| Ames mutagenesis | – |
| Acute oral Toxicity (c) | Class IV |
| Biodegradation | – |
| Carcinogenicity (binary) | – |
| Insaturation | – |
| Flexibility | – |

**CONCLUSION**

The progression of neurological disorders is the most prevalent non-communicable disease, with the highest burden among all diseases. Several studies convincingly proved that GSK-3β has an emerging potential for targeting neurological disorders. Our study revealed that ferulic acid phytochemicals from *Mangifera indica* have numerous potentials for inhibiting GSK-3β as a potential inhibitor, which highlighted their therapeutic efficacy. The virtual screening and molecular docking revealed that ferulic acid has strong binding interactions and inhibitory potential for GSK-3β, forming strong hydrogen bond interactions with GSK-3β residues Lys85 and Val135. Further, the MD simulation displayed a strong association of ferulic acid with GSK-3β residues Val135 and Asp200 for more than 90 and 70 ns simulation time, respectively. The MD simulation, ADME/Tox profile, and binding affinity predict that ferulic acid has better efficacy than the other compounds. These findings provide compelling evidence that the interaction between the phytocompound Ferulic acid and GSK-3β can be inhibitory to the enzymatic activity of GSK-3β. This study paved the way for harnessing the potential of the natural derivative ferulic acid for further experimental validation and exploration as a drug candidate for therapeutic intervention in neurological disorders.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

We hereby declare that, No generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

**FUTURE PERSPECTIVE**

These *in silico* results can be further validated through in vitro and in vivo experiments, to assess the GSK-3β inhibition potential of Ferulic acid.

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