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Xiao Liu Zhi Wei (XLZW) for Chronic Atrophic Gastritis: Mechanism of TNF-α Inhibition Revealed by Molecular Docking

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ABSTRACT

Introduction*: Xiao Liu Zhi Wei (XLZW) is a traditional herbal formula with therapeutic relevance in gastrointestinal disorders. Tumor Necrosis Factor-α (TNF-α) was selected as the target protein based on prior network pharmacology studies identifying its central role in inflammatory pathways.* ***Aims****: This study aimed to evaluate the drug-likeness, ADMET properties, binding cavity, and molecular docking interactions of XLZW compounds against TNF-α using computational approaches.* ***Methods****: Active compounds were screened for physicochemical and pharmacokinetic properties. CurPocket analysis was performed to identify potential binding cavities, followed by molecular docking to assess binding affinities and protein–ligand interactions.* ***Results****: Most compounds adhered to Lipinski's criteria, with favorable absorption and safety predictions. CurPocket analysis revealed a large druggable cavity (volume 3208 Å^3). Docking studies showed strong binding affinities, with CID 44257530 achieving the best score (−12.5 kcal/mol), surpassing the native ligand (−11.3 kcal/mol). Key residues including TYR119, TYR151, LEU120, LEU57, and TYR59 consistently mediated hydrogen bonding, van der Waals, and π interactions, forming a stable binding network.* ***Conclusion****: Computational predictions highlight XLZW compounds, particularly CID 44257530, as promising TNF-α modulators with potential anti-inflammatory and anti-gastritis activity. However, these findings remain in silico and require comprehensive experimental validation to confirm biological efficacy and therapeutic relevance.*

KEYWORDS: *Chronic atrophic gastritis, Xiao Liu Zhi Wei (XLZW) formula, TNF-α , molecular docking, ADMET prediction.*

INTRODUCTION

Chronic atrophic gastritis (CAG) is a precancerous gastric lesion characterized by persistent inflammation, glandular atrophy, and intestinal metaplasia, all of which significantly increase the risk of gastric carcinoma (Yu et al., 2025). Among the inflammatory mediators implicated in its pathogenesis, tumor necrosis factor-alpha (TNF-α) plays a central role by driving mucosal injury, amplifying cytokine cascades, and disrupting epithelial

regeneration. Current conventional regimens for CAG alleviate symptoms without sufficiently resolving the core inflammatory pathways at a molecular level, emphasizing the demand for novel interventions (Weng et al., 2024).

Xiao Liu Zhi Wei (XLZW), a traditional Chinese medicinal formulation, has been clinically used for gastrointestinal disorders, yet its mechanistic basis remains poorly defined. Previous studies on herbal formulations for CAG have largely focused on general anti-inflammatory or antioxidant effects, without clarifying direct molecular interactions with key cytokines such as TNF-α. This gap limits the translational potential of traditional remedies in modern pharmacology.

The present research aims to elucidate the inhibitory mechanism of XLZW against TNF-α through molecular docking simulations. By modeling the binding interactions between XLZW-derived phytochemicals and TNF-α, we provide structural insights into how this formulation may attenuate inflammatory signaling in CAG (Norman et al., 2020; H. Li et al., 2021). This approach positions our study at the intersection of traditional medicine and computational pharmacology, extending prior research that has emphasized empirical efficacy but lacked molecular-level validation (Agu et al., 2023; P. Zhang, 2024).

The novelty of this work lies in revealing TNF-α as a direct molecular target of XLZW, supported by docking-based evidence of stable ligand–protein interactions. Unlike earlier studies that described broad anti-inflammatory effects, our findings highlight a specific cytokine-inhibition pathway, thereby offering mechanistic clarity and a foundation for rational drug development (Jo et al., 2024; H. Li et al., 2021). Theoretically, this aligns with the concept of structure-based drug design, where computational docking serves as a predictive tool to bridge phytochemistry and molecular pharmacology.

METHODS

This study employed an in silico approach to investigate the molecular interactions between bioactive compounds from Xiao Liu Zhi Wei (XLZW) and tumor necrosis factor-α (TNF-α), a key cytokine implicated in chronic atrophic gastritis. The main objective was to evaluate the inhibitory potential of XLZW phytochemicals against TNF-α through computational modeling (Hosseinpour-Niazi et al., 2022). The three-dimensional structure of TNF-α was obtained from the Protein Data Bank (PDB ID: 6OOY). Protein preparation included removal of water molecules and co-crystallized ligands, followed by structural optimization to ensure docking accuracy. Candidate ligands were retrieved from the PubChem database,

then processed using BIOVIA Discovery Studio Visualizer for geometry optimization and hydrogen atom addition. Molecular docking simulations were conducted with AutoDock Vina to predict binding affinities and identify potential binding sites. A grid box was defined around the active site of TNF-α, and docking scores were used to rank ligand–protein complexes (Nurhidayah et al., 2024; Z. Zhang et al., 2024).

Interaction analysis focused on identifying hydrogen bonds, hydrophobic contacts, and critical amino acid residues involved in ligand binding. These results provide structural evidence of the compounds' ability to inhibit TNF-α activity. To complement docking results, ADMET predictions were performed to assess pharmacokinetic properties and toxicity profiles, thereby evaluating the compounds' safety and therapeutic potential. This integrated computational workflow offers mechanistic insights into the anti-inflammatory role of XLZW in chronic atrophic gastritis

Tools and Devices

Software

Molecular docking simulations were carried out using PyRx integrated with AutoDock Vina, which enabled ligand and protein preparation and binding affinity calculations. Structural visualization and interaction analysis were performed using BIOVIA Discovery Studio Visualizer (DSV). To improve docking accuracy, potential binding pockets in TNF-α were predicted using CB-Dock2 (http://183.56.231.194:8001/cb-dock2/index.php). Additionally, pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) was employed to estimate ADMET properties, including pharmacokinetics and toxicity profiles of the candidate compounds (Almuhayawi et al., 2023; Saravanan et al., 2022)

Hardware

All computational analyses were conducted on a personal computer equipped with an Intel Core i9 processor, 8 GB of RAM, and 500 GB of storage (HDD/SSD), which met the minimum requirements for the software used.

Research Materials

Target Protein

The protein structure analyzed in this study was tumor necrosis factor-alpha (TNF-α) (PDB ID: 6OOY), retrieved from the Protein Data Bank. This structure, determined by high-resolution X-ray crystallography, originates from *Homo sapiens*. TNF-α is a central pro-inflammatory cytokine implicated in chronic atrophic gastritis, making it a relevant therapeutic target (Rachmawati et al., 2023; Wu et al., 2024).

Ligands

Bioactive compounds from *Xiao Liu Zhi Wei* (XLZW) were selected based on literature reports and retrieved from the PubChem database. Ligands were initially prepared in three-dimensional (.sdf) format and converted into .pdbqt format for compatibility with AutoDock Vina. Each ligand was optimized for stable conformation and subsequently evaluated for binding affinity and pharmacological potential (Rachmawati et al., 2023; Wu et al., 2024).

Methods

Protein and Ligand Preparation

The TNF-α structure (PDB ID: 6OOY) was processed using BIOVIA DSV, including removal of water molecules, ions, and co-crystallized ligands, followed by addition of polar hydrogen atoms. Ligand structures obtained in .sdf format were converted to .pdbqt format using PyRx, and energy minimization was performed to obtain stable conformations prior to docking (L. Li et al., 2024).

Binding Site Prediction

Active binding sites within TNF-α were predicted using CB-Dock2, which provided optimal center coordinates and grid box dimensions to ensure that docking simulations focused on biologically relevant regions (L. Li et al., 2024).

Molecular Docking

Docking simulations were performed using PyRx with AutoDock Vina with coordinate X:133.55, Y: 100.88, Z: 67.28 grid box (x:y:z) 82.039; 115.07; 87.65. Each ligand generated a binding affinity score (kcal/mol) and a predicted binding pose representing the most favorable conformation within the active site. To validate docking accuracy, the root-mean-square deviation (RMSD) between predicted and experimental crystallographic poses was calculated using BIOVIA DSV. RMSD values below 2.0 Å were considered reliable, and all redocking results met this criterion (Dev Sharma et al., 2025; Xiong et al., 2022).

Ligand–Protein Interaction Analysis

Docking conformations were analyzed using BIOVIA DSV to identify hydrogen bonds, hydrophobic contacts, and key amino acid residues stabilizing the ligand–protein complexes.

ADMET Prediction

Finally, pkCSM was used to predict pharmacokinetic and toxicity profiles of the compounds, including oral absorption, hepatotoxicity, mutagenicity, and cytochrome P450 interactions. These predictions provided insights into the compounds' safety and suitability as potential TNF-α inhibitors (Nurhidayah et al., 2024).

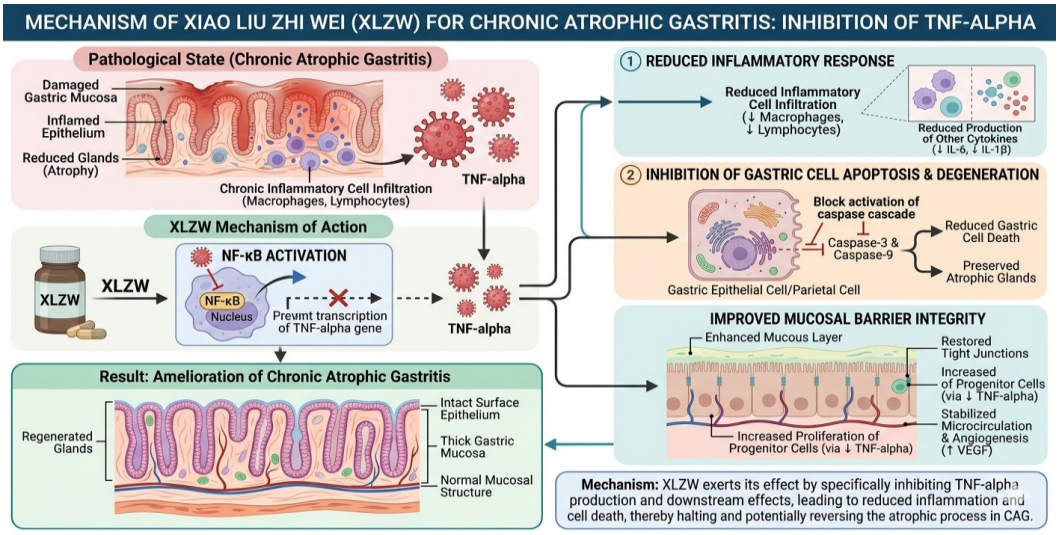


Figure 1. Predicted mechanism of TNF-α Inhibition by XLZW In chronic atrophic gastritis.

RESULTS AND DISCUSSION

This study provides a comprehensive in silico evaluation of bioactive compounds from XLZW targeting tumor necrosis factor-alpha (TNF-α) (PDB ID: 6OOY) in the context of chronic atrophic gastritis. The workflow was organized systematically to highlight the therapeutic potential of the compounds.

First, the physicochemical properties of each compound were assessed according to Lipinski's Rule of Five, ensuring drug-likeness and suitability for oral administration. This was followed by ADMET predictions to evaluate pharmacokinetic behavior and toxicity profiles, providing insights into absorption, distribution, metabolism, excretion, and safety (Almuhayawi et al., 2023). Next, molecular docking simulations were performed to estimate binding affinities and assess the stability of ligand protein complexes (Paggi et al., 2024). Docking scores were used to rank compounds, while interaction analyses identified hydrogen bonds, hydrophobic contacts, and critical amino acid residues within the TNF-α binding site. These findings elucidate the potential inhibitory mechanism of XLZW phytochemicals against TNF-α. Finally, the structural characteristics of the protein–ligand complexes were examined using two-dimensional (2D) and three-dimensional (3D) interaction models, which provided detailed visualization of binding conformations and interaction networks. Together, these results provide mechanistic evidence of XLZW's role in modulating TNF-α activity and highlight its promise as a candidate for anti-inflammatory therapy in chronic atrophic gastritis, the prediction of mechanism XLWZ formula as treatment of gastritis illustrated in Figure 1.

The diagram in Figure 1 illustrates how XLZW alleviates Chronic Atrophic Gastritis (CAG) by targeting and inhibiting TNF-α

production: 1). Pathological State (CAG): CAG is characterized by a damaged gastric mucosa, inflamed epithelium, reduced glands (atrophy), and infiltration of chronic inflammatory cells (macrophages and lymphocytes) that release TNF-alpha. 2). XLZW Mechanism of Action: XLZW blocks NF-kappaB activation in the nucleus, preventing the transcription of the TNF-alpha gene and significantly lowering TNF-alpha levels. 3). Downstream Effects: Reduced Inflammatory Response: Decreases inflammatory cell infiltration (macrophages and lymphocytes) and lowers other pro-inflammatory cytokines (IL-6 and IL-1beta); Inhibition of Cell Apoptosis & Degeneration: Blocks the caspase cascade (Caspase-3 & Caspase-9), leading to reduced gastric cell death and preservation of atrophic glands; Improved Mucosal Barrier Integrity: Enhances the mucous layer, restores tight junctions, increases progenitor cell proliferation (via reduced TNF-alpha), and stabilizes microcirculation and angiogenesis (via increased VEGF). The inhibition of TNF-alpha halts and reverses tissue damage, resulting in the amelioration of CAG with regenerated glands, an intact surface epithelium, a thick gastric mucosa, and restored normal mucosal structure.

Based on previous experimental findings and network pharmacology-derived target analysis, we hypothesize that the observed therapeutic potential of Xiao Liu Zhi Wei (XLZW) for Chronic Atrophic Gastritis (CAG) is largely mediated by its specific interaction with TNF-α. This hypothesis is based on the initial observation (as shown in Figure 1) that the XLZW intervention is associated with a marked reduction in overall TNF-α levels, which in turn leads to subsequent protective effects, including reduced inflammation, decreased gastric cell apoptosis, and improved mucosal barrier integrity (Bhatti et al., 2022). However, the precise biological mechanism underlying this decrease in the physical interaction between XLZW compounds and TNF-α remains theoretical.

To clarify this link, our ongoing research utilizes specialized molecular simulation techniques. It is crucial to emphasize that the binding analysis presented here is strictly a simulation. This computational modeling enables us to predict potential binding sites, interaction affinity (such as binding free energy), and the specific amino acid residues that stabilize the XLZW-TNF-α complex. By performing these simulations, we hope to demonstrate that components within XLZW can physically bind to TNF-α, effectively neutralizing its biological activity or preventing its interaction with its receptor.

This computational evidence is intended to provide a plausible "binding mode" that connects the predicted network

Table 1. Drug-likeness profile and admet prediction of active compounds from XLZW Targeting TNF-α Protein

Ligand	CID	MW	LOGP	HBA	HBD	SA	Caco2	P-glyc. II inh.	BBB	CYP1A2 inh.	Renal OCT2 subs.	Max. dose
Quercetin	5280343	302.238	1.988	7	5	122.108	-0.229	No	-1.098	Yes	No	0.499
Formononetin	5280378	268.268	3.1742	4	1	114.409	1.253	No	0.157	Yes	No	0.008
Acacetin	5280442	284.267	2.8798	5	2	119.203	1.137	No	-0.196	Yes	No	0.09
Luteolin	5280445	286.239	2.2824	6	4	117.313	0.096	No	-0.907	Yes	No	0.499
Stigmasterin	5280794	412.702	7.8008	1	1	186.349	1.213	Yes	0.771	No	No	-0.664
Kaempferol	5280863	286.239	2.2824	6	4	117.313	0.032	No	-0.939	Yes	No	0.531
Baicalein	5281605	270.24	2.5768	5	3	112.519	1.117	No	-1.061	Yes	No	0.498
Wogonin	5281703	284.267	2.8798	5	2	119.203	0.969	No	-0.232	Yes	No	0.151
Gancaonin	5317479	368.385	4.0941	6	3	155.133	0.132	Yes	-1.083	Yes	No	0.03
Phaseol	44257530	336.343	4.6123	5	2	141.961	0.734	Yes	-0.359	Yes	No	0.246

Note: MW (Molecular Weight); LOGP (Lipophilicity); HBA (Hydrogen Bond Acceptors); HBD (Hydrogen Bond Donors); SA (Surface Area); BBB (Blood-Brain Barrier); P-glyc. II inh. (P-glycoprotein II inhibition); Renal OCT2 subs. (Renal Organic Cation Transporter 2 substrate).

pharmacology targets to the observed *in vivo* and *in vitro* results. It is the necessary bridge to transform the correlation (XLZW results in low TNF-α) into a definitive, target-based pharmacological hypothesis. Ultimately, these simulations serve as pre-clinical, predictive data that must be confirmed by subsequent experimental studies, such as binding affinity assays (e.g., surface plasmon resonance) and structural biology studies (Fei et al., 2025).

To establish a solid foundation for our simulations, we screened the bioactive constituents of XLZW using Drug-Likeness profiling and ADMET predictions. This computational phase ensures that the compounds targeting the TNF-α protein possess the necessary oral bioavailability and safety profiles for therapeutic use. By applying Lipinski's Rule of Five, we identified high-potential candidates that are not only predicted to bind effectively but are also biologically feasible within the human body (Dey et al., 2023). The results below summarize the pharmacokinetics of the primary ligands used in this simulation.

The ADMET profiling (Table 1) shown of XLZW compounds targeting TNF-α revealed generally favorable drug-likeness properties, with most molecules adhering to Lipinski's criteria. Several compounds (CID 5280378, 5280442, 5281703, 5317479, and 44257530) showed good intestinal absorption and positive BBB penetration, suggesting potential activity in neuroinflammatory contexts. Importantly, none were predicted as P-glycoprotein inhibitors, minimizing efflux-related concerns. Safety predictions indicated consistent CYP1A2 inhibition, highlighting possible drug–drug interaction risks, though renal toxicity was not anticipated. Among the candidates, CID 5280378 and 5280442 emerged as promising leads due

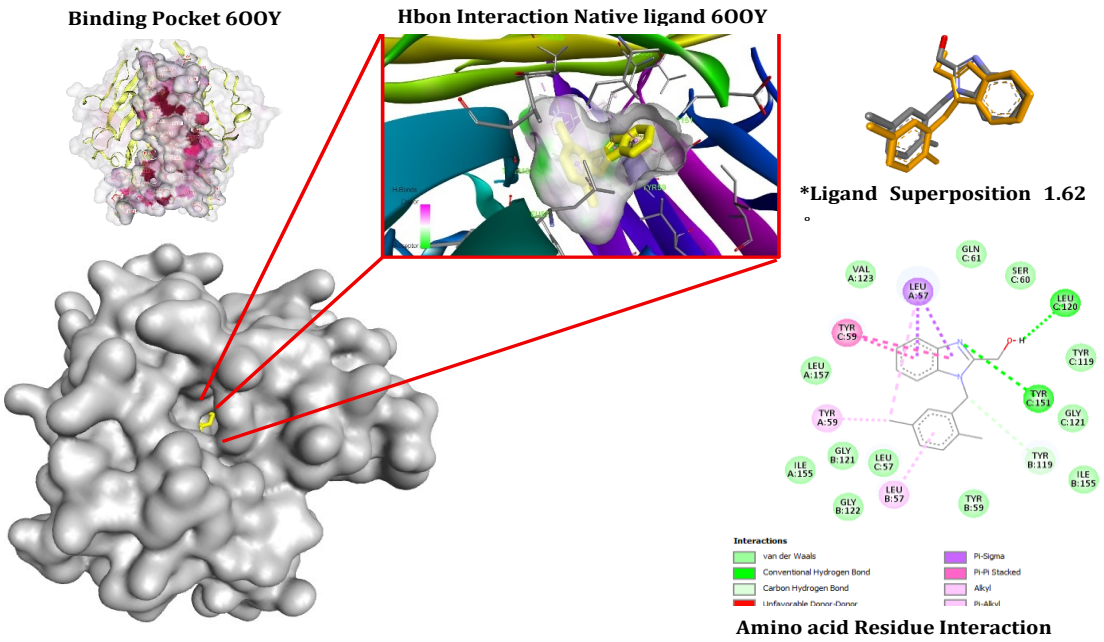


Figure 2. Superposition and interaction of the native ligand within the binding site of protein 6OOY

to balanced physicochemical properties, high absorption, and CNS accessibility, despite lower predicted tolerated doses. Overall, these findings support the use of XLZW compounds as potential TNF-α modulators with translational relevance, particularly for inflammation involving the gut–brain axis.

The pocket analysis using CurPocket identified a major binding cavity on the TNF-α protein (Figure 2). This cavity exhibited a substantial volume of 3208 $Å^3$, with its center located at coordinates (−7, −2, −13). The cavity dimensions (30 × 21 × 30 Å) suggest a spacious and well-defined binding pocket capable of accommodating diverse ligands. The large volume and balanced geometry indicate the potential for stable ligand–protein interactions, supporting the feasibility of XLZW compounds in effectively engaging TNF-α. These structural features highlight C1 as a promising pharmacological target, reinforcing the relevance of docking simulations and ADMET predictions for identifying lead candidates.

Interaction analysis revealed that the native ligand engages TNF-α through multiple stabilizing forces. Key hydrogen bonds were formed with LEU120 and TYR151, providing specificity and stability, while an additional conventional hydrogen bond with TYR119 reinforced binding affinity. Surrounding residues such as VAL123, LEU157, ILE155, GLY121, LEU57, GLY122, TYR59, SER60, and GLN61 contributed extensive van der Waals contacts, creating a supportive hydrophobic environment. Aromatic interactions further strengthened the complex: TYR59

Table 2. Molecular docking results and protein–ligand interaction profiles of selected compounds with the target of TNF-α protein

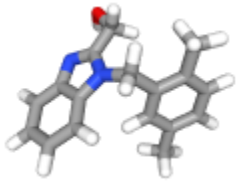
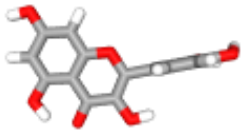
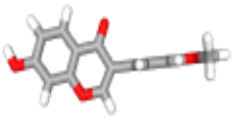
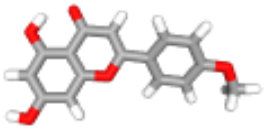
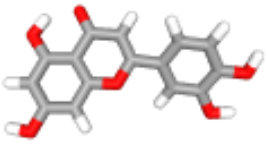
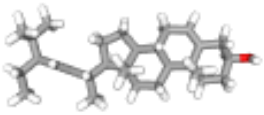
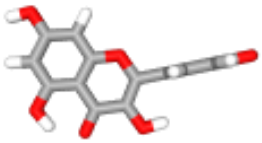
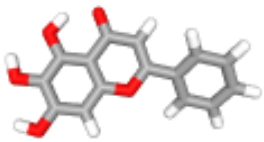
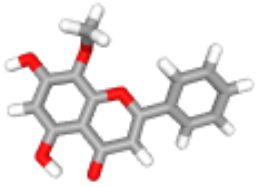
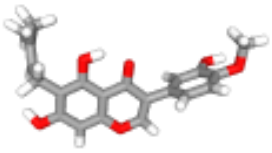
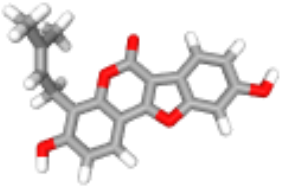
Structure	CID	Docking Result	Amino Acid Residue Interaction
	962431 *Native ligand*	-11.3	Hbond: LEU120, TYR151 Van Der Waals: VAL123, LEU157, ILE155, GLY121, LEU57, GLY122, TYR59, ILE155, GLY121, TYR119, SER60, GLN61 *Conventional* Hbond: TYR119 π interactions: LEU57, TYR59
	5280343	-10.1	Hbond: ILE58, GLY122 Carbon Hbond: TYR119, GLY121 Van Der Waals: GLN61, GLY121, GLY121, GLY122, LEU120, LEU57, LEU120, SER60, SER60, TYR59, TYR59, TYR59, TYR119, TYR151, TYR151, VAL123 π interactions: GLY121, TYR119, LEU57
	5280378	-8.7	Van Der Waals: GLY121, GLY121, GLY121, GLY122, GLY122, ILE155, LEU57, LEU120, SER60, TYR59, TYR59, TYR119 π interactions: TYR119, LEU57
	5280442	-9.7	Hbond: TYR119, TYR151 Carbon Hbond: GLY121 Van Der Waals: GLN61, GLN61, GLY121, GLY121, LEU120, LEU120, SER60, TYR59, TYR59, TYR119 π interactions: TYR119, ILE155, LEU57, TYR B 59 Alkyl: LEU57
	5280445	-10.6	H bond: TYR151, GLY121, TYR151, LEU120 Van Der Waals: SER60, TYR119, TYR59, LEU120, GLY121, GLN61, LEU94, LEU120, GLN61, TYR119, TYR59, GLY121, LEU57 *Unfavorable Donor-Donor*: SER60 π interactions: LEU57, TYR119
	5280794	-9.0	Van Der Waals: GLN61, GLY121, GLY121, GLY121, ILE155, LEU57, LEU120, LEU120, LEU157, SER60, TYR59, TYR119, TYR119, TYR151, TYR151, WAL123 H bond: SER60 *Unfavorable Bump*: LEU57 π interactions: TYR59, TYR119 Alkyl: LEU57
	5280863	-10.1	Van Der Waals: GLN61, GLY121, GLY121, LEU57, LEU 120, LEU120, SER60, SER60, TYR59, TYR59, TYR59, TYR119, TYR151 Hbond: GLY122, ILE58 Carbon Hbond: GLY121 π interactions: TYR119, LEU57
	5281605	-10.1	Hbond: TYR 151 Van Der Waals: GLN61, GLY121, GLY122, ILE155, LEU120, SER60, TYR59, TYR59, TYR119, TYR119, TYR151 π interactions: ILE58, GLY121, TYR119, LEU57

Table 2 (continue). Molecular docking results and protein–ligand interaction profiles of selected compounds with the target of TNF-α protein

Structure	CID	Docking Result	Amino Acid Residue Interaction
	5281703	-10.0	Van Der Waals: GLN61, GLY121, GLY121, GLY122, LEU57, LEU C 57, LEU A 120, SER60, TYR59, TYR59, TYR59, TYR119, TYR151 Hbond: LEU120, SER60, TYR151 π interactions: TYR119, LEU57
	5317479	-8.7	Van Der Waals: GLY121, GLY122, LEU120, LEU120, LEU120, SER60, SER60, TYR59, TYR59, TYR119 Hbond: ILE58 Carbon Hbond: GLN61, TYR151 π interactions: TYR119, ILE155, LEU57 Alkyl: LEU57, LEU57, LEU157,
	44257530	-12.5	Van Der Waals: GLN61, GLY121, GLY121, LEU57, LEU57, LEU120, SER60, TYR59, TYR59, TYR119, TYR151 π interactions: TYR119, TYR59, LEU57 Alkyl: LEU157, VAL123

participated in both π–stacking and π–alkyl interactions, while LEU57 contributed to π–sigma and π–alkyl contacts. Collectively, these interactions highlight a cooperative binding network, in which hydrogen bonding ensures specificity and hydrophobic and π interactions enhance stability, underscoring the suitability of this pocket for ligand accommodation and potential drug design (L. Li et al., 2024; Mahrosh & Mustafa, 2021).

Molecular docking analysis (Table 2) revealed strong binding affinities of XLZW compounds with TNF-α, comparable to or exceeding the native ligand (−11.3 kcal/mol). Several compounds demonstrated notable docking scores, including CID 44257530 (−12.5), CID 5280445 (−10.6), and CID 5280343/5280863/5281605 (−10.1), suggesting stable ligand–protein interactions. Residue mapping showed consistent involvement of TYR119, TYR151, LEU120, LEU57, GLY121, GLY122, SER60, GLN61, and TYR59, forming a recurrent interaction network across multiple compounds. Hydrogen bonding with TYR119, TYR151, and LEU120 was particularly frequent, underscoring their role as critical anchoring residues. Hydrophobic and π interactions (π–stacking, π–alkyl, and π–sigma) with TYR59 and LEU57 further stabilized the complexes, while van der Waals contacts provided additional support (Tao, Wang, & Huang, 2019).

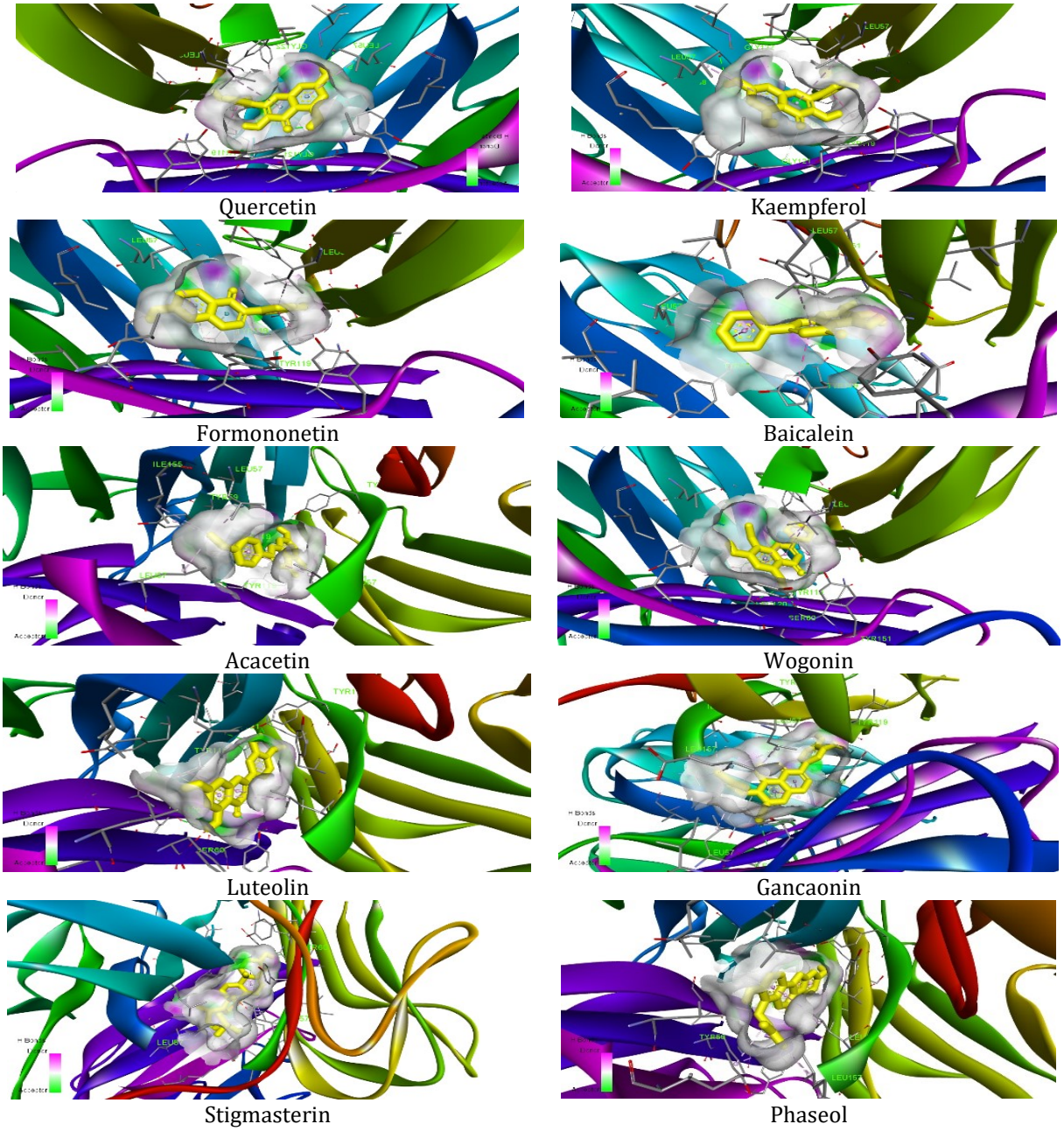


Figure 3. 3D interaction 10 compound visualization of XLZW targeted of TNF-α Protein

Importantly, CID 44257530 exhibited the strongest binding energy and extensive interactions, including π–donor hydrogen bonding and multiple hydrophobic contacts, positioning it as a lead candidate. Other compounds, such as CID 5280445 and 5280343, also exhibited favorable binding profiles, including multiple hydrogen bonds and π interactions, reinforcing their potential as TNF-α modulators. Overall, the docking results highlight a conserved binding pocket dominated by aromatic and hydrophobic residues, with several XLZW compounds exhibiting strong, stable interactions. These findings suggest that XLZW harbors promising bioactive molecules that target TNF-α, supporting its therapeutic relevance in inflammation-related pathways (Jo et al., 2024).

Figure 3. illustrates the three-dimensional molecular interaction and binding mode between bioactive compounds derived from XLZW and the TNF-α target protein. In this compound visualization, the central ligand a key active component of XLZW occupies the catalytic/active binding pocket of the TNF-α receptor complex. As shown in the 3D conformational structure, the stability of this ligand-protein complex is anchored by critical intermolecular forces: 1). HydrogenBonding: Represented by dashed lines targeting specific amino acid residues in the binding pocket, providing strong positional stability and binding affinity. 2). Hydrophobic & Van der Waals Interactions: The surrounding non-polar amino acid residues form a tight hydrophobic pocket that stabilizes the core aromatic ring structures of the XLZW compound.

Taken together, the ADMET profiling, cavity characterization, and molecular docking analyses provide a coherent picture of XLZW's therapeutic potential against TNF-α. The compounds demonstrated favorable drug-likeness and absorption properties, with several showing BBB penetration, supporting their relevance to neuroinflammatory pathways. Structural pocket analysis identified a spacious and druggable cavity, while docking studies highlighted consistent interactions with key residues, including TYR119, TYR151, LEU120, LEU57, and TYR59, underscoring a conserved binding environment. Importantly, compounds like CID 44257530, 5280445, and 5280343 exhibited strong binding affinities and extensive stabilizing interactions, positioning them as promising lead candidates (Souza Silva et al., 2021).

Overall, these findings emphasize the mechanistic plausibility of XLZW compounds as TNF-α modulators, bridging computational pharmacology with translational potential. This integrated evidence strengthens the rationale for further experimental validation and supports the prospect of XLZW as a source of novel anti-inflammatory agents.

CONCLUSION

This study provides computational predictions integrating ADMET profiling, cavity analysis, and molecular docking to evaluate the potential of XLZW compounds as TNF-alpha modulators in the targeted management of chronic atrophic gastritis (CAG). Notably, candidate Phaseol (CID: 44257530) demonstrated exceptional binding affinity (-12.5 kcal/mol), outperforming the native ligand (-11.3 kcal/mol), alongside favorable pharmacokinetic properties and key residue interactions with TYR119, TYR151, and LEU120. Mechanistically, targeting TNF-alpha inhibition directly mitigates the pro-inflammatory signaling cascade

responsible for gastric mucosal inflammation and lesion progression in CAG. Although these findings establish a strong computational foundation, experimental validation remains critical. Future research should prioritize top candidates such as Phaseol for in vitro evaluations (including binding affinity assays and cell-based TNF-alpha inhibition assays) and subsequent in vivo validation using animal models of CAG to fully establish the clinical potential of XLZW as an anti-gastritis herbal formulation.

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