To what extent can dual inhibition of TRPV1 (Transient Receptor Potential Vanilloid-1) and PTGS2 (Prostaglandin-Endoperoxide Synthase 2) be achieved to alleviate pain in patients with refractory primary dysmenorrhea?

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Abstract Refractory primary dysmenorrhea remains challenging to manage because conventional therapies, particularly those targeting prostaglandin synthesis through PTGS2 inhibition, may provide insufficient pain relief in some patients. This study investigated the feasibility of dual inhibition of Transient Receptor Potential Vanilloid 1 (TRPV1) and Prostaglandin-Endoperoxide Synthase 2 (PTGS2) as a potential multi-target strategy for pain management in refractory primary dysmenorrhea. Molecular docking simulations were conducted to evaluate the binding affinities of two naturally derived compounds, Astragaloside IV from Astragalus membranaceus and ligustilide from Angelica sinensis, together with six newly designed derivative ligands. Protein structures were obtained from the RCSB Protein Data Bank, while ligand preparation and structural modification were performed using PubChem, ChemDraw Pro, PyMOL, and UCSF Chimera. AutoDock Vina was used to assess protein–ligand binding interactions with TRPV1 and PTGS2. The results showed no detectable binding interactions for Astragaloside IV and its derivatives under the present docking conditions. In contrast, ligustilide demonstrated stronger binding affinity toward TRPV1 and showed comparatively weaker binding toward PTGS2, while its first derivative exhibited potential binding interactions with both targets. Overall, ligustilide and its derivative showed greater potential for dual TRPV1/PTGS2 targeting than Astragaloside IV-derived compounds. However, the observed binding affinities remain insufficient for establishing effective dual inhibition, and further structural optimization and experimental validation are required. These findings identify ligustilide as a potential lead compound for future investigation into multi-target therapeutic strategies for refractory primary dysmenorrhea.

Keywords Refractory primary dysmenorrhea; TRPV1; PTGS2; dual inhibition; molecular docking; ligustilide; Astragaloside IV; traditional Chinese medicine

Introduction

Dysmenorrhea is the professional term in medical area for menstrual cramps. Clinically, dysmenorrhea is categorized into two distinct types, namely primary dysmenorrhea (PD) and secondary dysmenorrhea (SD), which are differentiated by the presence or absence of underlying pelvic organic lesions.[1] For primary dysmenorrhea, it is a more prevalent gynecological condition characterized by recurrent pain in the lower abdomen during menstruation, which starts from the first period and continues throughout lifetime, affecting ranges from 45% to 90% of reproductive-aged women globally according to National Institutes of Health.[2] Among these women with primary dysmenorrhea, 20% to 40% of them suffered from refractory primary dysmenorrhea (RPD) , which accounts for 10% to 18% of all women. Refractory primary dysmenorrhea is described as primary dysmenorrhea that fails to respond to conventional therapeutic interventions, and it poses considerable challenges in clinical management currently.[3] Refractory primary dysmenorrhea and primary dysmenorrhea include severe symptoms of chronic pain in the lower abdomen, nausea, fatigue, headache, or lower back pain that leads to school or work absenteeism, significantly impairing quality of life and imposing substantial economic burdens. The pain associated with both refractory primary dysmenorrhea and primary dysmenorrhea is rooted in a complex interplay of inflammatory and neurogenic mechanisms, caused by the increased levels of prostaglandins, particularly PGF2a and PGE2 in the endometrium during menstruation, driven by PTGS2 activity. These prostaglandins induce intense and uncoordinated contractions

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of the smooth muscle in the uterine, leading to ischemia. Therefore, first-line treatments for primary dysmenorrhea mainly rely on nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibits the PTGS2 (COX-2) enzyme to reduce prostaglandin synthesis, and oral contraceptives. [4] However, the clinical utility of single-target inhibition of PTGS2 is frequently limited by three challenges, which are suboptimal analgesic efficacy, inadequate pain relief for instance, in a subset of patients, low tolerability due to treatment-related adverse effects, and the presence of contraindications. These limitations collectively contribute to the emergence of refractory pain phenotypes, which necessitate the exploration of alternative therapeutic strategies beyond sole PTGS2 inhibition.

To identify the research entry point, a comprehensive review was conducted to elucidate the mechanisms underlying pain sensing in the human body and central nervous system. Among the molecular targets implicated in pain signaling, TRPV1 and PTGS2 emerge as two of the most relevant mediators, particularly in the context of dysmenorrhea-associated pain reception. TRPV1 is a non-selective cation channel encoded by the TRPV1 gene, predominantly expressed in sensory neurons, with a primary functional role in pain perception. As a key molecular sensor, it responds to a spectrum of noxious stimuli, including hyperthermia (temperatures exceeding 43°C), capsaicin (the pungent component of chili peppers), and acidic microenvironments. Upon activation by such triggers, TRPV1 undergoes conformational changes that open its channel pore, enabling the influx of cations, calcium ions and sodium ions for example, into the cytoplasm of sensory neurons. This cation influx depolarizes the neuronal membrane, generating an action potential that propagates along the sensory nerve fiber to the spinal cord and ultimately to the brain, where it is integrated and perceived as pain. Notably, TRPV1 activity is dynamically modulated by intracellular signaling molecules, which can enhance or attenuate its sensitivity, thereby fine-tuning pain signaling under physiological or pathological conditions.[9]

On the other hand, PTGS2 is an inducible enzyme belonging to the cyclooxygenase family. Its expression is minimally detectable under basal physiological states but is rapidly upregulated in response to inflammatory cues, tissue injury, or cellular stress. Distinct from the constitutively expressed PTGS1 which sustains homeostatic prostaglandin synthesis for essential functions. PTGS2 plays a central role in mediating inflammatory processes and associated pain, primarily at sites of tissue damage or inflammation. In the context of pain signal transmission, PTGS2 exerts its effects indirectly but critically: following tissue injury, resident immune cells and damaged somatic cells secrete proinflammatory cytokines. These cytokines induce the de novo synthesis of PTGS2, which then catalyzes two sequential enzymatic reactions: first, as a cyclooxygenase, it incorporates two oxygen atoms into arachidonic acid (a

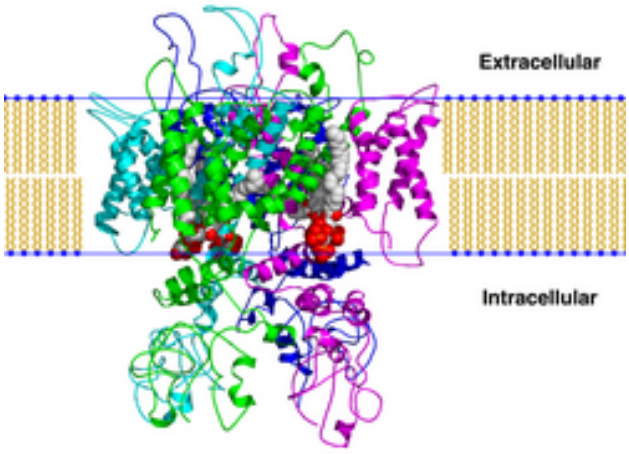

Figure 1. description of the structural architecture of the TRPV1 channel within a cell membrane, and illustration of how TRPV1 spans the cell membrane, with parts of the protein extending into the extracellular and intracellular environments

fatty acid released from damaged cell membranes) to form the cyclic endoperoxide prostaglandin ; second, as a peroxidase, it reduces to prostaglandin, a common precursor for downstream prostaglandins. is subsequently converted to bioactive prostaglandins, which bind to receptors on nociceptors, pain-sensing nerve endings, to lower their activation threshold. This nociceptive sensitization enhances responsiveness to mechanical, thermal, or chemical stimuli, amplifying pain signal transmission to the central nervous system and culminating in the perception of pain. The inducibility of PTGS2 ensures that prostaglandin production is restricted to sites of injury or inflammation, avoiding disruption of homeostatic prostaglandin levels regulated by PTGS1, which is a characteristic that explains why PTGS2-selective inhibitors alleviate inflammatory pain with fewer gastrointestinal adverse effects compared to non-selective cyclooxygenase inhibitors. [10]

Furthermore, prior preclinical studies have explored the therapeutic potential of dual inhibition of TRPV1 and PTGS2 through experiments, yielding preliminary positive outcomes that support the feasibility of this targeting strategy in terms of adequate pain relief, though it has not been widely put into practical use. Three studies explore novel phytochemical and pharmaceutical therapies for refractoriness. Wu et al. (2024) explored Ainsliaea fragrans extract, AF-ext, for primary dysmenorrhea. AF-ext from 25 to 100 milligram per kilogram dose-dependently reduced writhing in oxytocin-induced mice, inhibited uterine spasms, and targeted COX-2, TRPV1, and EGFR.[5] Alfieri et al. (2025) reviewed cannabis terpenes for chronic pain. These terpenes act via multiple pathways such as receptor activation (COX-2 related) and TRP channel modulation.[6] Liu et al. (2010) tested valproic acid for adenomyosis. In a study lasts for 6 months, VPA resolved dysmenorrhea, reduced uterine size by 26%, and lessened menorrhagia.[7] Hence, drawing on personal clinical experience of seeking treatment from a traditional Chinese medicine (TCM) practi-

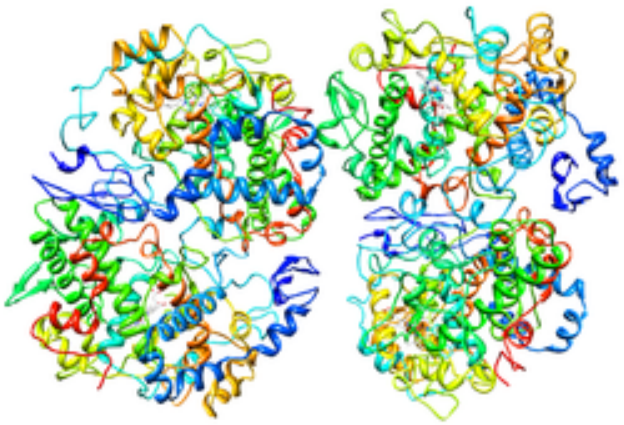

Figure 2. description of the structural architecture of PTGS2, where two main colorful chains intertwine and show the complex three-dimensional folding structure of PTGS2

tioner for refractory conditions, combined with relevant research findings, this study aims to explore the feasibility of achieving sufficient pain alleviation via the dual inhibition of TRPV1 and PTGS2 and put it into practical use. To this end, evaluations were done for the binding affinities of newly designed compounds derived from two plant species, milkvetch root and angelica sinensis respectively, documented in the TCM prescription previously utilized by the author, with the goal of verifying the dual-inhibition potential for effective pain management.

Methodology

This study aims to investigate the feasibility of achieving dual inhibition of TRPV1 and PTGS2 proteins by evaluating the binding affinities of two existing ligands and six newly designed ligands toward these two targets. Each ligand is required for binding with the two proteins. To enable molecular simulations and quantitative analysis of protein-ligand binding interactions, computational modeling of the target proteins and ligands was performed using specialized databases and bioinformatics tools.

Specifically, the following resources were employed for protein structure acquisition, ligand structure retrieval, novel compound design, and protein-ligand binding analysis:

- PubChem, a public chemical database, was utilized for retrieving the two-dimensional structure of existing ligands and as a reference for the rational design of six new ligand compounds.[12]
- RCSB PDB was served as the source for acquiring the three-dimensional structures of the target TRPV1 and PTGS2 proteins.
- PyMOL was used for file format conversion and preprocessing of ligand structures, ensuring that the newly designed compounds could be imported into UCSF chimera for subsequent three-dimensional structure optimization and visualization.
- UCSF chimera was employed for the visualization of molecular docking processes, post-docking structural analysis of protein-ligand complexes, and validation of binding conformations.
- ChemDraw Pro was served as a critical tool for the preprocessing of newly designed ligand compounds. It facilitated the conversion of the two-dimensional structural models of ligands and their export in the SDF format was an important part in converting two-dimensional structure of newly created ligand compounds and exporting it in the form of “SDF” file, a format compatible with downstream software.[13] This step was essential to enable subsequent generation of the three-dimensional structural models in the “PDB” format, a plain text file including the three-dimensional coordinates of atoms in a macromolecule, using PyMOL.[15]
- Autodock Vina, a molecular docking program, was used to perform docking simulations and calculate the binding affinity values of each ligand toward TRPV1 and PTGS2, with the results reported in units of kilocalories per mole (kcal/mol).

Materials and Preparation

Preparing the Ligands

For the two previously reported known ligands, the acquisition of their structural files from the PubChem database is sufficient to fulfill the requirements of subsequent research procedures. If the retrieved file is a three-dimensional crystal structure file with the CIF suffix, a standard text depicting crystal structures in science, it can be directly utilized within the UCSF chimera for molecular docking and visualization.[14] In instances where the retrieved file does not conform to the CIF format, the PyMOL molecular modeling tool can be employed to export the file into a three-dimensional molecular structure format, with “PDB” suffix, which is a step necessary to ensure compatibility with subsequent analytical processes.

In contrast, the structural preparation of the six newly designed target ligands involves a more complex sequence of operations in conjunction with the PubChem database, and this process proceeds as follows. Firstly, the SMILES (Simplified Molecular-Input Line-Entry System) string of the known parent ligand is extracted. This string functions as a concise textual encoding system for representing molecular structures, enables efficient transfer and reconstruction of structural information. Subsequently, the acquired SMILES string is imported into the "Draw Structure" functional module of the PubChem database, through which the two-dimensional molecular structure of the parent ligand is automatically generated, a critical step for visualizing and modifying the core framework of ligands. Next, targeted editing and modification of the molecular structure are performed, with the key requirement that the "ring backbone" structure of the parent ligand

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remains intact. It is important to note that the integrity of this ring backbone is essential for preserving the core functional properties of ligands, as structural alterations to this region may compromise its binding ability or biological activity. Following the completion of structural editing, the "Search for this Structure" button located at the bottom-left corner of the PubChem interface is activated, allowing for database comparison to verify whether the designed structure corresponds to an unreported novel compound. This verification step is crucial for avoiding redundancy in research and ensuring the novelty of the target ligands. Finally, the verified structure of the new ligand is exported into the SDF format using ChemDraw, a widely employed chemical drawing software. The SDF format is then further converted into the PDB format via the PyMOL software, as the PDB format is the standard format required for subsequent molecular docking experiments and molecular dynamics simulations.

Protein preparation guide

To prepare protein in UCSF chimera, RCSB PDB database was first utilized to acquire the three-dimensional structures of proteins TRPV1 (extended PDB ID: 00003j5p) and PTGS2 (extended PDB ID: 00001pxx). Following file download, the structures were able to be opened in chimera, where chain B and all non-standard ligands were removed. Subsequently, the “Surface binding Analysis” tool within chimera and Autodock vina was employed to identify the coordinates and volume of the target proteins.

Results and Discussion

The original ligands are Astragaloside IV from milkvetch root and ligustilide from angelica sinensis. Each of them possesses three derivative ligands.

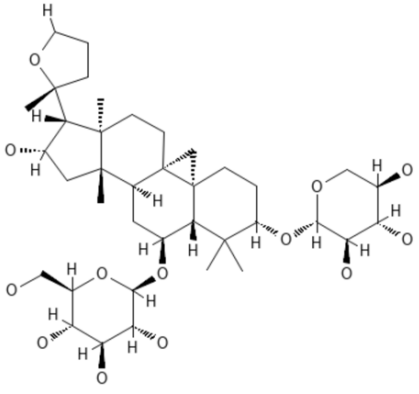

Figure 3. the two-dimensional structure of Astragaloside IV, with SMILE of C[C@]12CC[C@@]34C[C@@]35CC[C@@H](C([C@@H]5[C@H](C[C@H]4[C@@]1(C[C@@H]([C@@H]2[C@]6(CC[C@H](O6)C(C)(C)O)C)O)C)O[C@H]7[C@@H]([C@H]([C@@H]([C@H](O7)CO)O)O)O)(C)C)O[C@H]8[C@@H]([C@H]([C@@H](CO8)O)O)O

Ligands creation and binding analysis for Astragaloside IV

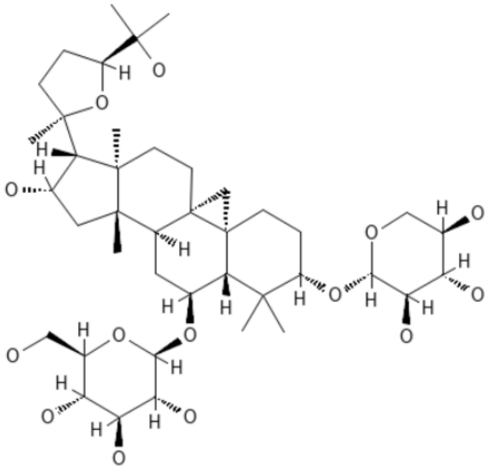

Figure 4. the two-dimensional structure of the first derivative ligand compound of Astragaloside IV, with the SMILE of C[C@]45CC[C@@]13C[C@@]12CC[C@@H](C([C@@H]2[C@H](C[C@H]3[C@@]4(C[C@@H]([C@@H]5[C@]6(CCC([H])O6)C)O)C)O[C@H]7[C@@H]([C@H]([C@@H]([C@H](O7)CO)O)O)O)(C)C)O[C@H]8[C@@H]([C@H]([C@@H](CO8)O)O)O

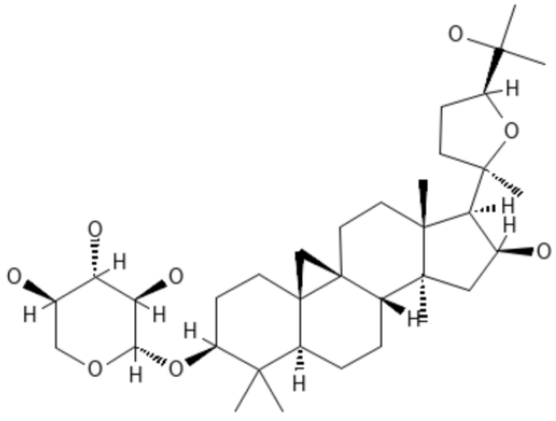

Figure 5. the two-dimensional structure of the second derivative ligand compound of Astragaloside IV, with the SMILE of C[C@]45CC[C@@]13C[C@@]12CCCC([C@@H]2[C@H](C[C@H]3[C@@]4(C[C@@H]([C@@H]5[C@]6(CC[C@H](O6)C(C)(C)O)C)O)C)O[C@H]7[C@@H]([C@H]([C@@H]([C@H](O7)CO)O)O)O)(C)C

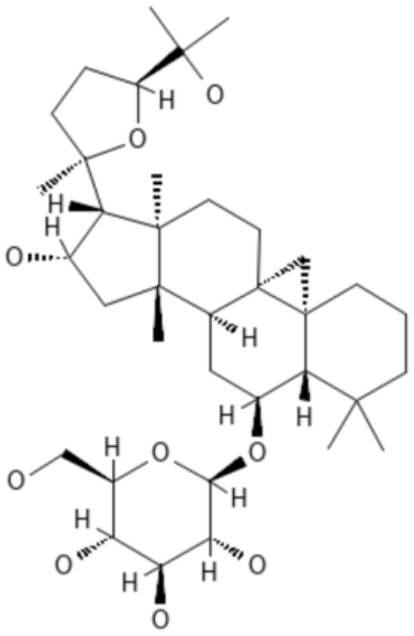

Figure 6. the two-dimensional structure of the third derivative ligand compound of Astragaloside IV, with the SMILE of C[C@]45CC[C@@]13C[C@@]12CC[C@@H](C([C@@H]2CC[C@H]3[C@@]4(C[C@@H]([C@@H]5[C@]6(CC[C@H](O6)C(C)(C)O)C)O)C)(C)C)O[C@H]7[C@@H]([C@H]([C@@H](CO7)O)O)O

Molecular docking simulations with Autodock vina and visualization via UCSF chimera produced no detectable binding interactions, with only runtime logs recorded for Astragaloside IV and its derivatives. From the framework of Traditional Chinese Medicine and functions of the prescription, this outcome implies the pharmaceutical effect of the agent is oriented toward the "Qi-tonifying" or “Qi-supplementing” paradigm, which demonstrates the focus of TCM on regulating systemic physiological balance rather than direct molecular targeting. Additionally, this finding highlights a key consideration for formulating treatments for refractory primary dysmenorrhea: to mitigate potential adverse effects of the principal bioactive components, whether acting via dual or single inhibition, the agent should be combined with other milder ingredients. This approach not only enhances treatment safety but also may improve overall efficacy by leveraging the synergistic multi-component principles central to TCM practice.

Ligands preparation and binding analysis for ligustilide

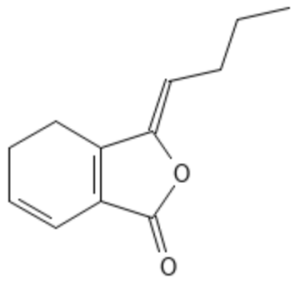

Figure 7. the two-dimensional structure of ligustilide, with the SMILE of CCC/C=C\1/C2=C(C=CCC2)C(=O)O1

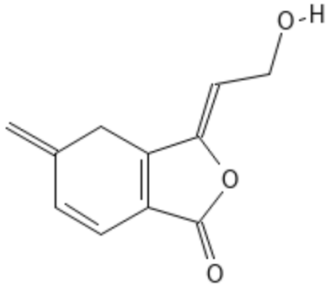

Figure 8. the two-dimensional structure of the first derivative ligand compound of ligustilide, with the SMILE of C(C=C2C1=C(C=CC(C1)=C)C(=O)O2)O[H]

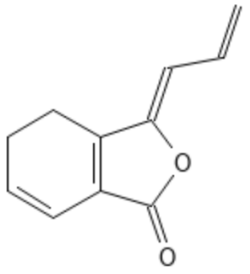

Figure 9. the two-dimensional structure of the second derivative ligand compound of ligustilide, with the SMILE of C(C=C2C1=C(C=CCC1)C(=O)O2)=C

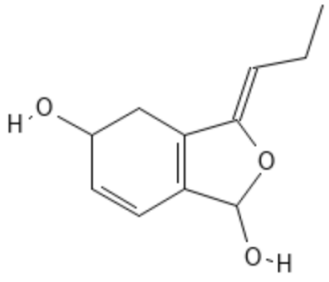

Figure 10. the two-dimensional structure of the third derivative ligand compound of ligustilide, with the SMILE of CCC=C2C1=C(C=CC(C1)O[H])C(O2)O[H]

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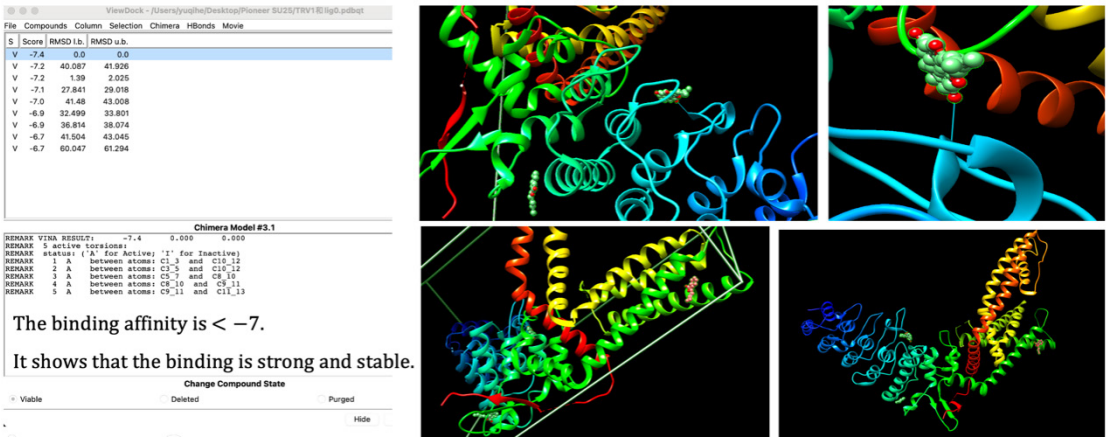

Figure 11. binding analysis between protein TRPV1 and ligustilide

The binding affinity is smaller than negative seven, which shows that the binding is strong and stable.

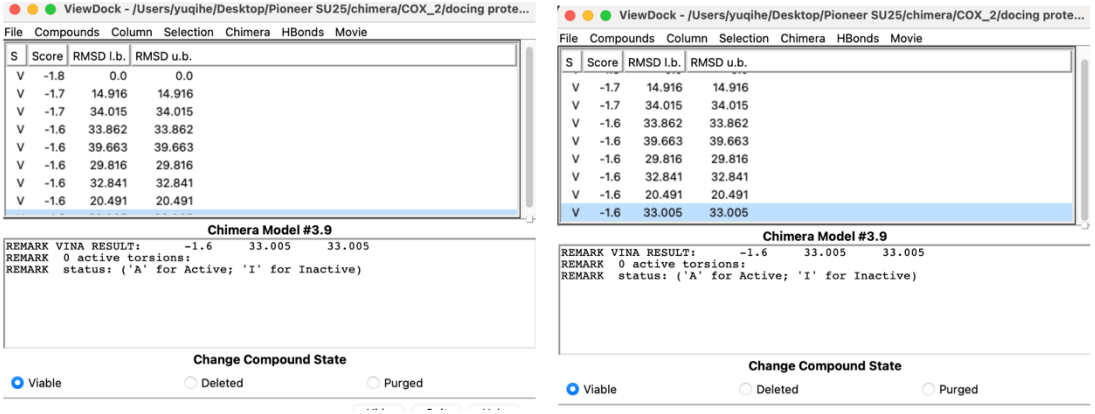

Figure 12. binding analysis between protein PTGS2 and ligustilide

The binding affinity is greater than negative five, which shows that the binding is weak and not stable.

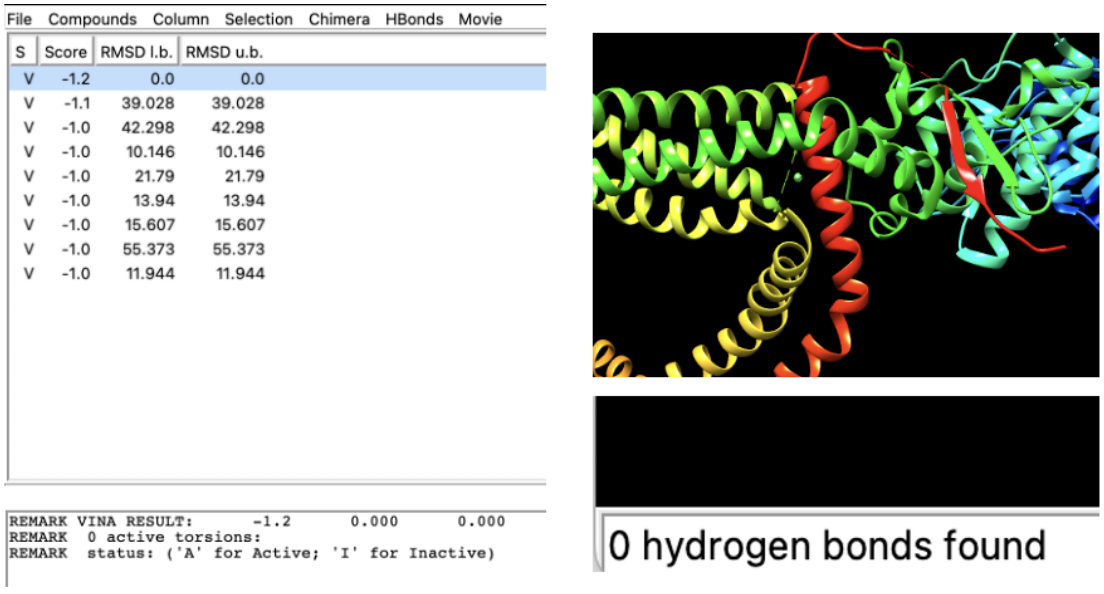

Figure 13. binding analysis between protein TRPV1 and the first derivative ligand compound of ligustilide

The binding affinity is greater than negative five, which shows that the binding is weak and not stable. Moreover, 0 hydrogen bonds were found.

S	Score	RMSD l.b.	RMSD u.b.
V	-1.1	0.0	0.0
V	-1.1	26.594	26.594
V	-1.1	25.739	25.739
V	-1.1	4.823	4.823
V	-1.1	22.513	22.513
V	-1.1	7.187	7.187
V	-1.0	14.219	14.219
V	-1.0	23.353	23.353
V	-0.9	9.757	9.757

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REMARK VINA RESULT:      -1.1      0.000      0.000
REMARK  0 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
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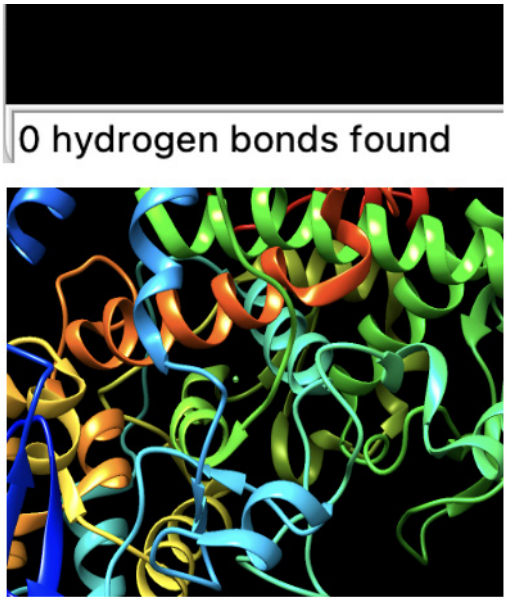

Figure 14. binding analysis between protein PTGS2 and the first derivative ligand compound of ligustilide

The binding affinity is greater than negative five, which shows that the binding is weak and not stable. Moreover, 0 hydrogen bonds were found.

Molecular docking simulations with Autodock vina and visualization via UCSF chimera produced no detectable binding interactions, with only runtime logs recorded for the second and third derivative ligand compound of ligustilide.

Thus, it can be concluded that ligustilide and its first derivative ligand compound exhibits a better binding affinity compared to Astragaloside IV. Meanwhile, the result implies that ligustilide aligns with pain relief function in the prescription of TCM. However, the overall values remain relatively low.

Limitations

The present study is subject to several limitations. First, the scope of plant extracts included in the binding analysis was restricted due to time constraints, which may have limited the breadth of potential lead compounds identified. Second, the number of comparison groups was insufficient, which could affect the robustness and generalizability of the conclusions drawn regarding binding affinity differences. Third, there remains a high degree of dependency on existing pharmaceutical frameworks, which may have constrained the exploration of alternative mechanisms or novel molecular targets.

Advantages and Implications for Further Research

Despite these limitations, the study offers notable advantages. The selection of typical and highly representative plant extracts aligns with two core therapeutic principles of TCM, which are pain reduction and qi-blood tonification and root consolidation. These TCM-derived concepts provide valuable insights for guiding modern pharmaceutical research, particularly in the development of multi-targeted analgesics. Furthermore, the identification of the potential of ligustilide for dual TRPV1 and PTGS2 inhibition opens new avenues for addressing refractory primary dysmenorrhea, which is a condition where single-target therapies have often shown limited efficacy. The clear comparative design of the study also enhances the interpretability of results, facilitating the translation of findings into future experimental work.

Future research should prioritize several directions, such as expanding the library of plant extracts to include a broader range of TCM-derived compounds, increasing the number of comparison groups, and optimizing the binding affinity of lead compounds through structural modification or formulation engineering. Additionally, in vitro and in vivo validation studies are needed to confirm the dual inhibitory activity of these compounds and evaluate their safety and efficacy profiles, ultimately advancing the development of novel treatments for primary dysmenorrhea and related pain disorders.

Conclusion

Binding affinity analysis via chimera and Autodock vina revealed that the first derivative ligand of ligustilide and ligustilide exhibits superior binding affinity to both TRPV1 and PTGS2 compared to Astragaloside IV and its derivatives. This finding suggests that the relatively low feasibility of dual inhibition based on these two plant extractions and ligustilide holds greater potential for achieving dual inhibition of TRPV1 and PTGS2, a mechanism that could be pivotal for alleviating pain. Notably, ligustilide demonstrates stronger binding affinity toward TRPV1 than PTGS2, which is a characteristic that distinguishes it from most previously reported analgesic agents that typically prioritize PTGS2 binding. This unique bind-

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ing profile positions ligustilide as a promising lead and entry point for investigating novel therapeutic strategies for refractory primary dysmenorrhea. Additionally, the first derivative ligand compound of ligustilide displayed comparable binding affinity to both TRPV1 and PTGS2, representing another valuable discovery for further exploration. However, it is important to acknowledge that the current binding affinity values require optimization, a process that will necessitate additional time and experimental refinement.

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