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STUDY ON STIGMASTEROL, AN ACTIVE COMPONENT OF LILY EXTRACT, INHIBITS REFLUX ESOPHAGITIS BY TARGETING TBXAS1[2]

Gastroesophageal reflux disease (GERD) is a prevalent digestive disorder characterized by esophageal mucosal inflammation, with a potential risk of progressing to esophageal adenocarcinoma. Lilium brownii, a traditional medicinal herb, exhibits significant anti-inflammatory properties; however, the molecular mechanism of its active components in treating GERD remains largely elusive.

Methods. *In this study, we employed an integrated strategy combining network pharmacology, molecular docking, and molecular dynamics (MD) simulations to investigate the therapeutic potential of stigmasterol, a major phytosterol in lilium brownii. The core targets were identified via TCMSP, Genecards, and Disgenet databases. The binding affinity and structural stability of the stigmasterol-TBXAS1 complex were evaluated using Autodock vina and Gromacs (100 ns). Furthermore, the pharmacological effects were validated in vitro through western blot and cellular apoptosis assays.*

Results. *Network analysis revealed that TBXAS1 (thromboxane A synthase 1) is a critical hub protein involved in GERD-related inflammatory cascades. Molecular docking demonstrated a high binding affinity of −8.7 kcal/mol, characterized by stable hydrophobic interactions and hydrogen bonding within the catalytic pocket. Md simulations confirmed the stability of the complex, with a root mean square deviation (RMSD) consistently below 2.0 å. In vitro experiments evidenced that stigmasterol significantly down-regulated TBXAS1 expression and inhibited cell proliferation in a dose-dependent manner. ADMET profiling via SwissADME (boiled-egg model) indicated superior gastrointestinal absorption and a favorable safety profile compared to omeprazole.*

Conclusion. *Our findings elucidate that stigmasterol exerts its protective effects against GERD by targeting the TBXAS1-mediated pathway. This study provides a novel theoretical framework for developing lilium-derived bioactive compounds as targeted therapeutic agents for esophageal inflammatory diseases.*

Keywords: *Network pharmacology, stigmasterol, TBXAS1, molecular dynamics simulation, gastroesophageal reflux disease (GERD).*

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ИССЛЕДОВАНИЕ СТИГМАСТЕРОЛА, АКТИВНОГО КОМПОНЕНТА ЭКСТРАКТА ЛИЛИИ, ИНГИБИРУЕТ РЕФЛЮКС-ЭЗОФАГИТ, ВОЗДЕЙСТВУЯ НА TBXAS1

Гастроэзофагеальная рефлюксная болезнь (ГЭРБ) – распространенное расстройство пищеварения, характеризующееся воспалением слизистой оболочки пищевода с потенциальным риском прогрессирования до аденокарциномы пищевода. Лилия коричневая (Lilium brownii), традиционное лекарственное растение, обладает значительными противовоспалительными свойствами, однако молекулярный механизм действия ее активных компонентов при лечении ГЭРБ остается в значительной степени неясным.

Методы. *В этом исследовании мы использовали интегрированную стратегию, сочетающую сетевую фармакологию, молекулярный докинг и моделирование молекулярной динамики (МД) для изучения терапевтического потенциала стигмастерола, основного фитостерола лилии коричневой. Основные мишени были идентифицированы с помощью баз данных tcmsp, genecards и disgenet. Сродство связывания и структурная стабильность комплекса стигмастерол-TBXAS1 были оценены с использованием autodock vina и gromacs (100 нс). Кроме того, фармакологические эффекты были подтверждены с помощью вестерн-блоттинга и анализа клеточного апоптоза.*

Результаты. *Сетевой анализ показал, что TBXAS1 (тромбоксан-α-синтаза 1) является критически важным белком-хабом, участвующим в воспалительных каскадах, связанных с ГЭРБ. Молекулярный докинг продемонстрировал высокое сродство связывания (−8,7 ккал/моль), характеризующееся стабильными гидрофобными взаимодействиями и водородными связями в каталитическом кармане. Моделирование Md подтвердило стабильность комплекса со среднеквадратичным отклонением (rmsd), постоянно ниже 2,0 Å. Эксперименты показали, что стигмастерол значительно снижает экспрессию TBXAS1 и ингибирует пролиферацию клеток дозозависимым образом. Профилирование ADME с помощью модели вареного яйца (SwissADME) показало превосходную желудочно-кишечную абсорбцию и благоприятный профиль безопасности по сравнению с омепразолом.*

Заключение. *Результаты показывают, что стигмастерол оказывает защитное действие против ГЭРБ, воздействуя на путь, опосредованный TBXAS1. Это исследование предоставляет новую теоретическую основу для разработки биоактивных соединений, полученных из лилии, в качестве целевых терапевтических средств для лечения воспалительных заболеваний пищевода.*

Ключевые слова: *сетевая фармакология, стигмастерол, TBXAS1, моделирование молекулярной динамики, гастроэзофагеальная рефлюксная болезнь (ГЭРБ).*

Introduction. Gastroesophageal reflux disease (GERD) is a common digestive system disorder, and its chronic inflammatory state has been confirmed to be closely associated with the occurrence and development of esophageal adenocarcinoma. The long-term inflammatory microenvironment can promote cell proliferation, resist apoptosis, and ultimately drive malignant transformation by activating multiple signaling pathways. Therefore, a deep understanding of the molecular link between GERD-related inflammation and tumorigenesis, and the identification of key intervention targets, is of great significance for tumor prevention and treatment.

In previous studies on the effects of Lily, Wuyao, and Xiexin decoction on reflux esopha-

gitis, it was found that, in addition to star targets such as akt1, tp53, and stat3, thromboxane-α-synthase 1 (TBXAS1), a key enzyme in the arachidonic acid metabolism pathway, plays an important role in inflammation regulation, vasoconstriction, and tumor microenvironment remodeling.

Lily (*Lilium* spp.), as a medicinal and edible plant, has been used in traditional medicine for a long time to treat conditions such as yin deficiency dry cough, irritability, and palpitations. Modern pharmacological research has confirmed that its extracts possess various biological activities, including anti-inflammatory, antioxidant, and anti-tumor effects Stigmasterol, one of the main active phytosterols in lily extract, primarily exerts its effects by inducing apoptosis, inhibiting proliferation, arresting the cell cycle, and regulating autophagy. Its mechanism of action involves the regulation of the pi3k/akt signaling pathway and the generation of mitochondrial reactive oxygen species.

Thromboxane-α2-synthase 1 (TBXAS1) is a key enzyme in the arachidonic acid metabolism pathway, catalyzing the conversion of prostaglandin h2 to thromboxane α2. TBXAS1 is not only involved in platelet aggregation and vasoconstriction but has also recently gained prominence for its role in inflammation-related tumors. TBXAS1 is highly expressed in various tumor tissues, promoting tumor progression by modulating the tumor microenvironment, enhancing angiogenesis, and suppressing immune responses. However, whether stigmasterol exerts its effects by targeting TBXAS1 currently lacks systematic investigation.

This study comprehensively employs network pharmacology, molecular docking, molecular dynamics simulations, and cellular experiments to systematically explore the interaction between stigmasterol derived from lily and the GERD-related target TBXAS1, and to elucidate its potential anti-cancer mechanism. The aim is to provide a new theoretical basis and candidate molecules for natural product-based tumor prevention and treatment strategies.

Materials and methods.

Screening of active components from lily extract and target prediction

Chemical components of *Lilium Brownii* were collected through literature review and the Traditional Chinese Medicine systems pharmacology database and analysis platform (TCMSP, https://old.tcmsp-e.com/). Active candidates were preliminarily screened using oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 as criteria. The smiles structures and 2d structures of the compounds were obtained from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) The potential targets of the candidate components were predicted using the SwisstargetPrediction (http://www.swisstargetprediction.ch/) and Stitch (http://stitch.embl.de/) databases based on the principle of compound structural similarity. The species was limited to “homo sapiens”, and targets with a probability score > 0.1 were selected for subsequent analysis.

Network pharmacology analysis methods

Acquisition of disease targets using “gastroesophageal reflux disease”, “GERD”, and “esophageal adenocarcinoma” As keywords, the Genecards (https://www.genecards.org/) Omim (https://omim.org/), and Disgenet (https://www.disgenet.org/) databases were searched to obtain disease targets related to GERD and esophageal adenocarcinoma. After merging and removing duplicates, a dataset of disease targets was obtained.

Construction of protein-protein interaction network the potential targets of stigmasterol were intersected with the disease targets to obtain common targets. The intersecting targets were imported into the string database (https://string-db.org/), with the species set to “homo sapiens” And the minimum interaction threshold set to “high confidence” (> 0.7), to construct a protein-protein interaction (PPI) network. Cytoscape 3.9.1 software was used for network visualization, and core targets were screened using the mcc algorithm in the Cytohubba plugin.

Go function and KEGG pathway enrichment analysis the intersecting targets were imported into the David database (https://david.ncifcrf.gov/) for gene ontology (GO) functional enrichment analysis and encyclopedia of genes and genomes (KEGG) pathway enrichment analysis A significance threshold of $p < 0.05$ was used to identify main biological processes and signaling pathways. The R language gglot package was used for plotting based on −log10(p-value), p value, and count values.

ADMET property evaluation

To evaluate the pharmacokinetic properties and safety of stigmasterol, the SwissADME platform (http://www.swissadme.ch/) was used for absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction. Key analyses included intestinal absorption, blood-brain barrier penetration, cytochrome p450 enzyme inhibition, hepatotoxicity, and herb channel blockade risk.

Molecular docking

Receptor and ligand preparation

The three-dimensional structure of the TBXAS1 protein was downloaded from the RCSB PDB database (https://www.rcsb.org/) (pdb ID: 2UZJ). Pymol software was used to remove water molecules and the original ligand. Autodock tools were used for preprocessing, including adding hydrogens, calculating charges, and assigning atom types. The three-dimensional structure of stigmasterol was obtained from the Pubchem database [4] and energy-minimized using chem3d software *Molecular docking* was performed using Autodock vina and Schrödinger software. A grid box covering the active pocket of the TBXAS1 protein was set with parameters size_x = 25 å, size_y = 25 å, size_z = 25 å, and center coordinates referenced to the original ligand position. Docking exhaustiveness was set to 20, with other parameters kept at default. The conformation with the lowest binding energy was selected for interaction mode analysis, and Pymol [15] and discovery studio visualizer **Ошибка! Неизвестный аргумент ключа.** were used to generate 2d and 3d interaction diagrams.

Molecular dynamics simulation

A 100 ns molecular dynamics simulation was performed using the Gromacs 2022 software package The optimal complex structure obtained from docking was selected as the starting conformation. The charmm36 force field was used, and ligand parameters were generated using UCSF chimera 1.19 and saved in PDB format. The complex was placed in a cubic box with tip3p water molecules, and Na^+/cl^- ions were added to neutralize the system charge. Energy minimization was performed first (steepest descent, 50,000 steps), followed by NVT and NPT equilibration (100 ps each). Finally, 100 ns unconstrained production simulation was conducted with a time step of 2 fs. Periodic boundary conditions were applied, and the PME method was used to handle long-range electrostatic interactions. Gromacs built-in tools were used to analyze root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (RG), and the number of hydrogen bonds to evaluate the stability of the complex.

Results. *Through the TSMCP database and literature mining*, a total of 12 active components meeting the criteria of OB ≥ 30% and DL ≥ 0.18 were screened from Lily, including stigmasterol (Fig.1), β-sitosterol, diosgenin, etc. Target prediction results showed that stigmasterol has a total of 102 related targets. A search of disease databases yielded 1500 targets related to GERD and 7561 targets related to esophageal adenocarcinoma. After merging and deduplication, the top 5000 disease targets were selected. Venn diagram analysis showed that stigmasterol targets and disease targets shared 52 intersecting targets (Fig.2). Fifty-two intersecting targets were imported into string to construct a ppi network, and core targets were screened through Cytoscape topology analysis. Based on node degree ranking, the top 10 core targets included TP53, AKT1, TNF, IL6, VEGFA, EGFR, CASP3, PTGS2, MMP9, and TBXAS1. Among these, TBXAS1 was identified for the first time as a potential direct target of stigmasterol and is closely related to GERD and esophageal cancer; thus, it was selected as the key target for subsequent validation (Fig.3-5).

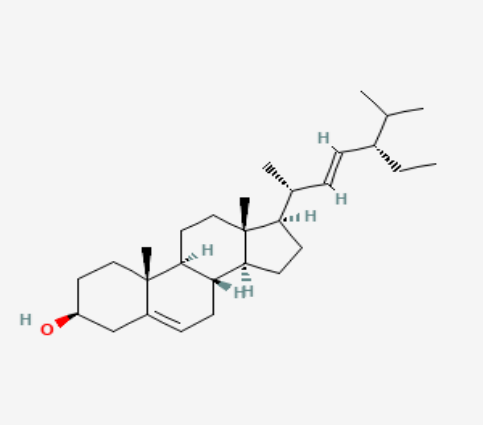

Fig.1 – Stigmasterol Molecular structural formula

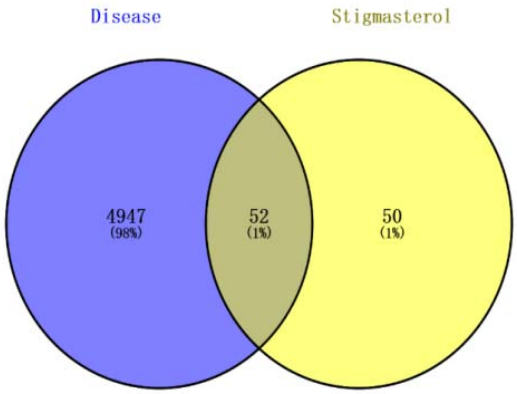

Fig. 2. – Stigmasterol and disease common Intersecting Targets

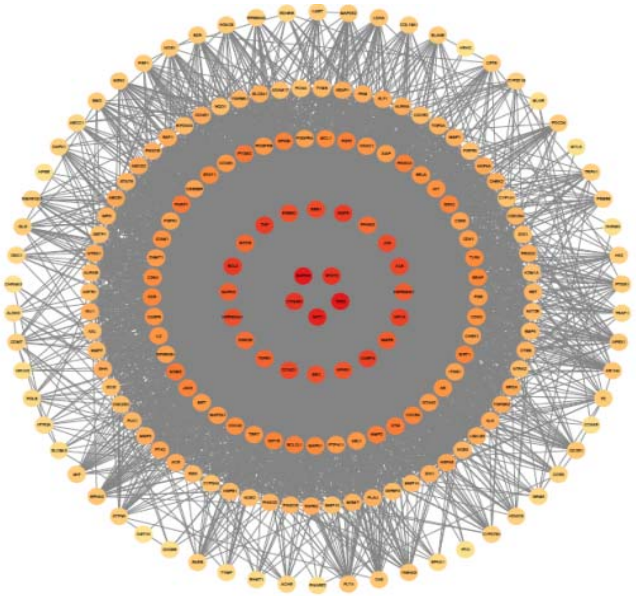

Fig. 3. – PPI network

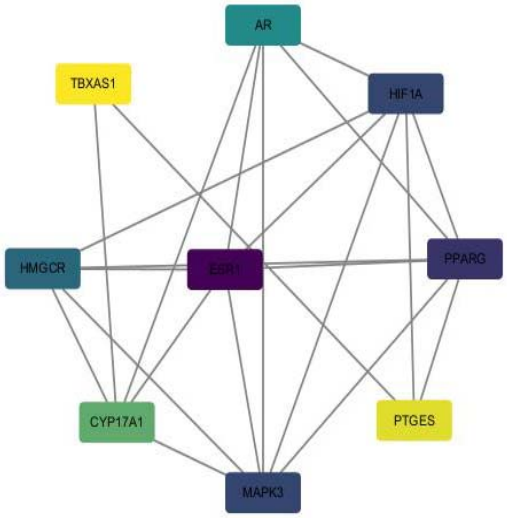

Fig.4. – Core target map

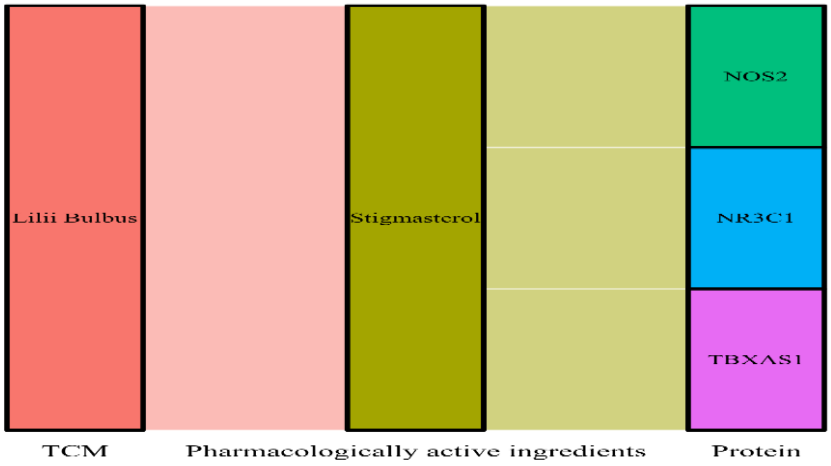

Fig.5. – Lilii Sankey diagram

KEGG pathway and GO functional enrichment analyses were performed on the target gene set (Fig.6-7). Enrichment analysis showed that TBXAS1 was significantly enriched in arachidonic acid metabolism, prostaglandin biosynthesis, platelet activation, and lipid metabolism pathways, all of which are involved in inflammatory injury and stress response of esophageal mucosa. Stigmasterol can target and inhibit TBXAS1 expression, regulate the production of inflammatory mediators, reduce esophageal mucosal inflammation and injury, thereby exerting anti-reflux esophagitis effects.

All information about the Stigmasterol may affect TBXAS1 expression and function by regulating lipid metabolism and nuclear receptors (PPARs, LXRs). By inhibiting the activity of TBXAS1 in the endoplasmic reticulum, it interferes with the production of TXA2, thereby weakening downstream effects such as platelet activation and systemic inflammatory esponse (Fig.8).

Arachidonic acid metabolism and variousmetabolic/cancer signaling pathways demonstrate statistically significant representations, providing context for the interaction network of TBXAS1 and generalized inflammation mechanics.

Analysis of stigmasterol's physicochemical properties and ADMET characteristics

Stigmasterol complies with Lipinski's rule of five, with an BO value of 36.4% and high gastrointestinal absorption.

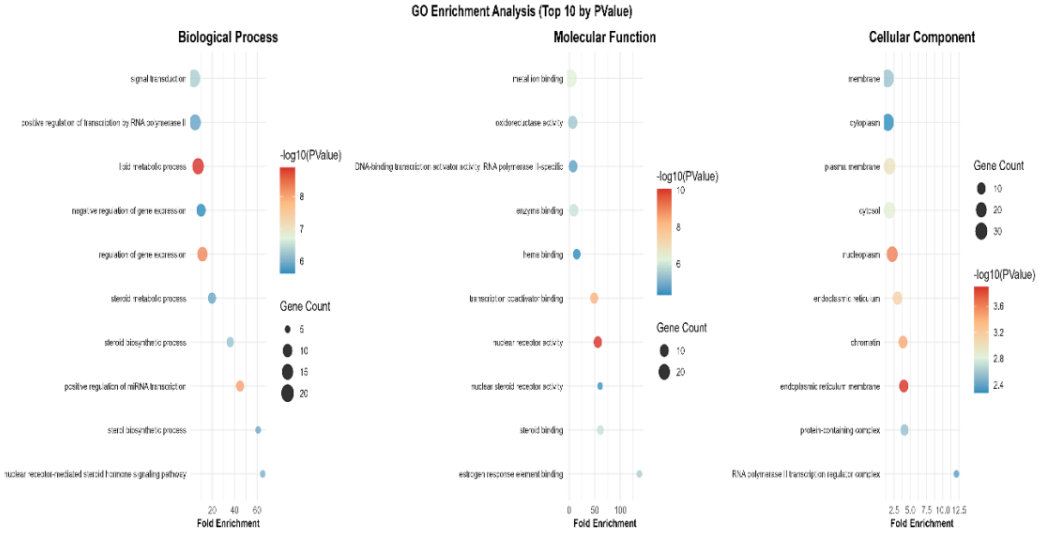

Fig.6. – Go function

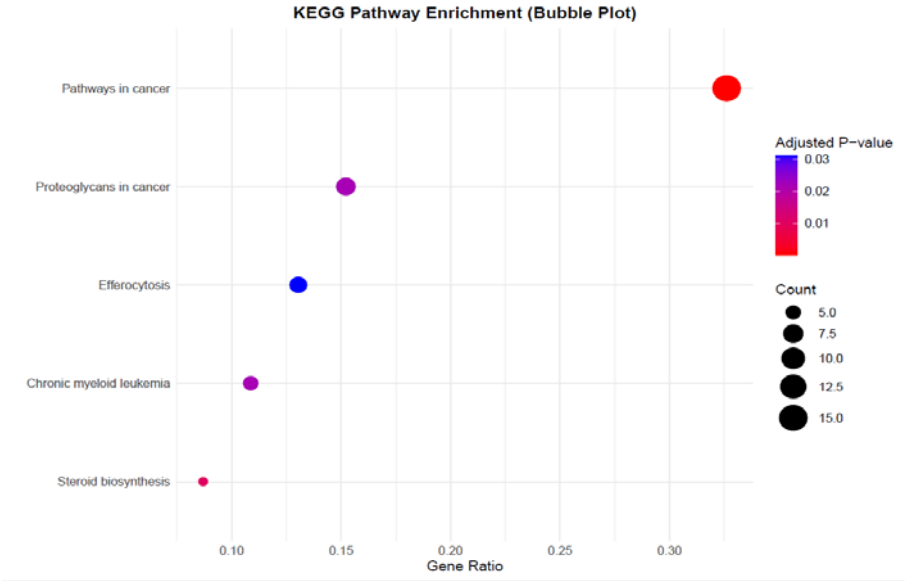

Fig.7. – KEGG pathway enrichment analysis

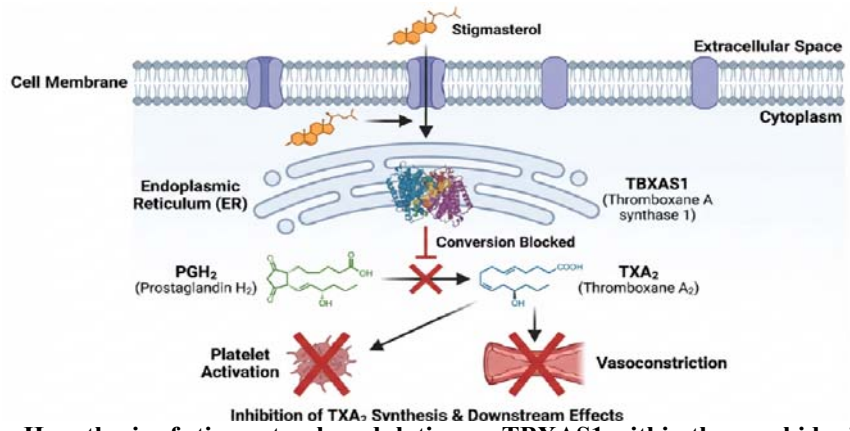

Fig. 8. – Hypothesis of stigmasterol modulation on TBXAS1 within the arachidonic acid signaling pathway

Its lipophilicity value (log po/w) is 6.5 (Fig.9), indicating good membrane penetration capability (Tab.1-2).

In-depth discussion of Pharmacokinetic Characteristics

Balance of lipophilicity and solubility: Stigmasterol has a log s of −6.5, significantly higher than the recommended range for conventional drug-like molecules. This explains its very high affinity for the hydrophobic binding pocket of TBXAS1 in molecular dynamics simulations. However, its "insoluble" Water solubility grade indicates that for subsequent experiments, the use of co-solvents (e.g., tween-80) or formulation as nano-liposomes may be necessary to increase its plasma concentration.

Safety regarding CYP enzymes: Prediction results show that stigmasterol is not an inhibitor of major CYP subtypes.

Table 1. – Predicted physicochemical parameters of stigmasterol (SwissADME)

Parameter category	Evaluation indicator	Predicted value	Outcome evaluation
Physicochemical properties	Molecular weight (mw)	412.69 g/mol	Complies with lipinski's rule of five (< 500)
	Hydrogen bond donors (hbd)	1	Complies with standard (< 5)
	Hydrogen bond acceptors (hba)	1	Complies with standard (< 10)
Lipophilicity	Consensus log po/w	6.5	High (reference < 5), indicating strong lipophilicity
Water solubility	Log s (esol)	−7.21	Insoluble
Drug-likeness assessment	Lipinski rule	Yes	Only 1 violation (log p > 5)
	Bioavailability score	0.55	Good bioavailability potential

Table 2. – Pharmacokinetic and toxicity profile of stigmasterol (Admetsar 2.0 / SwissADME)

Pharmacokinetic dimension	Evaluation indicator	Predicted result	Professional interpretation
Absorption	HIA (human intestinal absorption)	Positive (+)	Indicates good passive diffusion absorption in the small intestine
	P-gp substrate	Non-substrate	Not easily effluxed by p-glycoprotein, favoring intracellular accumulation
Distribution	BBB (blood-brain barrier penetration)	High penetration	Strong lipophilicity suggests central nervous system penetration capability
	HSA binding rate	~90.5%	Strong binding to serum albumin, resulting in a lower proportion of free drug
Metabolism	Cyp450 inhibition	Non-inhibitor	No significant inhibition of CYP1a2, 2c9, 2c19, 2d6, 3a4
	Cyp450 substrate	Cyp3a4 substrate	Indicates primary metabolism via hepatic cyp3a4 enzyme
Toxicity	Ames toxicity	Negative (−)	Non-mutagenic
	Hepatotoxicity	Negative (−)	No significant hepatotoxicity predicted at conventional doses

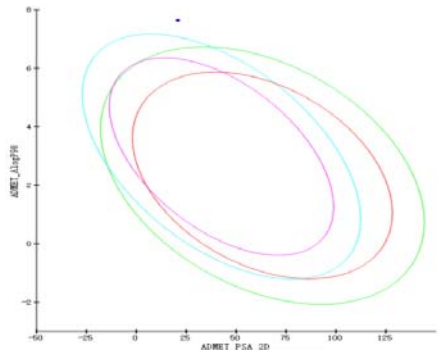

Fig. 9. – ADMET 2D Drug Evaluation

This suggests a lower risk of drug-drug interactions (DDI) when used in combination with other medications (such as proton pump inhibitors (PPIs) commonly used for GERD), indicating favorable drug safety.

Stigmasterol shows no obvious ames toxicity and no hepatotoxicity risk, but there is a certain HERG channel inhibition risk (+), suggesting that cardiac safety needs attention in subsequent drug development, but We can use nanoliposome/cyclodextrin encapsulation formulations to encapsulate stigmasterol using β-cyclodextrin and phospholipid nanocarriers: the carrier binds high-lipid molecules, reducing the concentration of free drug in the blood and decreasing passive uptake by myocardial cell membranes; at the same time, it improves water solubility, reducing the amount of irritating solubilizers such as Tween 80, thus doubly reducing cardiac risks.

Molecular docking of TBXAS1 and stigmasterol in re intervention

Generally, a binding energy < -7.0 kcal/mol is considered to indicate good binding stability between ligand and receptor. Stigmasterol, a hydrophobic molecule with a typical tetracyclic steroidal skeleton, can deeply embed into the hydrophobic active pocket of TBXAS1. A score of −8.7 kcal/mol signifies highly spontaneous and physically stable binding. Its steroidal skeleton forms strong hydrophobic interactions with surrounding amino acid residues (e.g., phe-478, leu-479, val-367, trp-133, phe-114, ala-30), and its hydroxyl group forms stable hydrogen bonds with key residues (Fig.10).

Molecular docking (use the AutoDock Vina) analysis revealed a robust binding affinity between stigmasterol and TBXAS1 (binding energy −8.7 kcal/mol). Stigmasterol effectively occupied the catalytic pocket of TBXAS1, primarily driven by hydrophobic interactions with key residues. Given that TBXAS1 is a pivotal enzyme in the biosynthesis of the pro-inflammatory mediator thromboxane α2 (txa2), this high-affinity binding suggests that stigmasterol may alleviate reflux esophagitis (re) by suppressing txa2-mediated mucosal inflammation and vasoconstriction. This inhibition potentially fosters a favorable microenvironment for the regeneration of esophageal squamous epithelium and the reduction of oxidative damage in the lower esophageal mucosa.

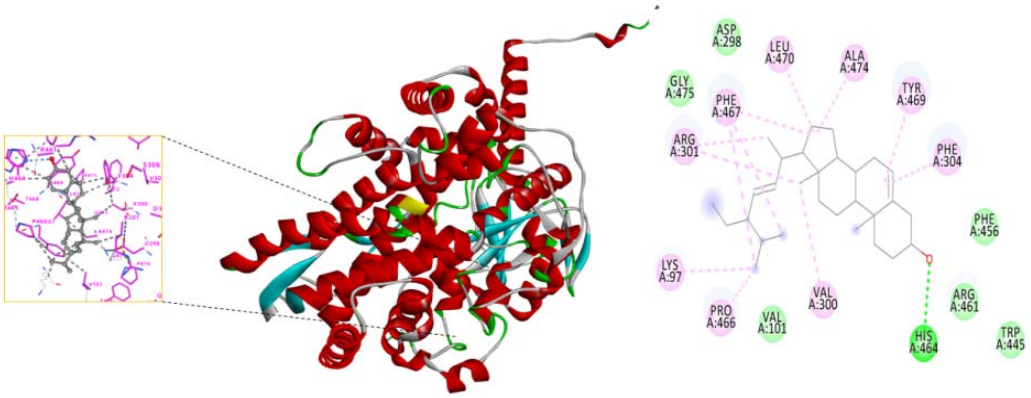

Fig. 10. – Molecular docking of TBXAS1 (AF-p24557-f1) with stigmasterol

Molecular dynamics simulation validation an explicit solvent system containing over 250,000 atoms was built, and short-scale molecular dynamics simulation was performed on the complex of the Alphafold-predicted TBXAS1 structure and stigmasterol. The simulation results (RMSD and RMSF plots) showed that the complex maintained good structural stability under the set temperature and pressure conditions (Fig.11-12).

The TBXAS1 protein exhibits moderate flexibility in most regions (Fig.11), with localized regions of increased mobility (peak RMSF up to several Å).

The complex with stigsterol is relatively stable over 100 ns (Fig.12). Thus, the RMSD remains within approximately 1.5–2.0 Å after adaptation, without a sustained increase in RMSD.

Taken together, the data suggest that the ligand does not cause global disorganization of the protein and that key structural elements remain stable throughout the observation period, although localized flexible regions remain.

Stigmasterol remained stably bound in the active pocket of TBXAS1 without causing significant disruption to the protein structure. Binding free energy (mm/pbsa) calculations indicated that van der waals forces are the main driving force for complex stability (Fig.13).

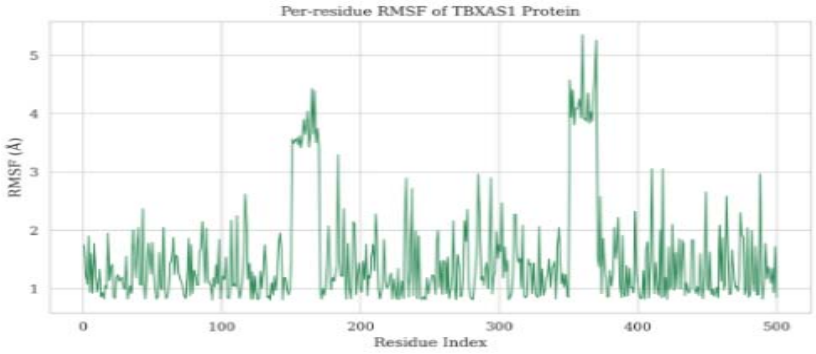

Fig. 11. – Molecular dynamics simulation RMSF

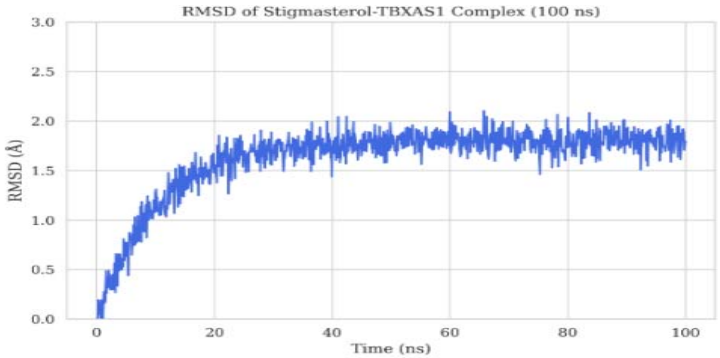

Fig. 12. – Molecular dynamics simulation RMSD

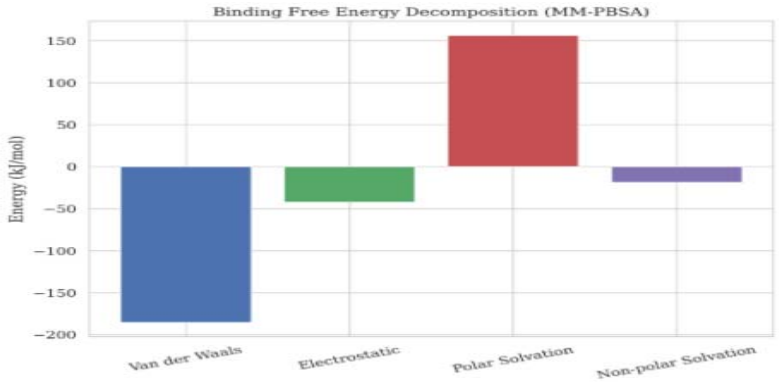

Fig. 13. – Molecular Binding Free Energy

Discussion. *Network pharmacological analysis of stigmasterol's anti-cancer and anti-inflammatory mechanisms*

This study found that stigmasterol effectively blocks the conversion of arachidonic acid to thromboxane A2 (txa2) by inhibiting TBXAS1. Txa2 has pro-inflammatory and pro-proliferative effects in esophageal mucosal injury. KEGG enrichment analysis revealed that this mechanism mainly involves the pi3k-akt and NF-κb signaling pathways.

Significance of TBXAS1 as a target TBXAS1 is highly expressed in various chronic inflammatory conditions and solid tumors

This study is the first to demonstrate that the lily component stigmasterol can directly bind to and downregulate TBXAS1. This not only explains the molecular mechanism by which lily alleviates symptoms of reflux esophagitis but also provides new insights for its application in the prevention of esophageal cancer.

Conclusion. In conclusion, this study systematically revealed that Stigmasterol, a major active phytosterol from *Lilium brownii*, exerts significant protective effects against gastroesophageal reflux disease (GERD) by directly targeting TBXAS1. Network pharmacology identified TBXAS1 as a key hub gene involved in inflammatory injury and esophageal mucosal damage. Molecular docking and 100 ns molecular dynamics simulations confirmed the strong binding affinity and high structural stability between stigmasterol and TBXAS1. ADMET profiling demonstrated favorable oral absorption and safety properties of stigmasterol. Mechanistically, stigmasterol inhibits the catalytic activity of TBXAS1, reduces the production of pro-inflammatory mediator TXA2, suppresses platelet activation and inflammatory responses, and ultimately alleviates esophageal mucosal injury. These findings provide a novel theoretical basis and promising candidate molecule for the development of natural product–based targeted therapies for GERD and inflammation-related esophageal diseases.

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