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"UNRAVELING CARDIAC HYPERTROPHY: EXPLORING THE MECHANISM OF TERMINALIA ARJUNA THROUGH NETWORK PHARMACOLOGY AND MOLECULAR DOCKING"

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Abstract :

Introduction:- Terminalia arjuna has been reported to exhibit beneficial effects in ventricular hypertrophy, a serious consequence of hemodynamically stressful conditions like hypertension and valve disease, indicating its potential therapeutic role in mitigating this condition.

Method:- This study aimed to identify potential compounds responsible for Terminalia arjuna's activity against cardiac hypertrophy and elucidate their mechanisms through network pharmacology and molecular docking. Databases including PubChem, KEGG, TTD, and PDB were mined to extract compound structures, probable targets, and relevant 3D structures. Molecular docking analysis was then conducted to assess interactions between active compounds and target proteins associated with cardiac hypertrophy.

Result:- Network pharmacology unveiled the potential interaction of two compounds from TA, Luteolin and Apigenin, with MAP Kinase, a key enzyme implicated in pathological hypertrophic gene expression. Docking analysis further validated their capability to interact with MAPK.

Conclusion:- TA might be having efficacy in cardiac hypertrophy via inhibition of MAPK through Luteolin and Apigenin.

Keywords:- Network pharmacology, molecular docking, *Terminalia arjuna*, Cardiac hypertrophy, 3D structures, PubChem, KEGG, TTD

➢ INTRODUCTION (1) (2) (3)

Cardiovascular diseases (CVD) encompass a range of conditions affecting the heart and blood vessels, presenting a significant global health challenge. These diseases include coronary artery disease, hypertension, heart failure, and stroke, among others. CVD is a leading cause of morbidity and mortality worldwide, with risk factors such as high blood pressure, unhealthy diet, physical inactivity, and tobacco use contributing to its prevalence (4) .Understanding the underlying mechanisms and risk factors associated with CVD is crucial for effective prevention, diagnosis, and management strategies (5).

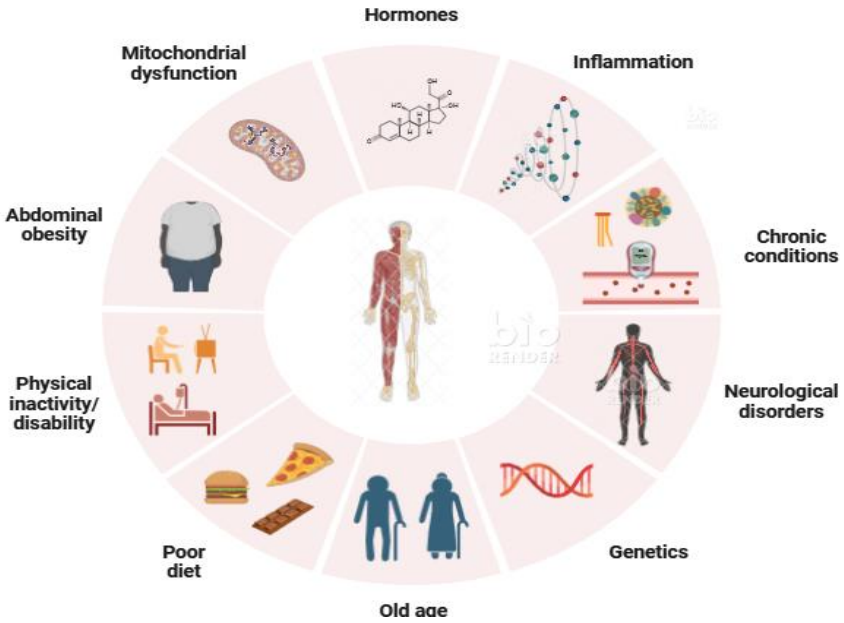

figure:-1 Risk factor of cardiovascular diseases

- **Ayurvedic approach to treat Hridroga (valvular heart disease):**

In Ayurveda, the term 'Hrudaya' denotes the heart, reflecting its vital function of forcibly collecting and supplying body fluids and blood. The heart, originating from the essence of Rakta and Kapha, is primarily controlled by Vyanavayu, with valvular disorders attributed to vitiated rasa and rakta leading to inflammation and eventual degeneration of valves. Valvular heart disease, often rheumatic in origin, manifests with murmurs and can be likened to amavatha. Ayurvedic treatment focuses on correcting imbalances in vata, rasa, rakta, and mamsa, with numerous formulations available for effective management. This holistic approach typically includes dietary modifications, lifestyle adjustments, herbal remedies, and specific Ayurvedic therapies (6)

1. Dietary modifications: Ayurvedic practitioners may recommend a heart-healthy diet that includes fresh fruits, vegetables, whole grains, lean proteins, and healthy fats. Avoiding processed foods, excessive salt, saturated fats, and refined sugars is also emphasized.

2. Lifestyle adjustments: Stress management techniques, regular exercise, adequate sleep, and maintaining a healthy weight are essential components of the Ayurvedic approach to managing Hridroga. Practices such as yoga, pranayama (breathing exercises), and meditation may also be recommended to promote relaxation and reduce stress.

3. Herbal remedies: Ayurvedic herbs such as Arjuna (Terminalia arjuna), Guggulu (Commiphora mukul), Punarnava (Boerhavia diffusa), and Hawthorn (Crataegus) may be prescribed to support heart health, strengthen the cardiovascular system, and improve circulation.

4. Ayurvedic therapies: Panchakarma, a detoxification and rejuvenation therapy, may be recommended to eliminate toxins from the body, improve digestion, and support overall health. Additionally, specific therapies like Abhyanga (oil massage) and Shirodhara (a soothing oil therapy) may help promote relaxation and reduce stress.

5. Individualized treatment: Ayurvedic treatment for Hridroga is personalized based on an individual's unique constitution (Prakriti) and imbalances (Vikriti). Ayurvedic practitioners tailor treatment plans to address specific imbalances and health concerns of each individual.

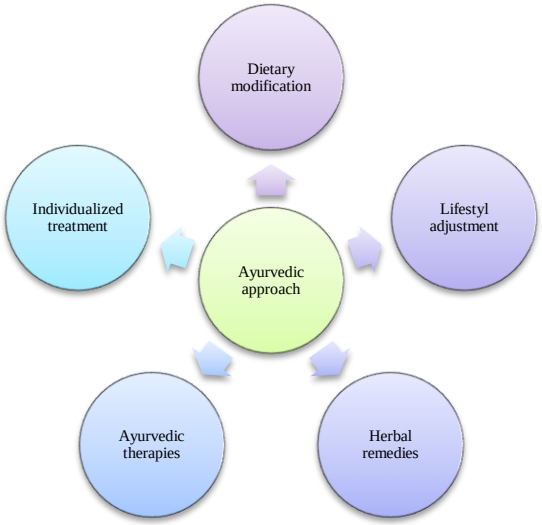

figure: 2 Ayurvedic approach to treat hridroga

- **Aim and Objective :-**

The objective of this research is to pinpoint the phytochemicals present in Terminalia arjuna (**Family:-** Combretaceae) that exhibit notable cardioprotective properties, specifically targeting APOE4 (7) (8) .

Pharmacological Action: Different extracts derived from the stem bark of Terminalia arjuna (**Family:-** Combretaceae) have demonstrated a variety of pharmacological effects, such as enhancing cardiac contractility, reducing ischemic damage, combating oxidative stress, lowering blood pressure, inhibiting platelet aggregation, decreasing lipid levels, preventing atherosclerosis, and reducing cardiac hypertrophy (9)

Mechanism:- The plant was found to increase the force of cardiac contraction, exert negative or positive inotropic/chronotropic effects on heart, and cause a dose-dependent decrease in blood pressure (BP) and hypolipidemic effect. It improves cardiac muscle function and subsequently enhances pumping activity of the heart (10) (11) (12) (13)

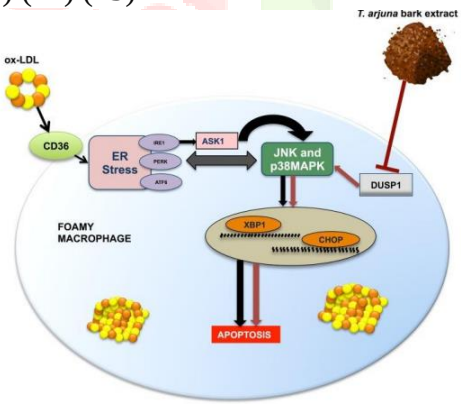

figure 3: Mechanism of terminalia arjuna

These findings indicate that TA promotes macrophage and foam cell apoptosis via enhancing UPRmediated activation of JNK/p38MAPK-CHOP pathway in a DUSP1-dependent manner, implying a possible interplay between ox-LDL-induced ER stress- and TA-mediated MAPK signalling.

Docking Compounds (14)(15)

Luteolin	MAP kinase-interacting serine/threonine-protein kinase 1
	MAP kinase-interacting serine/threonine-protein kinase 2
Apigenin	MAP kinase-interacting serine/threonine-protein kinase 2
Sorafenib	MAP kinase-interacting serine/threonine-protein kinase 2

- **Network pharmacology** (16)

Network pharmacology is a multidisciplinary approach that integrates computational and experimental techniques to study the complex interactions between biological systems and drugs or natural compounds. The method typically involves the following steps:

1. Data collection: Gather information on drug compounds or natural products of interest, as well as their targets, pathways, and biological functions. This may involve mining databases such as PubChem, DrugBank, or the Therapeutic Target Database (TTD).

2. Network construction: Build network models representing the interactions between drugs or compounds and their targets, as well as the relationships between targets, pathways, and diseases. This can be done using various network analysis techniques, including protein-protein interaction networks, drug-target networks, and pathway analysis.

3. Data integration and analysis: Integrate data from multiple sources to identify key nodes (e.g., drug targets, signaling pathways) and network properties (e.g., centrality, modularity) associated with drug efficacy or disease pathogenesis. Analytical methods such as network topology analysis, pathway enrichment analysis, and clustering algorithms can be employed to identify relevant biological pathways and functional modules.

4. Prediction and validation: Use computational algorithms to predict the efficacy and safety of drug candidates or natural compounds based on their network properties and interactions. Experimental validation of predicted drug-target interactions or biological activities is essential to confirm the accuracy and reliability of the predictions.

5. Application in drug discovery and development: Utilize network pharmacology approaches to identify potential drug targets, repurpose existing drugs for new indications, optimize drug combinations, and design more effective therapeutic strategies for complex diseases.

Overall, network pharmacology provides a powerful framework for understanding the molecular mechanisms of drug action, elucidating complex biological processes, and accelerating drug discovery and development efforts.

- **What is docking?** (16) (17)

Docking predicts the optimal physical arrangement and energy between two molecules by maximizing their interaction and minimizing binding energy. It optimizes the binding orientation to maximize interaction and evaluates total energy to minimize binding energy. Additionally, it assesses structural changes resulting from the interaction.

- **Types of docking** (18)

There are several types of docking methods used in molecular modeling and drug discovery, each with its own strengths and applications. Some common types of docking include.

1. Rigid docking: - It is involves treating both the ligand and receptor as rigid structures, without allowing for conformational changes during docking. While computationally efficient, this method may overlook flexibility in binding interactions.

2. Flexible docking: Flexible docking permits adjustments in ligand, receptor, or both conformations during docking, enhancing accuracy at the cost of computational intensity.

3. Ligand-based docking:- Ligand-based docking, or ligand-based virtual screening, involves docking a library of ligands into a predetermined binding site on the receptor to identify compounds with favorable binding affinities, useful when receptor structure is known but binding sites vary among ligands.

4. Structure-based docking :- Structure-based docking positions ligands within a receptor's binding site using its 3D structure, relying on experimental techniques such as X-ray crystallography or homology modeling for receptor structure determination.

5. Target-specific docking: Target-specific docking involves docking ligands into a specific binding site on the receptor, guided by experimental data or known binding interactions. This approach is tailored to a particular target and is often used in structure-based drug design.

6. **Blind docking:** Blind docking explores potential binding sites on the receptor by docking ligands across its entire surface, facilitating the discovery of novel ligand-receptor interactions.

7. Virtual screening:- Virtual screening rapidly evaluates numerous compounds against a target protein, aiding in the identification of potential drug candidates for further experimental investigation.

- **The mechanism of molecular docking involves several key steps:** (19)

1. Preparation: Ligands and receptors are prepared by generating their 3D structures and optimizing their conformations.

2. Grid generation: A 3D grid is created around the receptor to define the search space for ligand binding.

3. Docking algorithm: The ligand is flexibly docked into the binding site of the receptor using computational algorithms, exploring various ligand conformations and orientations within the search space.

4. Scoring and ranking: Docked ligand poses are scored and ranked based on their predicted binding affinities and interactions with the receptor.

5. Analysis and validation: Docked ligand-receptor complexes are analyzed to understand the molecular interactions driving binding specificity and affinity, often validated by experimental techniques.

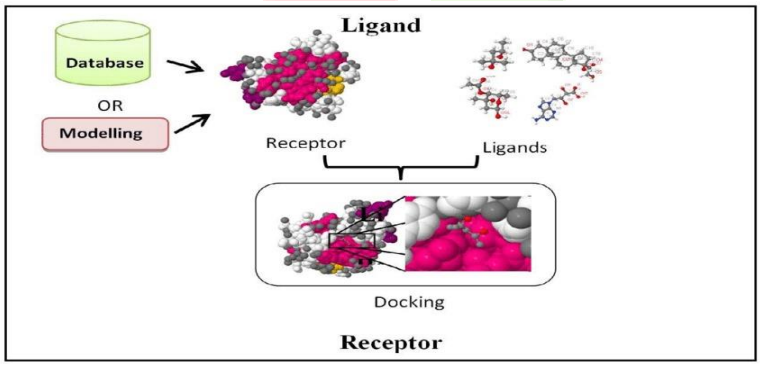

figure 4: Mechanism of molecular docking

- **Methodology:-**

1. SwissDock (20)

SwissDock, offered by the Swiss Institute of Bioinformatics (SIB), is an online platform facilitating protein-ligand docking simulations. It predicts binding modes and affinities between ligands and target proteins using a rapid algorithm based on the EADock DSS engine and CHARMM force field. Users submit jobs by providing protein structures in PDB format and specifying ligands. The server conducts docking simulations, generating favorable binding poses ranked by estimated binding energies. SwissDock aids in drug discovery and structural biology research, offering insights into ligand-protein interactions, potential drug candidates, and ligand binding affinities.

Steps:-

1. Input Preparation: Obtain the 3D structures of the ligand and receptor molecules.

2. File Formatting: Ensure ligand and receptor files are in appropriate formats (e.g., PDB).

3. Upload Files: Submit ligand and receptor files through the SwissDock web interface.

4. Parameter Selection: Specify docking parameters such as search space and docking method.

5. Docking Execution: Initiate the docking simulation on the SwissDock server.

6. Results Retrieval: Access and download the docking results once the simulation is complete.

7. Analysis and Interpretation: Analyze the docking poses and interactions to understand ligand-receptor binding.

8. Follow-up Studies: Validate docking predictions experimentally or through further computational analyses.

By following these steps, researchers can utilize SwissDock for molecular docking studies to explore ligand-protein interactions and identify potential drug candidates.

2. PyRx (21)

PyRx is a widely used virtual screening software for molecular docking and drug discovery, offering a user-friendly interface and seamless integration with AutoDock Vina. It enables users to prepare ligands and receptors, perform docking simulations, and visualize results, with support for grid-based docking, flexible handling, and batch processing. PyRx is a versatile tool for exploring ligand-protein interactions and identifying potential drug candidates efficiently and accurately.

Steps:-

1. Input Preparation: Import ligand and receptor structures into PyRx.

2. Parameter Setup: Define docking parameters like search space and scoring function.

3. Docking Execution: Initiate docking simulations to predict ligand-receptor binding.

4. Results Analysis: Evaluate docking results for potential interactions and affinity scores.

5. Optional Optimization: Refine docking poses through energy minimization or molecular dynamics.

6. Virtual Screening: Identify hit compounds based on docking outcomes.

7. Validation and Analysis: Validate predictions and assess hit compounds for drug-likeness and off-target effects.

By following these steps, researchers can effectively utilize PyRx for molecular docking and virtual screening studies in drug discovery and structural biology research.

- **Result:**

1) Apigenin+ MAP kinase-interacting serine/threonine-protein kinase 2:-

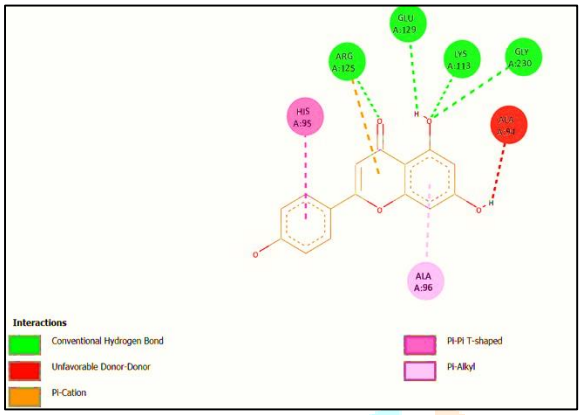

figure 5: Apigenin+ map kinase-interacting serine/threonine-protein kinase 2d structure

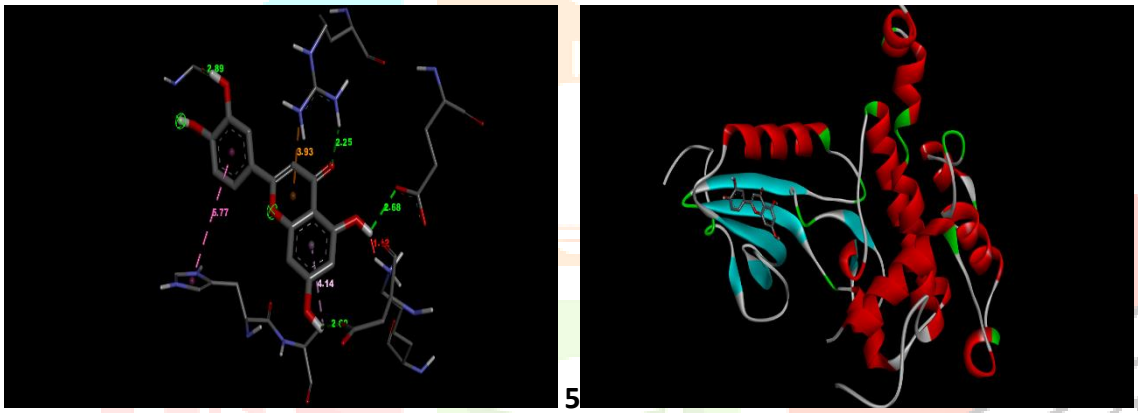

Figure 6: Apigenin+ MAP kinase-interacting serine/threonine-protein kinase 3D structure

In this 2D structure of Apigenin+ MAP kinase-interacting serine/threonine-protein kinase 2, the four conventional Hydrogen bonds are had with arginine (ARG), Glutamic acid (GLU), lysine (LYS), and Glycine (GLY), along with one Unfavourable Donor-Donor bond. No Pi-Cation bond had in this 2D structure, and there is one Pi-Pi T-Shaped bond had with Histidine (HIS) and one Pi-Alkyl bond had with Alanine (ALA) in this Structure. Binding affinitiy is -7.2

2) **Luteolin+ MAP kinase-interacting serine/threonine-protein kinase 1:-** (22)

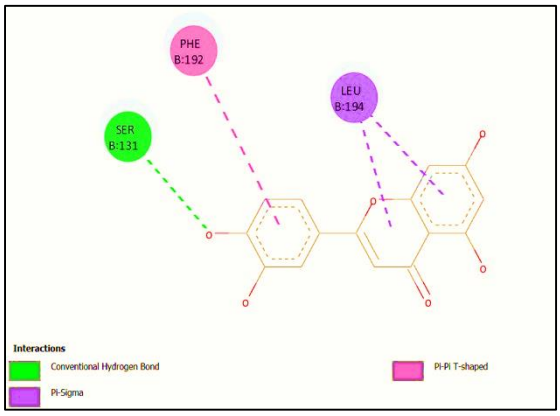

figure 7: Luteolin+ map kinase-interacting serine/threonine-protein kinase- 1 (2D structure)

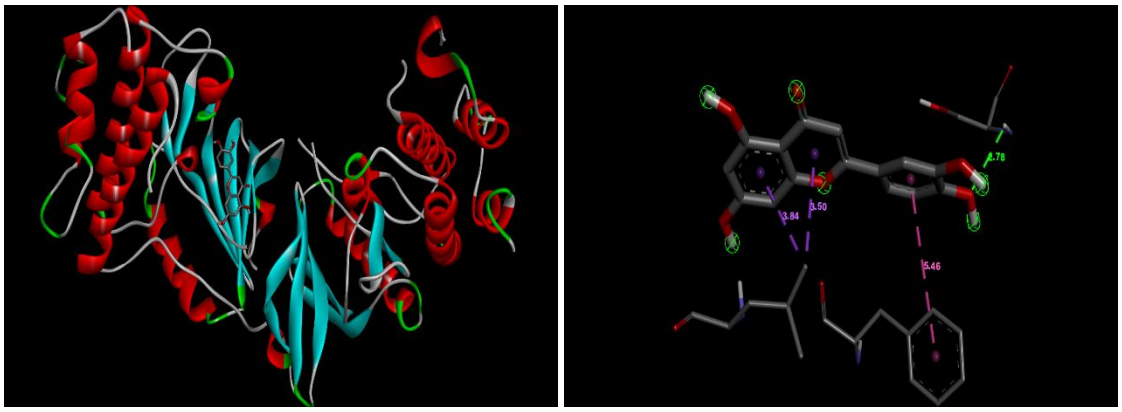

figure 8: Luteolin+ map kinase-interacting serine/threonine-protein kinase- 1 (3D structure)

In this Luteolin+ MAP kinase-interacting serine/threonine-protein kinase 1, the one Conventional Hydrogen Bond with Serin (SER), a Pi-Pi T-Shaped bond with Phenylalanine (PHE), and one Pi-Sigma bond with Leucine (LEU) have been taken in this 2D Structure.
Binding affinity is -7.2 .

3) Sorafenib+ MAP kinase-interacting serine/threonine-protein kinase 1:- (23)

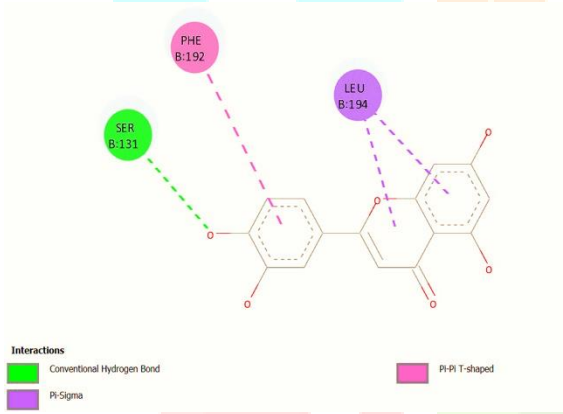

figure 9: Sorafenib+ map kinase-interacting serine/threonine-protein kinase -1 (2D structure)

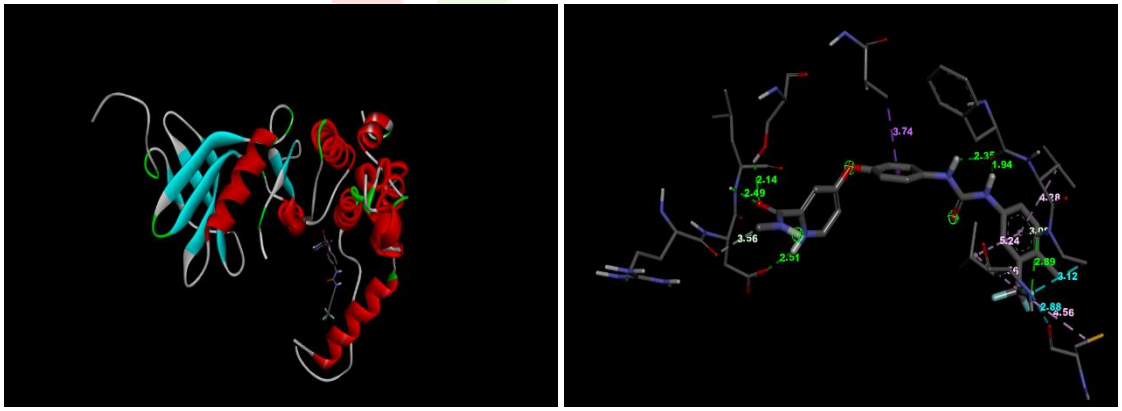

figure 10: Sorafenib+ map kinase-interacting serine/threonine-protein kinase -1 (3D structure)

In this 2D structure of Sorafenib+ MAP kinase-interacting serine/threonine-protein kinase 1, the five Conventional Hydrogen Bonds with Serin (SER), Leucin (LCU), Aspartic Acid (ASP), Phenylalenin (PHE), Glycin (GLY) have been observed. A Carbon Hydrogen Bond with Arginine (ARG) has been seen. A Halogen (fluorine) bond with cystien (CYS) and only one Pi-Sigma bond with Valine (VAL) have been identified. An

alkyl bond and one Pi-Alkyl bond with Valine (VAL), Leucin (LEU) have been noted in this 2D Structure. Binding affinity is -8.5

➢ Conclusion

In summary, our study explored the binding interactions of luteolin and apigenin from Terminalia arjuna with the MAP kinase interacting serine/threonine-protein kinase protein, along with sorafenib, an allopathic drug targeting MAP kinase. We identified shared binding properties and comparable binding affinities among these compounds, indicating a potential activity via the MAP kinase pathway. Interestingly, we observed an inverse relationship between binding affinity and efficacy. These findings underscore the need for further clinical investigations to evaluate the safety and efficacy of Terminalia arjuna in the management of cardiac hypertrophy

➢ Feature perspective:

1. Comprehensive Exploration: This article delves into the mechanism of Terminalia arjuna in treating cardiac hypertrophy using cutting-edge methods like network pharmacology and molecular docking, providing a holistic understanding of its therapeutic potential.

2. Integration of Network Pharmacology and Molecular Docking: By combining network pharmacology to identify potential compounds and targets with molecular docking to elucidate their binding mechanisms, this study offers a multi-dimensional analysis of Terminalia arjuna's effects on cardiac hypertrophy.

3. Insights into Molecular Interactions: Through molecular docking, the article uncovers the specific interactions between Terminalia arjuna compounds and target proteins involved in cardiac hypertrophy, shedding light on the underlying molecular mechanisms.

4. Potential Therapeutic Targets: Identification of key proteins and pathways targeted by Terminalia arjuna compounds provides valuable insights for future drug development and therapeutic interventions aimed at combating cardiac hypertrophy.

5. Validation of Traditional Medicine: By employing modern computational techniques, this study validates the traditional use of Terminalia arjuna in Ayurvedic medicine for cardiac health, bridging the gap between traditional knowledge and contemporary scientific approaches.

6. Implications for Drug Discovery: The findings of this research have implications for drug discovery efforts, potentially leading to the development of novel therapies or formulations based on Terminalia arjuna for the management of cardiac hypertrophy.

7. Clinical Relevance: Understanding the mechanism of Terminalia arjuna in cardiac hypertrophy can pave the way for clinical trials to evaluate its efficacy and safety, offering new avenues for the treatment of cardiovascular diseases.

In summary, this article offers a feature perspective on how the exploration of Terminalia arjuna's mechanism through network pharmacology and molecular docking can contribute to advancements in cardiovascular research and drug discovery

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