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In silico exploration of bioactive compounds from *Acorus calamus* L. for targeted treatment of ischemic heart disease: Molecular insights and therapeutic prospects

Tripura Sahu[1], Giridhar Vedantam[1], Umashankar Vetrivel[2]

[1]*Department of Dravyaguna, KAHER's Shri BMK Ayurveda Mahavidyalaya, Belagavi, Karnataka, India,* [2]*Indian Council of Medical Research-National Institute for Traditional Medicine, Belagavi, Karnataka, India*

Address for correspondence:
Dr. Giridhar Vedantam, Department of Dravyaguna, KAHER's Shri BMK Ayurveda Mahavidyalaya, Shahapur, Belagavi, Karnataka 590003, India.
E-mail: drgiridharay@gmail.com

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Abstract

BACKGROUND: Ischemic heart disease (IHD) accounts for 80%–85% of mortality, highlighting the need to develop effective and noninvasive management strategies. *Lekhana karma* (therapeutic scrapping) helps in balancing the imbalanced *Kapha* and *Medodhatu,* which are important factors in the pathogenesis of IHD. *Vacha—Acorus calamus* Linn (*AC*) is 1 of the 10 *Lekhaneeya* drugs described in *Charaka Samhita* and is widely available and cost-effective. However, its bioactive phytoconstituents' mode of action and molecular entities remain unexplored. Hence, this study aimed to elucidate the mode of action of its bioactive compounds and their interaction with IHD disease targets and pathways.

METHODS: Phytochemicals from *AC* were collected, followed by screening of bioactive phytochemicals, collecting gene identifications, and pathways related to IHD. Later, common compounds and pathways were identified, and common targets between phytochemicals and pathways were sorted. A further network of phytochemicals-pathways-targets was constructed followed by molecular docking of highly enriched disease targets and phytochemicals.

RESULTS: *An in silico* study revealed that 19 main active compounds of *AC* are interacting with 48 targets involved in regulating biological processes in the IHD. Molecular docking analyses were performed to explore the potential and affinity of these compounds with disease targets. Galangin, alpha-asarone, beta-asarone, and isoelemicin exhibited significant interactions with IHD disease targets, such as prostaglandin G/H synthase 2, cytochrome P450 1A2, transcription factor p65, vascular endothelial growth factor A, and tyrosine-protein kinase. Additionally, the study identified the interaction between the top 4 phytochemicals and the five most enriched disease targets.

CONCLUSION: These findings provide a promising avenue for transforming bioactive phytoconstituents in *AC* into novel drug entities for treating IHD. The *in silico* approach identifies therapeutic targets, guides wet lab studies, and aids multi-compound management for IHD.

Keywords:

Ayurveda, *Lekhana*, molecular docking, network pharmacology, *Vacha*

Introduction

According to the fact sheets of the World Health Organization, an estimated 17.9 million people died from cardiovascular diseases in 2016, representing 31% of all global deaths. Of these deaths, 85% were due to ischemic heart disease (IHD), thus referred to as "Global Burden."[1] Though progress toward managing the related issues of disease prevention and cure has

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been elusive, it remains the leading cause of death attributing more than 15.96%to IHD of all deaths.[2] Therefore, the need of the hour is to find a safe, effective, and noninvasive alternate method to prevent increasing mortality rates. Though various Ayurveda classical drugs are mentioned and being practiced, the evidence-based molecular-level mechanism of action remains elusive.

Network pharmacology explains the mechanism of disease and drug action from the perspective of biological overview by predicting the complex "drug-target-disease" relationship; it is helpful for clinical drug safety and effectiveness evaluation.[3] Furthermore, the multi-component, multi-target, and regulatory network can reveal the mechanism of action of drugs, which is particularly suitable for studying the mechanism of herbal compounds and their complex components from a "holistic perspective." The drug-target network helps understand the interaction between active compounds and molecular details of *Acorus calamus* L. *(AC*) against IHD. Hence, the present study is used to apply network pharmacology analysis of *AC* on targets of IHD. *AC* is described in Ayurveda as *Lekhana*,[4] the ideal line of treatment for *Hridroga* (Cardiovascular disease). *Lekhana* is defined as reducing abnormally accumulated fat and *Kapha (Lekhanamkaphamedso*) by Acharya Dalhana.[5] Acharya Sharngadhara described *Lekhana* as a pharmacological action, which expels excessive and accumulated *dhatus* (tissue elements) and *malas* (metabolites), for example, hot water, *Vacha* (*AC*), and *Yava* (barley).[6]

The underlying action induced by *AC* and its components and targets are often multiple. Though classical references are there for the therapeutic effect of *Hridroga* reported, the mechanisms of action of these phytochemicals have been extensively studied in the context of IHD onset modulation. So the specific molecular mechanism triggered by the bioactive phytocompounds of *AC* in IHD needs further investigation. In this study, bioinformatics methods were used to predict the candidate compounds and mechanisms of *AC* in the treatment of IHD, along with classical literature for validation of the interactions between the herbal active components and disease targets leading to the prevention and treatment of IHD.

Materials and Methods

Work flow of the study is shown as flow chart in Figure 1.

Screening of bioactive phytochemicals

Databases, such as IMPPAT[7] and Dr. Dukes[8] were searched, along with research articles on PubMed,[9] using the Latin name of the plant "*Acorus calamus* L." to obtain the phytochemical contents of *AC* (Steroids, lipids, glucose), and simple structured chemicals were later excluded by removing duplicate compounds and those with aliphatic chains, as they may not be the primary drug targets. The total number of phytochemicals found was subsequently screened to assess their drug-likeness profile using SWISS ADME.[10]

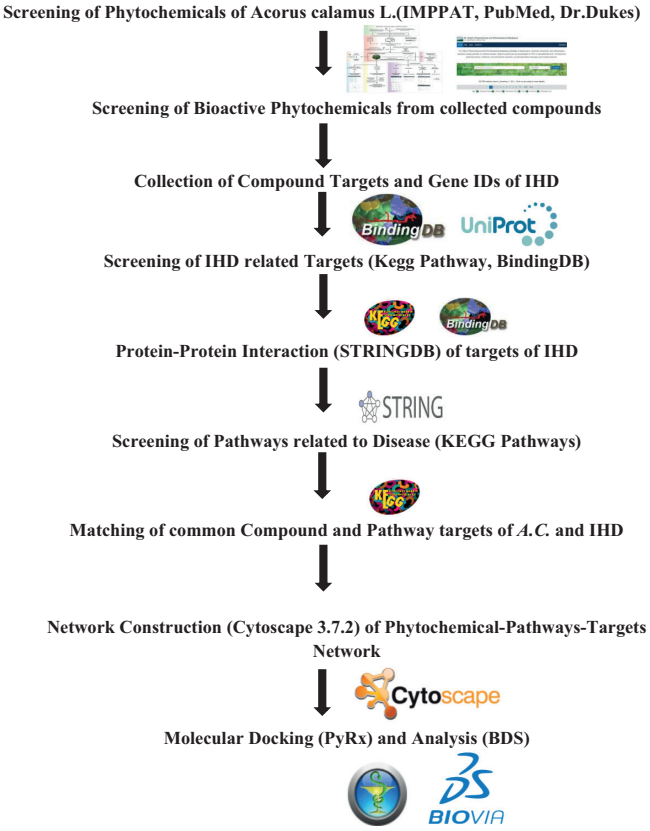

Figure 1: Workflow of the methodology adopted in the construction of the Chemical-Target-pathways network and molecular docking of *AC* in IHD

Target identification

After shortlisting the phytochemicals, their canonical SMILES and PubChem IDs were queried in the PubChem database.[11] Compound targets were obtained from the BindingDB database (an experimentally determined ligand-protein interaction database)[12] using the canonical SMILES, with a similarity threshold set at 0.7. Gene IDs/UniProt IDs of each protein target were also obtained from the UniProt database.[13] Protein targets for the selected phytocompounds were predicted using the BindingDB server.

Gene Set Enrichment Analysis

The Gene IDs of the targets were queried in the STRING 11.0 version to identify the molecular pathways they regulated, which were associated with IHD pathogenesis.[14] IHD-associated protein targets were obtained through the Kyoto encyclopedia of gene and genomes (KEGG) pathway.[15] Highly modulated targets

were then subjected to molecular docking using the PyRx software (Forge Headquarters, San Diego, CA), and the intermolecular interaction of the compound was analyzed based on binding energy and docking scores.[16]

Protein–protein interaction network and key gene screening

The protein–protein interaction (PPI) network was obtained through the STRING database (an experimentally determined protein-protein interaction database). The KEGG pathway was downloaded, and pathways associated with IHD were screened.

"Herbal-Compound-Target" network construction

After sorting the IHD-related pathways in *AC* phytocompounds, the common targets of *AC* phytochemicals and IHD were matched and sorted. The "Compound-Targets-Pathways" network was constructed using the Cytoscape 3.7.2 software version (Cytoscape Developer: Institute of system biology in Seattle, US).[17]

Molecular docking

The three-dimensional structures of the protein targets were retrieved from the Research Collaborator for Structural Bioinformatics—Protein Data Bank, whereas the three-dimensional structures of enriched phytochemicals were retrieved from the PubChem database.[18] Biovia Discovery Studio was used to remove water molecules and heteroatoms from the protein molecules.[19] Subsequently, the PyRx software was used to predict the binding affinity through molecular docking.

Results

Screening of bioactive phytochemicals

Databases such as IMPPAT and Dr. Dukes were searched, along with research articles, using the Latin name of the plant "*Acorus calamus* L." to obtain the phytochemical contents of *AC* Steroids, lipids, glucose, and simple structured chemicals were subsequently excluded by removing duplicate and aliphatic chain compounds, as they may not be the primary drug targets. A total of 358 phytochemicals were found, out of which 32 phytocompounds were shortlisted based on their drug-likeness profile. Finally, 19 phytochemicals were finalized, namely (Z)-isoelemicin, (Z)-methyl isoeugenol, acoradin, acorenone, alpha-asarone, aristolone, beta-asarone, calameone, *cis*-isoeugenol, elemicin, eugenol, galangin, gamma-asarone, isocalamendiol, isoelemicin, isoeugenol, isoshyobunone, methyl eugenol, and β-sitosterol [Table 1].

Target identification

Predicted protein targets were obtained for the 32 phytocompounds using the BindingDB server (an experimentally determined ligand–protein interaction database). These compounds were predicted to target 218 proteins, of which 48 were related to IHD pathogenesis (confirmed by the Therapeutic Target Database). Among the 32 compounds, 19 were found to target these 48 protein targets.

Protein–protein interaction network, key gene screening, and gene set enrichment analysis

The gene IDs of the 19 targets were queried in STRING, and the KEGG pathway enrichment was downloaded and

Table 1: Phytochemicals of *AC* enlisted which have interaction with targets associated with IHD pathophysiology

S. No	Phytochemical	Molecular weight	Molecular formula	PubChem ID	Lipinski
1.	(Z)-Isoelemicin	208.25	C12H16O3	5851118	Yes
2.	(Z)-Methyl isoeugenol	178.23	C11H14O2	1549045	Yes
3.	Acoradin	416.5	C24H32O6	126324	Yes
4.	Acorenone	220.35	C15H24O	12480741	Yes
5.	Alpha-asarone	208.25	C12H16O3	636822	Yes
6.	Aristolone	218.33	C15H22O	165536	Yes
7.	Beta-asarone	208.25	C12H16O3	5281758	Yes
8.	Calameone	238.37	C15H26O2	181982	Yes
9.	*Cis*-isoeugenol	164.2	C10H12O2	1549041	Yes
10.	Elemicin	208.25	C12H16O3	10248	Yes
11.	Eugenol	164.2	C10H12O2	3314	Yes
12.	Galangin	270.24	C15H10O5	5281616	Yes
13.	Gamma-asarone	208.25	C12H16O3	636750	Yes
14.	Isocalamendiol	238.37	C15H26O2	12302240	Yes
15.	Isoelemicin	208.25	C12H16O3	5318557	Yes
16.	Isoeugenol	164.2	C10H12O2	853433	Yes
17.	Isoshyobunone	220.35	C15H24O	5318673	Yes
18.	Methyl eugenol	178.23	C11H14O2	7127	Yes
19.	β-Sitosterol	414.7	C29H50O	222284	Yes

AC: *Acorus calamus* Linn, IHD: ischemic heart disease

screened to identify the molecular pathways regulated by these targets. The 19 targets were found to modulate 84 pathways, out of which 13 were associated with IHD pathogenesis. The enriched pathways identified included apoptosis, calcium signaling pathway, cyclic adenosine monophosphate signaling pathway, Fluid shear stress and atherosclerosis, mitogen activated protein kinase signaling pathway, phosphoinositide-3-kinase-protein kinase B/Akt signaling pathway, nuclear factor (NF)- κB signaling pathway, drug metabolism—cytochrome P450, focal adhesion, hypoxia inducible factor 1 signaling pathway, insulin resistance, relaxin signaling pathway, and vascular endothelial growth factor A (VEGFA) signaling pathway. These pathways were modulated by various proteins including tubulin alpha-1A chain, Poly [ADP-ribose] polymerase 1, E3 ubiquitin-protein ligase XIAP, transcription factor p65 (RELA), cathepsin L2, DNA damage-inducible transcript 3 protein, 5-hydroxytryptamine receptor 2B, epidermal growth factor receptor, 5-hydroxytryptamine receptor 2C, adenosine receptor A2a, D(1A) dopamine receptor, glutamate receptor ionotropic, NMDA 2A, 5-hydroxytryptamine receptor 2A, cystic fibrosis transmembrane conductance regulator, adenosine receptor A1, cAMP-specific 3',5'-cyclic phosphodiesterase 4A, glutamate receptor ionotropic, NMDA 2B, 72 kDa type IV collagenase, integrin alpha-V/beta-3, matrix metalloproteinase-9, nuclear factor erythroid 2-related factor 2, vascular endothelial growth factor A, receptor-type tyrosine-protein kinase, heat shock factor protein 1, MAP kinase-interacting serine/threonine-protein kinase 2, insulin-like growth factor 1 receptor, BDNF/NT-3 growth factors receptor, mast/stem cell growth factor receptor, hepatocyte growth factor receptor, microtubule-associated protein tau, MAP kinase-interacting serine/threonine-protein kinase 1, placenta growth factor, Cyclin-dependent kinase 6, glycogen synthase kinase-3 beta, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform, 5'-AMP-activated protein kinase catalytic subunit alpha-2, toll-like receptor 4, casein kinase II subunit alpha, tyrosine-protein kinase (LCK), prostaglandin G/H synthase 2 (PTGS2), casein kinase II subunit alpha 3, amine oxidase [Flavin-containing] A, cytochrome P450 1A2 (CYP1A2), cytochrome P450 2D6, amine oxidase B, oxysterols receptor LXR-beta, tyrosine-protein phosphatase non-receptor type 1, oxysterols receptor LXR-alpha, which are associated with IHD.

"Herbal-Compound-Target" network construction

After sorting the IHD-related pathways for *AC* phytocompounds, the common targets of *AC* phytochemicals and IHD were matched and sorted. Furthermore, Compounds-Targets-Pathways were constructed using the Cytoscape 3.7.2 software version [Figure 2].

Molecular docking

On molecular docking, phytochemicals of *AC* L. namely galangin, alpha-asarone, beta-asarone, and isoelemicin show an excellent binding affinity with disease targets of IHD like PTGS2, CYP1A2, RELA, VEGFA, and LCK. Interactions between most five enriched disease targets and the top 4 phytochemicals were subjected to molecular docking. The results of molecular docking scores are tabulated [Table 2]; [see Figures 3 and 4].

After molecular docking amino acids undergoing modulations are tabulated for galangin as it shows good docking scores among all [Table 3].

Discussion

This study focused on the interaction and behavior of biological entities, aiming to understand the relationship between drug molecules and biological targets. It also aimed to relate the function of protein complexes through network analysis and explore significant pathways associated with disease pathophysiology. The role of key protein targets in IHD manifestation can be understood through the following points.

CYP1A2

CYP1A2 is a cytochrome P450 monooxygenase involved in metabolizing various endogenous substrates, including fatty acids, steroid hormones, and vitamins. Mechanistically, it metabolizes cholesterol toward 25-hydroxycholesterol, a physiological regulator of cellular cholesterol homeostasis. It may act as a major enzyme in the biosynthesis of bonds with polyunsaturated fatty acids, which preferentially form plaques in coronary arteries.[13] Studies have shown that the CYP1A2 poor inducibility genotype was linked to an elevated risk of MI, indicating that a CYP1A2 substrate plays a role in CHD.[20]

PTGS2

PTGS2 is the principal isozyme responsible for producing inflammatory prostaglandins. Inhibition of PTGS2 acutely reduces inflammation. It is also known as cyclooxygenase2, reflecting its physiological role in antiplatelet and atherothrombotic events that affect endothelial function. Increased platelet activation at sites of fissured or ruptured atherosclerotic plaques and prolonged increases in blood pressure contribute to adverse cardiovascular consequences.[13] A recent study on mice with ischemic stroke shows that PTGS2 silencing increased expression cell proliferation, migration, and angiogenesis and declined apoptosis promoting angiogenesis.[21]

VEGFA

VEGFA is a growth factor that promotes angiogenesis, vasculogenesis, and endothelial cell growth. It

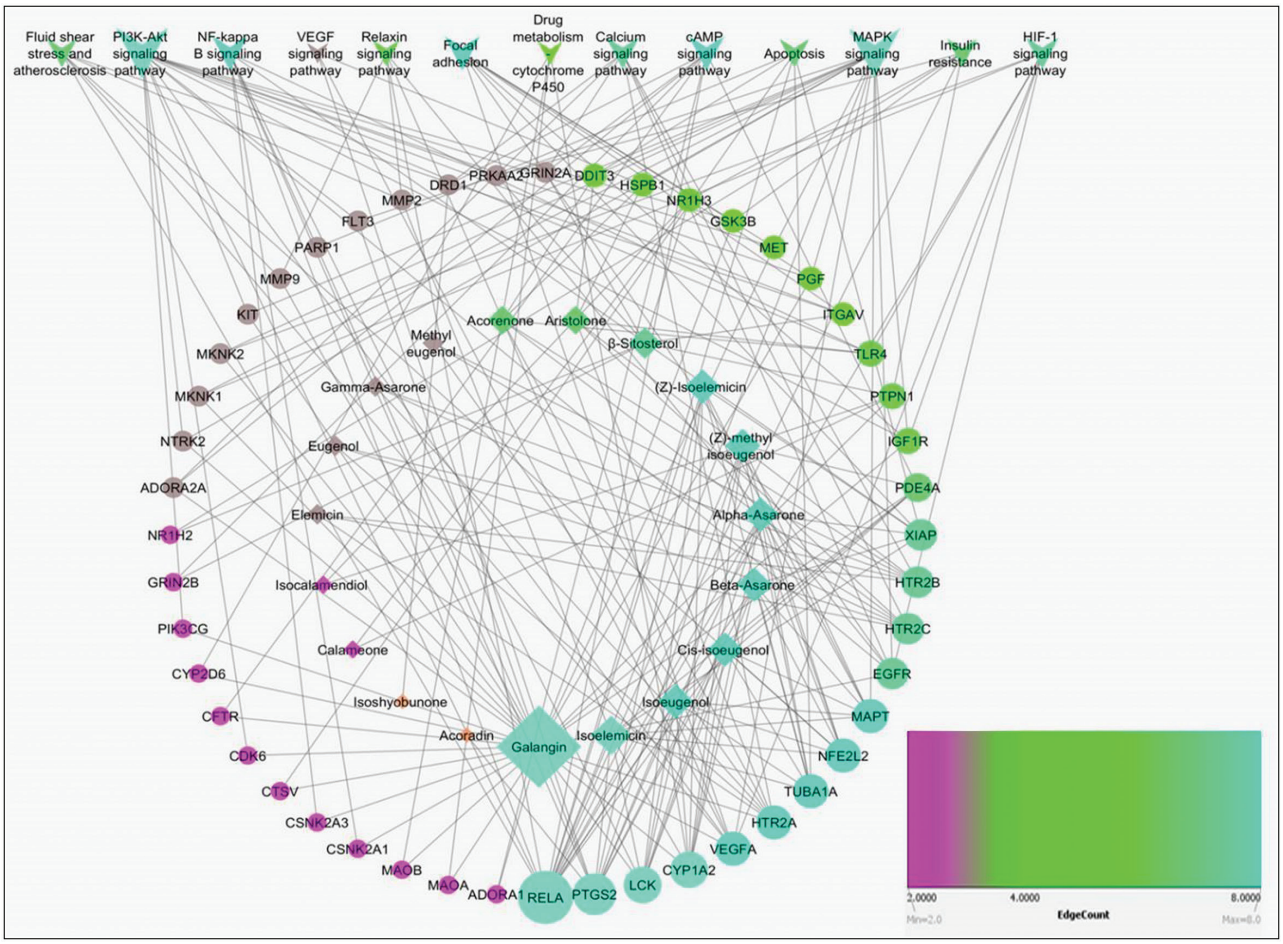

Figure 2: Represents network interaction between phytocompounds from *AC* with their modulated protein targets and pathways

Table 2: Binding energy and interaction of phytocompounds with enriched disease targets

Compound name	Molecular weight	Molecular formula	PubChem CID	Target names	Binding energy (kcal/mol)
Galangin	270.24	C15H10O5	5281616	**CYP1A2**	**–10.2**
				VEGFA	–6.1
				PTGS2	**–9**
				LCK	–7
				RELA	–6.7
Beta-asarone	208.25	C12H16O3	5281758	CYP1A2	–5.1
				VEGFA	–4.6
				PTGS2	–5.2
				LCK	–4.9
				RELA	–5
Isoelemicin	208.25	C12H16O3	5318557	CYP1A2	–5.8
				VEGFA	–4.3
				PTGS2	–5.7
				LCK	–5.2
				RELA	–5.3
Alpha-asarone	208.25	C12H16O3	636822	CYP1A2	–5.4
				VEGFA	–4.8
				PTGS2	–5.4
				LCK	–5.2
				RELA	–4.8

CYP1A2: cytochrome P450 1A2, LCK: tyrosine-protein kinase, PTGS2: prostaglandin G/H synthase 2, RELA, transcription factor p65, VEGFA: vascular endothelial growth factor A.
Bold values show the interactions score/Binding scores are good as compare to others

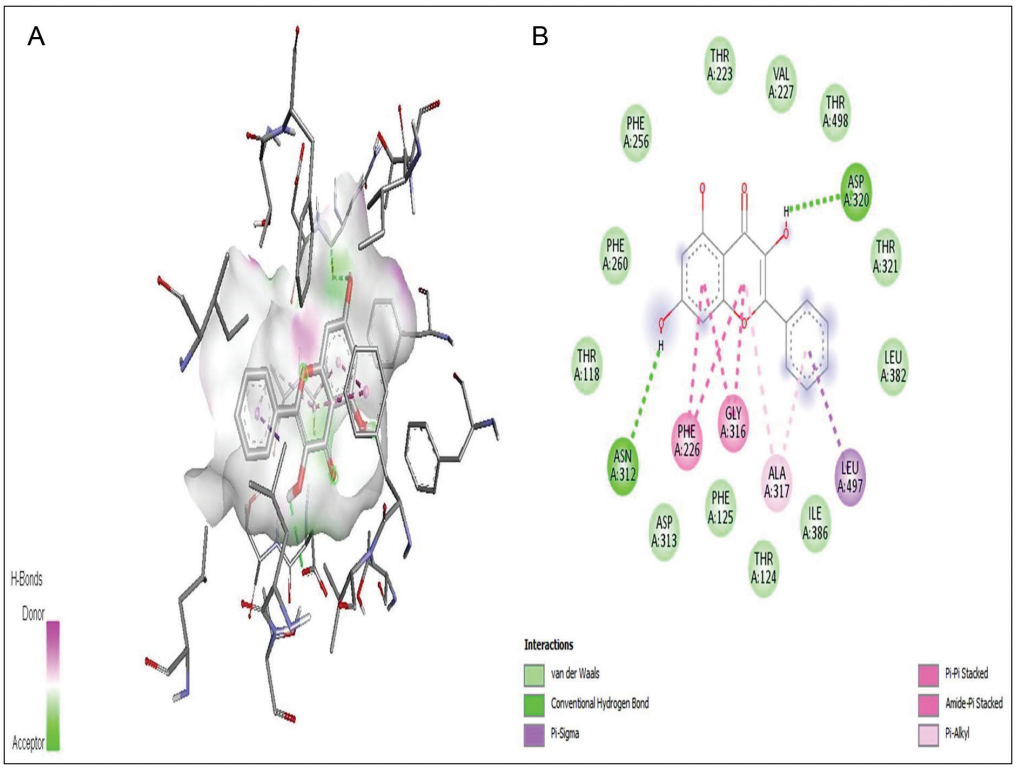

Figure 3: Interaction of galangin with CYP1A2. (A) binding mode representation and (B) 2D representation. CYP1A2: cytochrome P450 1A2, 2D: two-dimensional

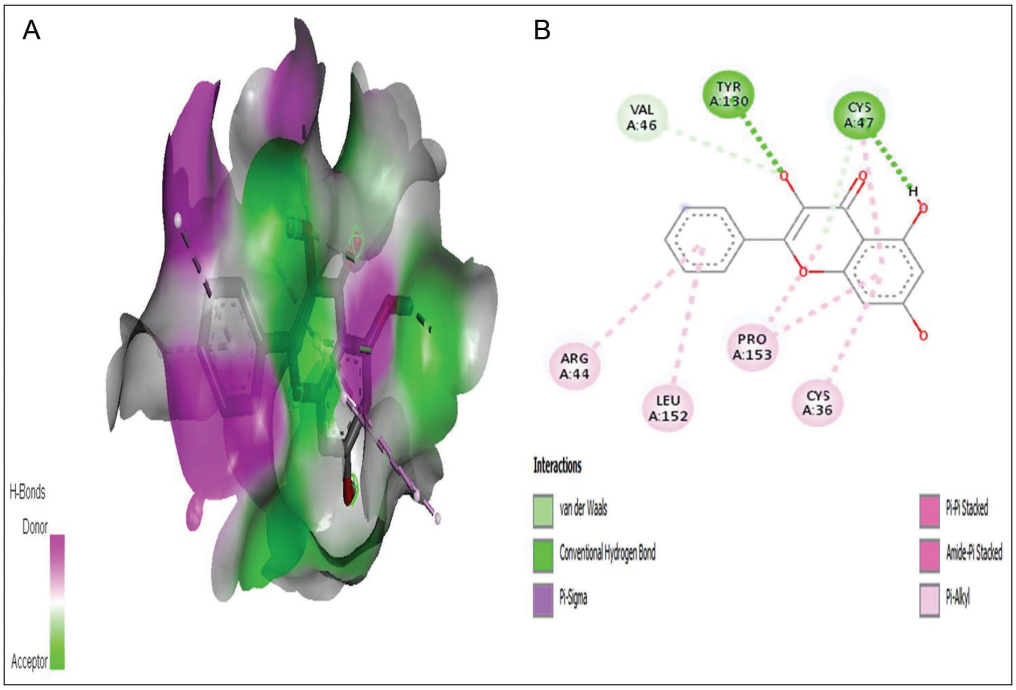

Figure 4: Interaction of galangin with PTGS2. (A) Binding mode representation. (b) 2D representation. PTGS2: prostaglandin G/H synthase 2, 2D: two-dimensional

induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis, and increases the permeability of blood vessels.[13] In this regard, a study found that VEGFA increases functions like angiogenesis, growth and vulnerability of plaques, intraplaque hemorrhage, inflammatory cell, erythrocyte recruitment, and coronary artery revascularization leading to IHD.[22]

Table 3: Phytoconstituent of *AC*-IHD targets-amino acids undergoing modulation on docking

Bioactive phytoconstituent	Targets	Amino acids undergoing modulation
Galangin	CYP1A2	LEU A: 497, ALA A:317, GLY A:316, PHE A:226
	PTGS2	VAL A:46, TYR A:130, CYS A: 47, CYS A: 36, PRO A:153, LEU A:152, ARG A:44

AC: *Acorus calamus* L., IHD: ischemic heart disease, CYP1A2: cytochrome P450 1A2, PTGS2: prostaglandin G/H synthase 2

LCK

LCK plays a role in reverse cholesterol transport (RCT). Studies have revealed that HSP65 inhibits RCT via an LCK-mediated pathway. Intracellular cholesterol transportation resulting from an immune-inflammatory response is well-established as one of the causes of atherosclerosis. Blocking LCK may provide a therapeutic approach to promote RCT and manage atherosclerosis.[23] A study found that raised LCK is an active marker candidate in diagnosing this serious heart disease.[24]

RELA

Also known as NF-κB, it is a target involved in arterial inflammation. RELA expression in endothelial cells (ECs) plays a role in arterial inflammation. It promotes focal arterial inflammation, as genetic deletion reduces expression and macrophage accumulation at an athero-susceptible site, leading to disturbed blood flow and arterial inflammation in endothelial cells, which influences atherosclerosis. RELA promotes vascular inflammation by inducing adhesion proteins and other inflammatory molecules in vascular ECs. Thus, it contributes to plaque formation in blood vessels and atherosclerosis.[13] A study found that an increase in NF-κB leads to the manifestation of atherosclerosis.[25] The research finding shows that the transcription factor NF-κB is inked to downstream target genes involved in atherosclerosis. It is a potential therapeutic target in treating atherosclerosis and related CVDs. Several biologics, small molecules, and peptides/proteins have been shown to regulate NF-κB dependent signaling pathways.

Conclusion

The results of this study show the network interactions between the predicted active phytoconstituents of *AC* and their probable targets and enriched pathways. Key phytoconstituents, such as galangin, alpha-asarone, beta-asarone, and isoelemicin, have modulatory activities on several pathways involved in IHD, including the calcium signaling pathway, fluid shear stress and atherosclerosis, MAPK signaling pathway, PI3K-Akt signaling pathway, NF-kappa B signaling pathway, HIF-1 signaling pathway, insulin resistance, relaxin signaling pathway, and VEGF signaling pathway, among others. Four compounds exhibit strong interactions with disease targets of IHD, namely PTGS2, CYP1A2, RELA, VEGFA, and LCK. The constructed network demonstrates that galangin, beta-asarone, and alpha-asarone have the highest edge count [Figure 3]. Molecular docking results show that galangin demonstrates an excellent binding affinity with targets like PTGS2 and RELA, which are important target proteins associated with IHD. These findings provide new insights into the potential action mechanism of *AC* phytochemicals in managing IHD.

Galangin, as a compound in *AC*, may serve as a new bioactive phytochemical due to its strong binding affinity with two major protein targets in the IHD pathway, contributing to its pathophysiology. This validates the role of *AC* as a single drug therapy for IHD associated with atherosclerosis. The *in silico* approach offers a reliable strategy for identifying potential therapeutic targets of drugs, which can guide the design of wet lab studies for validation through experimentation and aid in finding multi-compound management strategies for IHD.

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Conflicts of interest

There are no conflicts of interest.

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हिंदी सारांश

इस्केमिक हृदय रोग के लक्षित उपचार के लिए एकोरस कैलमस एल से बायोएक्टिव यौगिकों का सिलिको अन्वेषण: आण्विक अंतर्दृष्टि और चिकित्सीय संभावनाएं

पृष्ठभूमि: इस्केमिक हृदय रोग (आईएचडी) 80%-85% मृत्यु दर के लिए जिम्मेदार है, जो प्रभावी और गैर-आक्रामक प्रबंधन रणनीतियों को विकसित करने की आवश्यकता पर प्रकाश डालता है। लेखन कर्म (चिकित्सीय स्क्रैपिंग) असंतुलित कफ और मेदोधातु को संतुलित करने में मदद करता है, जो आईएचडी के रोगजनन में महत्वपूर्ण कारक हैं। वचा- एकोरस कैलमस लिन (एसी) चरक संहिता में वर्णित 10 लेखनीय औषधियों में से एक है और व्यापक रूप से उपलब्ध और लागत प्रभावी है। हालाँकि, इसके बायोएक्टिव फाइटोकंस्टिट्यूएंट्स की क्रिया का तरीका और आण्विक इकाइयां अज्ञात हैं। इसलिए, इस अध्ययन का उद्देश्य इसके बायोएक्टिव यौगिकों की क्रिया के तरीके और आईएचडी रोग के लक्ष्यों और मार्गों के साथ उनकी बातचीत को स्पष्ट करना है।

विधिया: एसी से फाइटोकेमिकल्स एकत्र किए गए, इसके बाद बायोएक्टिव फाइटोकेमिकल्स की स्क्रीनिंग, जीन पहचान और आईएचडी से संबंधित मार्ग एकत्र किए गए। बाद में, सामान्य यौगिकों और मार्गों की पहचान की गई, और फाइटोकेमिकल्स और मार्गों के बीच सामान्य लक्ष्यों को क्रमबद्ध किया गया। फाइटोकेमिकल्स-पथ-लक्ष्यों का एक और नेटवर्क बनाया गया, जिसके बाद अत्यधिक समृद्ध रोग लक्ष्यों और फाइटोकेमिकल्स की आण्विक डॉकिंग की गई।

परिणाम: सिलिको अध्ययन में पता चला है कि एसी के 19 मुख्य सक्रिय यौगिक आईएचडी में जैविक प्रक्रियाओं को विनियमित करने में शामिल 48 लक्ष्यों के साथ क्रिया (इंटरेक्शन) कर रहे हैं। रोग लक्ष्यों के साथ इन यौगिकों की क्षमता और आत्मीयता का पता लगाने के लिए आण्विक डॉकिंग विश्लेषण किया गया। गैलांगिन, अल्फा-एसारोन, बीटा-एसारोन और आइसोलेमिसिन ने आईएचडी रोग लक्ष्यों, जैसे प्रोस्टाग्लैंडीन जी/एच सिंथेज़ 2, साइटोक्रोम पी450 1ए2, ट्रांसक्रिप्शन फैक्टर पी65, वैस्कुलर एंडोथेलियल ग्रोथ फैक्टर ए और टायरोसिन-प्रोटीन काइनेज के साथ महत्वपूर्ण इंटरैक्शन प्रदर्शित की। इसके अतिरिक्त, अध्ययन में शीर्ष 4 फाइटोकेमिकल्स और पांच सबसे समृद्ध रोग लक्ष्यों के बीच परस्पर क्रिया की पहचान की गई।

निष्कर्ष: प्रस्तुत निष्कर्ष आईएचडी के उपचार के लिए AC में जैवसक्रिय फाइटोकंस्टिट्यूएंट्स को नवीन औषधि में रूपांतरित करने का एक आशाजनक मार्ग प्रदान करते हैं। इन सिलिको दृष्टिकोण चिकित्सीय लक्ष्यों की पहचान करता है, वेट लैब अध्ययन का मार्गदर्शन करता है, और आईएचडी के लिए बहु-यौगिक प्रबंधन में सहायता करता है।

शब्दकुंजी: आयुर्वेद, लेखन, आण्विक डॉकिंग, नेटवर्क फार्माकोलॉजी, वचा