Annals of Biology **42** (1) : 8-16, 2026 **http://agribioj.com** **Impact Score : 0.32 (Scopus)**

In-Silico Screening and Molecular Docking of *Cinnamomum verum* Phytochemicals Targeting the RyR2 N-Terminal Region in Ventricular Heart Arrhythmia

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(Received: November 20, 2025; Accepted: December 25, 2025)

ABSTRACT

Ventricular heart arrhythmia (VHAD) is a life-threatening cardiac disorder often associated with sudden cardiac death, underscoring the need for safer and more effective therapeutic alternatives. In this study, phytochemicals from *Cinnamomum verum*, a renewable and environmentally sustainable botanical resource, were investigated for their potential to modulate the N-terminal region of the ryanodine receptor 2 (RyR2), a key regulator of intracellular calcium release implicated in arrhythmogenic pathways. More than 40 phytochemicals were identified and evaluated using an eco-friendly, fully *in silico* workflow that involved molecular modelling, virtual screening and molecular docking. Among the screened compounds, Cinnzeylanol exhibited the most favourable binding affinity (“7.8 kcal/mol) and strong conventional hydrogen bonding with critical RyR2 n-terminal residues, having role in pathogenesis. These findings provide potential evidence for the therapeutic promise of natural lead molecule from *C. verum* for controlling aberrant calcium signalling associated with VHA.

Key words: Ventricular heart arrhythmia, drug likeliness, binding affinity, pharmacokinetic properties

INTRODUCTION

Cardiovascular diseases (CVDs) are a major cause of death across the world, with arrhythmias being a significant contributor to morbidity and mortality in affected individuals. Among these, ventricular heart arrhythmias (VHA) pose particularly critical risks, often leading to sudden cardiac death and requiring urgent intervention. Ventricular Heart Arrhythmia stimulates a complex of unusual coagulating signalling pathways (Minja *et al*., 2022). Degeneration of the vessels causes vasomotor hysteresis, leading to vessel-heart coupling and steering of heart-sided dysfunction (VHAD), which ultimately ends up in cardiomyopathies due to arrhythmias (Sossalla and Vollmann, 2018). Calcium release is mediated by large ion channels called Ryanodine (RyRs) from the sarcoplasmic reticulum that had been stored earlier. Mammalian structure, it has a RyRs homo-tetramerize352528 to form a mushroom-like 352528 large cytoplasmic head and a transmembrane stalk (Williams *et al*., 2018). Conventional antiarrhythmic agents often come with considerable side effects, prompting a search for safer, more effective alternatives, including natural products known for their therapeutic potential (Mohammadabadi and Jain, 2024). The sarcoplasmic reticulum (SR) of the ryanodine receptor (RyR)/calcium release an important source of calcium (Ca channel is^{2+}) that is essential for cardiac muscle activation and contraction coupling. The channel is a tetramer (FKBP12.6) of four type 2RyR polypeptides (RyR2) and four FK 506-binding proteins. The RyR2 phosphorylated by protein kinase A (PKA) dissociates FKBP12.6, which impacts the open channel. PKA

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hyperphosphorylation of RyR2 promotes defective RyR2 channels, resulting in the increased sensitivity to Ca 2+ dependent stimulation (Wang *et al.,* 2023). RyR2 is a membrane protein that is present in cardiac myocytes and acts as a transport medium of Ca^{2+} from the sarcoplasmic reticulum to the cytoplasm, which results in cardiac contraction. It is a 4,967 long amino acid sequence containing different domains at various sites responsible for the different functions of RyR2 in human myocytes (www.ncbi.nlm.nih.gov). RyR2 is vital for the stimulation of cardiac muscle contraction as a calcium channel that ensures the release of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm. Abnormal channel activation can lead to VHA (Steinberg *et al*., 2023). The ryanodine receptor 2 (RyR2), a key calcium release channel in cardiac myocytes, has emerged as a promising target for modulating calcium dynamics critical to maintaining cardiac rhythm (Ko *et al*., 2022). The N-terminal region of the RyR2 was instrumental in the activation of RyR2 by the CPVT mutation from 164-507 amino acids, named as DP_{cpvtN2} ($hRyR2^{410"438}$). This peptide represents the central helix of the N-terminal region i.e. fully conserved RyR2 channel in human, mouse and rat (Jiwani and Noheria, 2023). The amino acids 410-438 are susceptible to seven different mutations, which could result in arrhythmias and reduce the stability of NTR. Therefore, it seems possible that binding of DPcpvtN2 might impair the stability of RyR2 and so enhance channel opening (Faltinova *et al*., 2017). Thus, n-terminal region of the RyR2 has emerged as a potential target for the VHA. Compounds derived from *C. verum* possess pharmacological properties as per ethnopharmacological evidence that could be viable options for targeting N-terminal RyR2 for the treatment of VHA (Pathak and Sharma, 2021). However, a significant gap exists in exploring the specific interactions between these bioactive compounds and the RyR2, which could lead to new treatment avenues for arrhythmias. This work aimed at addressing the research problem of the insufficient understanding of the molecular mechanisms through which compounds from *C. verum* exert their effects on the ryanodine receptor and their potential therapeutic efficacy against ventricular arrhythmias. The primary objective was to utilize *in silico* screening and molecular docking techniques to identify and characterize the binding affinities of these compounds to the structure of n-terminal RyR2, thereby providing an evidence-based foundation for future pharmacological developments. The significance of this research lied not only in its potential to uncover novel therapeutic agents derived from traditional medicinal sources but also in its broader implications for the field of cardiovascular pharmacotherapy. By investigating the therapeutic properties of *C. verum* and their interaction with the RyR2, this study contributed to the ongoing efforts in natural product research and the quest for safer, more effective treatments for VHA.

MATERIALS AND METHODS

The sequence of the RyR2 was retrieved from NCBI's GenBank/UniProt with accession number NP_001026.2 and length 4967aa. According to the sequence analysis and literature reference reveals that the n-terminal region of the RyR2 has a potential role in the pathogenesis of VHA. The 3Dstructure of the N-terminal region of the RyR2 receptor was considered for further docking and screening with the phytochemicals retrieved from *Cinnamomum verum*.

N-terminal structure of RyR2 was predicted and analyzed based on the Energy Minimisation and ProSA-Web. The PrankWeb identified the potential binding site of the predicted RyR2 n-terminal structure: Ligand Binding Site Prediction and GHECOM: Grid-based HECOMi finder. Finally, the binding site amino acids were shortlisted based on the results and literature references.

Different phytochemicals from *C. verum* were accessed from the PubChem (*https://pubchem.ncbi.nlm.nih.gov/*). The ACD ChemSketch software Version 2020.2.1 was used to draw and optimise the photochemical structure. The format converter software Open Babel (Version 3.1.1) was run down for the molecular file format conversion. Further, the library of photochemical was subjected to docking-based virtual screening using PyRx software. It categorised the phytochemicals according to their binding affinity with the receptor. The compounds with the lowest

binding affinity (Kcal/mol) were chosen for further study.

Investigations were made using ADME (Absorption, Distribution, Metabolism, Excretion) and OSIRIS Properties Explorer to identify the pharmacological properties of different phytochemicals. Lipinski's rule, molecular weight, H-bond acceptor and donor, ClogP, drug likeness and drug score were evaluated. Software also determined whether the chemicals had mutagenic, tumorigenic, irritating or reproductive effects. Other analyses were performed, such as drug likeness, drug score, water solubility, topological polar surface area (TPSA), and molecular weight. The partition coefficient between n-octanol and water, log (Coctanol/Cwater), was used by the software to calculate the hydrophilicity of compounds. Compounds with a clog P< 5.0 were expected to be well absorbed because high scores point to low absorption. Blood-brain barrier formation and function were investigated. It was a valuable predictor of the behaviour of drugs in transit. The water solubility affected drug's absorption low solubility associated with poor distribution. AutoDock Vina once again validated the drug potential for ligand compounds approved after screening. The docking complexes of interest were selected and visualised with Discovery Studio Visualizer. AutoDock Vina, the flexible molecular docking software, docked a ligand molecule to a receptor in a dozen ways. After verifying a few distance interactions to the binding site residued, the lowest binding energy optimum mode was selected.

RESULTS AND DISCUSSION

Phytochemicals found in *C. verum* were identified, designed, optimised and screened by docking for the best photochemical that can suppress the arrhythmic manifestations brought on by mutations in RyR2 n-terminal region.

The sequence of the RyR2 was retrieved from the NCBI's GenBank/UniProt database with accession number NP_001026.2, with the N-terminal region from 1-606 amino acids (Table 1). Different conserved regions present in the sequence were retrieved from the SMART and InterProdata bases (Fig. 1). In the N-terminal region, the MIR domain was predicted to range from 110-165aa, 225-280aa, 286-343aa and 351-408aa. The MIR was the combination of three proteins, i.e. Mannosyltransferase, Inositol 1,4,5 trisphosphate Receptor (IP3R) and Ryanodine Receptor (RyR). Inositol 1,4,5-trisphosphate (InsP3) was an intracellular second messenger that regulated responses to growth factors and neurotransmitters. InsP3 triggered the release of Ca^{2+} from intracellular stores through its interaction with specific Ca^{2+} channel-associated receptors. Ryanodine SRCA2 communicated in muscleocytes of the heart. The receptors and T-tubule/ proteins functioned as Ca^{2+} release channels following depolarisation of the transverse tubules (Fowler and Zissimopoulos, 2022). Further, the mir_2 signature i.e. Ryanodine receptor signatures, was predicted by the SMART database. The RyDR_ITPR domained from 455-605 aa was a Ryanodine (RyR) and Inositol 1,4,5-trisphosphate (IP3) receptor were intracellular Ca^{2+} release channel. The RIH (RyR and IP3R Homology) domain was an extracellular domain from these two types of calcium channels. Thereafter IP3 represented receptor type 1 binding core, RIH domain from 409-547 aa. The number of other conserved regions and amino acids (240aa, 241aa, 348aa and 399aa), in the N-terminal region of the RyR2, represented its potential role in the pathogenesis, as the potential Ca^{2+} channel gets affected in the progression of disease. The crystal structure of the N-terminal region of RyR2 (PDB ID: 4JKQ) was retrieved from the RCSB PDB database (*www.rcsb.org*). After refinement, the RyR2 structure was energy minimised by the steepest descent method and validated the structure by the PROCHECK validation server.

To identify the N-terminal region binding site of RyR2, the top five cavities were predicted by PrankWeb and GHEECOM server (Fig. 2). Finally, the key amino acids ILE-419, ARG-420, LEU-565, LEU-572, etc. which were the part of binding site1, had been identified based on the

Table 1. Ryanodine receptor 2 sequence information

Recommended name	Ryanodine receptor 2
NCBI Accession number	NP_001026.2
Encoding gene	RyR2 gene
Protein symbol	Q92736-RYR2_HUMAN
UniPROT ID	Q92736
Protein length	4967aa
Molecular weight	564567 Da
N-terminal region	1-606 aa

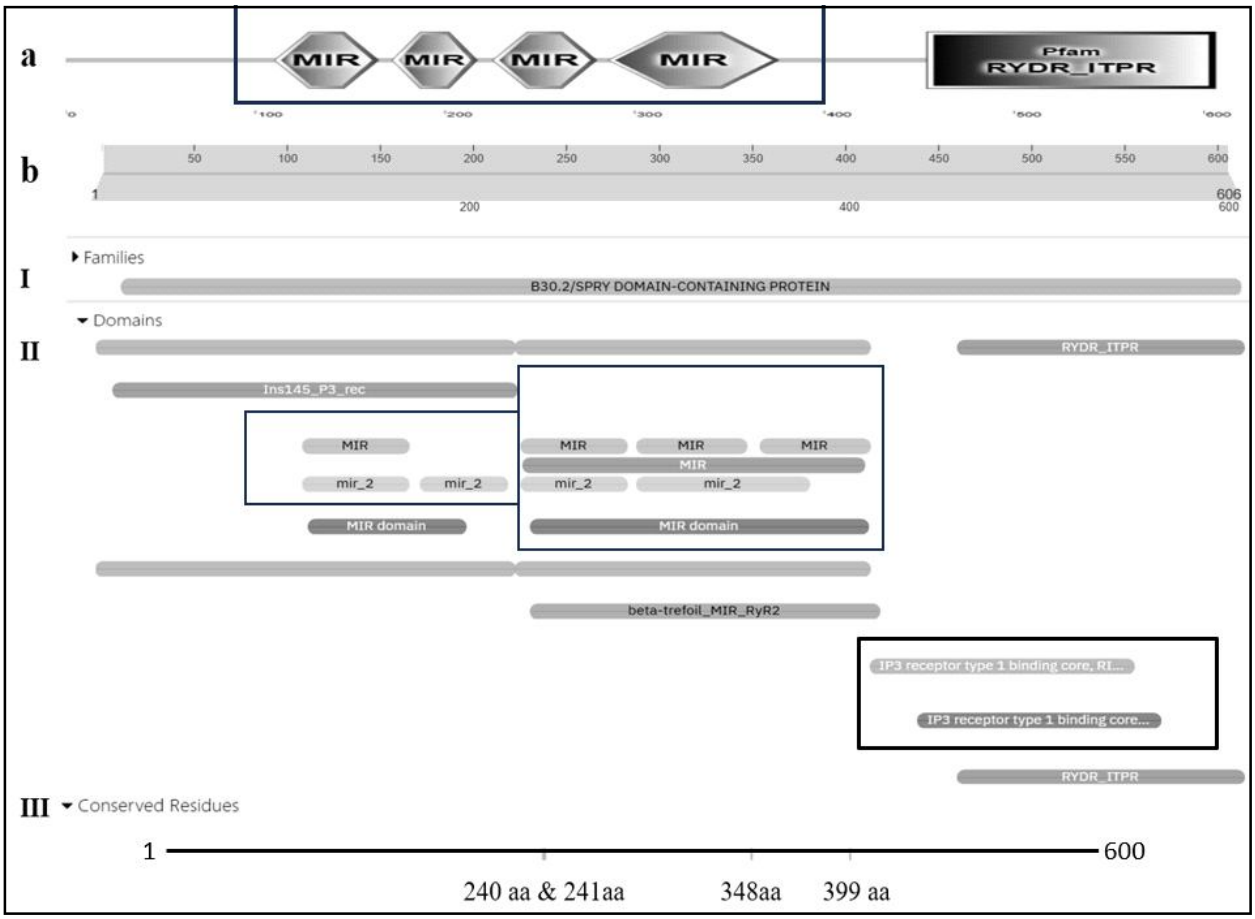

Fig. 1. RyR2 n-terminal motif, domain and family prediction comparative representation. (a) SMART database result and (b) InterPro result.

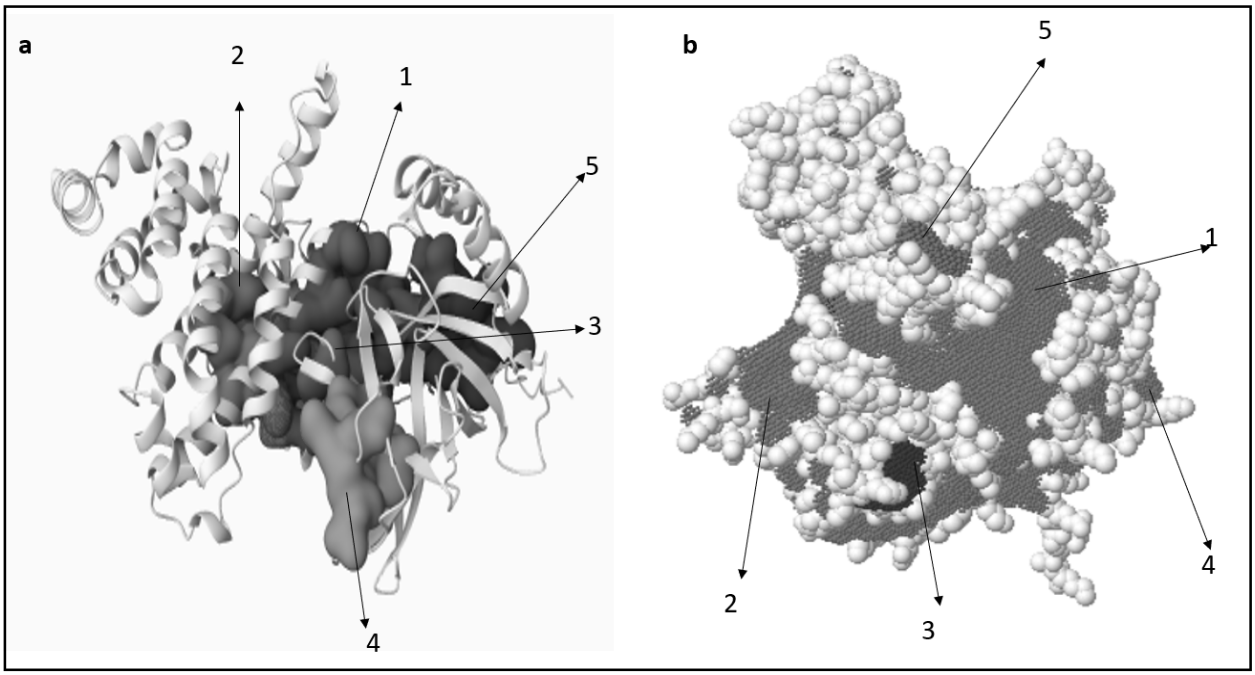

Fig. 2. Top five cavities for ligand binding site in n-terminal RyR2 protein (a) PrankWeb: Ligand binding site prediction and (b) GHECOM Server binding sites.

above-mentioned tools and literature references (Faltinova *et al*., 2017).

The structures of the different phytochemicals from *C. verum* were designed by the ChemSketch (ACD/Labs Version 2020.2.1) (Table 2), which were stored in mol2 format, and after optimisation, all the chemical structures were translated from mol2 topdb format using Open Babel Software (Version 3.1.1). The grid dimensions (¢) X = 1.4749 +!, Y = -0.0278 +!, Z = 2.2913 +! of the RyR2 n-terminal target protein were identified by the AutoDock software. Further, the PyRx software was used for the screening of the library of phytochemicals/ligand molecules in PDB format for docking-based screening against the RyR2 n-terminal region as the target protein with the same grid dimensions. Thereafter, the phytochemicals with binding energy greater than 6 kcal/mol were used for further binding site amino acids and bonding analysis. Based on the above analysis, binding energies of the cinnzeylanol i.e. -7.8 kcal/mol and caffeic acid -6.3 kcal/mol were selected for

Table 2. Phytochemicals retrieved from the *C. verum*

S. No.	Class of compound	Name of phytocompound and pubchem ID	Part of the plant from where extracted	Molecular formula	Molecular weight (g/mol)
1.	Aldehyde	Cinnamaldehyde (637511)	Bark of stem	C9H8O	132.16
2.		Hydrocinnamic aldehyde (7707)	Bark of stem	$C_9H_{10}o$	134.17
3.		Benzaldehyde (69884)	Stem and root	C11H16O2	180.24
4.		Vanillin (1183)	Bark of stem	$C_8H_8O_3$	152.15
5.		Cuminaldehyde (326)	Bark of stem	$C_{10}H_{12}O$	148.2
6.		Benzene propanal (7707)	stem and leaf	$C_9H_{10}O$	134.17
7.		2-methyl, 3-phenyl, propanal (95593)	Bark of stem	$C_{10}H12O$	148.2
8.		Citronillalal (7794)	Bark of stem	$C_{10}H_{18}O$	154.25
9.	Alcohols	Cinnamyl alcohol (5315892)	stem and leaf	$C_9H_{10}O$	134.17
10.		±-Terpineol (17100l)	Bark of stem	$C_{10}H_{18}O$	154.25
11.		Linalool (6549)	Bark of stem	$C_{10}H_{18}O$	154.25
12.		±–Bisabolol (442343)	Bark	$C_{15}H_{26}O$	222.37
13.	Esters	3-cinnamylpentane-2,4-dione 5282110	Leaf/root and stem	$C_{11}H_{12}O_2$	176.21
14.		Cinnamaldehyde diethyl acetatal 5356250	Bark of stem	$C_{13}H_{18}O_2$	206.28
15.		Methyl cinnamate (637520)	Bark of stem	$C_{10}H_{10}O_2$	162.18
16.		Ethyl cinnamate (637758)	Stem and leaf	$C_{11}H_{12}O_2$	176.21
17.		Hydrocinnamyl acetate (31226)	Stem and leaf	$C_{11}H_{14}O2$	178.23
18.		Eugenyl acetate (7136)	Bark of stem	$C_{12}H_{14}O_3$	206.24
19.		Benzyl benzoate (2345)	Bark of stem	$C_{14}H_{12}O_2$	212.24
20.	Phenols	Eugenol (3314)	Bark of stem	$C_{10}H_{12}O_2$	164.2
21.		Pyrogallol (1057)	Leaf	$C_6H_6O_3$	126.11
22.		Cinnamic acid (444539)	Bark of stem	$C_9H_8O_2$	148.16
23.		Ferulic acid (445858)	Bark and stem	$C_{10}H_{10}O_4$	194.18
24.		Caffeic acid (689043)	Bark of stem	$C_9H_8O_4$	180.16
25.		Gallic acid (370)	Root and stem bark	$C_7H_6O_5$	170.12
26.		Protacatechuic acid (72)	Leaf and root	$C_7H_6O_4$	154.12
27.		Oleic acid (445639)	Root and stem bark	$C_{18}H_{34}O_2$	282.5
28.		3-acetyl-4-hydroxy-benzoic acid 13071646	Bark of stem	$C_7H_5ClO_3$	172.56
29.	Monoterpenes	p- cymene (7463)	Bark and root	C10H14	134.22
30.		Limonene (22311)	Bark of stem	$C_{10}H_{16}$	136.23
31.		α – terpinene (7462)	Bark of stem	C 10H16	136.23
32.		α –Pinene (6654)	Stem bark and root	$C_{10}H_{16}$	136.23
33.		Camphene (6616)	Bark of root and stem	$C_{10}H_{16}$	136.23
34.		1-4, Cineole (10106)	Bark of stem	$C_{10}H_{18}O$	154.25
35.		β – Phellendrene (7460)	Leaf and stem bark	$C_{10}H_{16}$	136.23
36.	Diterpenes	Cinnzeylanine (6008559)	Bark of root and stem	$C_9H_{11}N$	133.19
37.		Cinnzelanol (44559448)	Bark of root and stem	$C_{20}H_{32}O_7$	384.5
38.	Sesquiterpenes	Alpha Humulene (5881520)	Bark of stem	$C_{15}H_{24}$	204.35
39.		Caryophyllene oxide (1752210)	Bark of stem	$C_{15}H_{24}O$	220.35
40.		β –Caryophyllene (5281515)	Bark of stem	$C_{15}H_{24}$	204.35

further analysis (Table 3). The binding site interactions based on the hydrophobicity, solvent assessable surface area, ionizability and H-bonding of caffeic acid and cinnzeylanol were identified (Figs. 3 and 4). The conventional hydrogen bonding revealed that the cinnzeylanol showed H-bonding with Arg-A298, Gly-A303, Lys-A:319 and AspA:61, the key amino acids involved in the binding site of the RyR2 n-terminal region, as compared to caffeic acid (Fig. 5). The virtual screening approach used in this study minimised the

Table 3. PyRx docking based screening of the phytochemicals from *C. verum* against RyR2 n-terminal region

S. No.	Ligand	Binding affinity (Kcal/mol)
1.	Caryophyllene oxide	-6.7
2.	Cinnzeylanol	-7.8
3.	Alpha Bisabolol	-6.3
4.	Alpha Humulene	-6.7
5.	Benzylbenzoate	-6.8
6.	Caffeic acid	-6.3
7.	Ferulic acid	-6.4

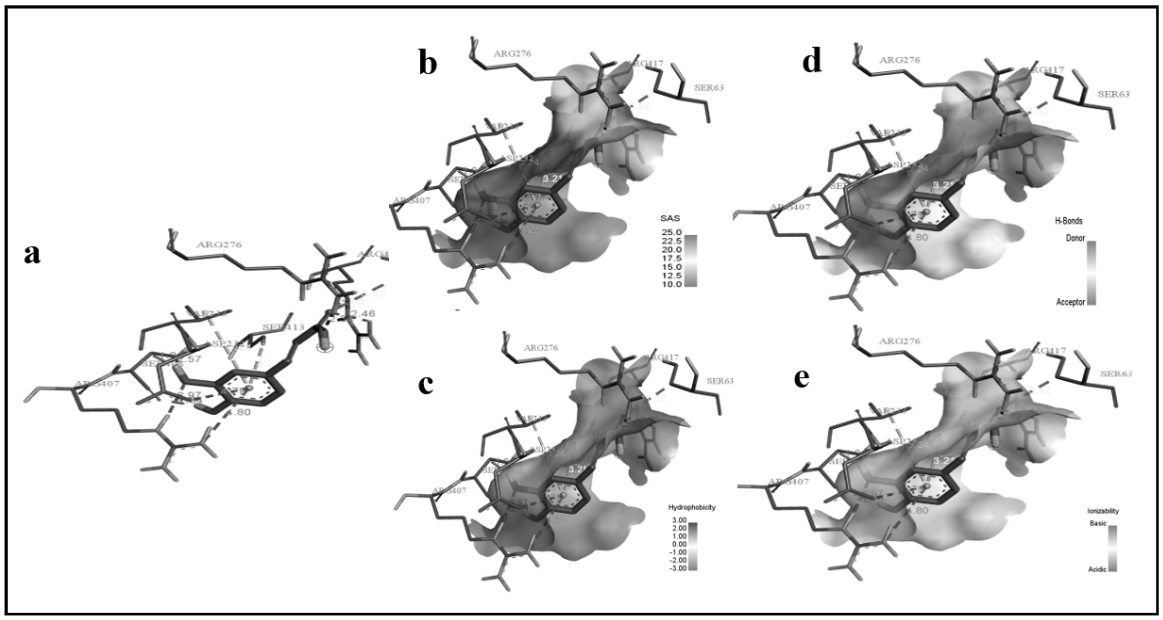

Fig. 3. Bonding interactions of n-terminal RyR2 with caffeic acid.

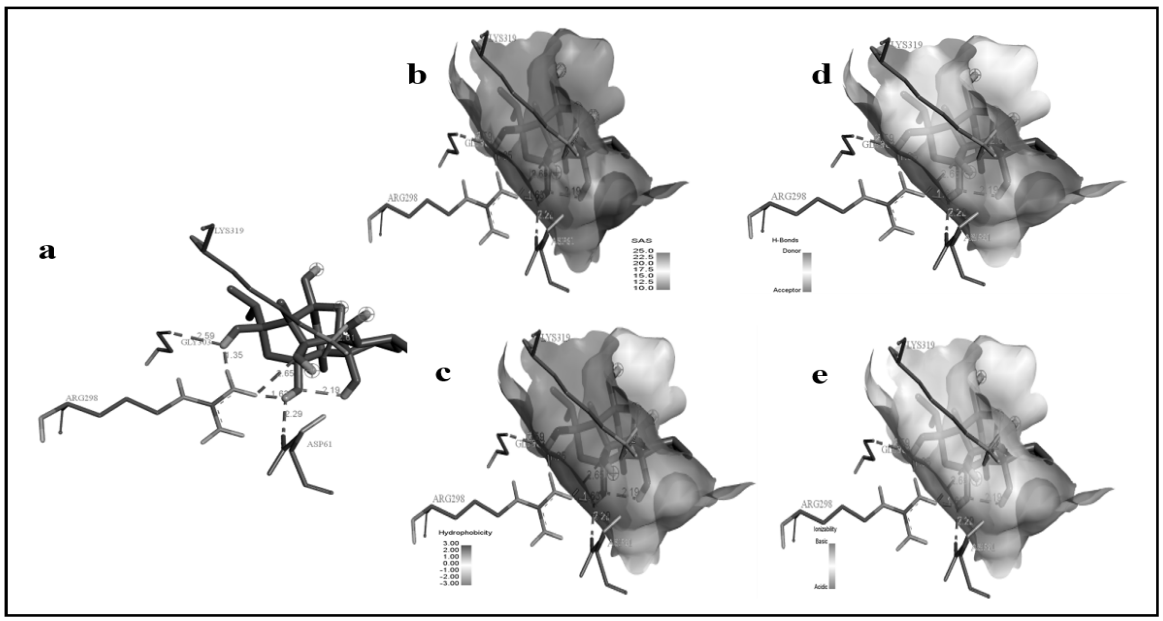

Fig. 4. Bondig interactions of RyR2 n-terminal with cinnzeylanol.

Table 4. Pharmacological properties of the phytochemicals from *C. verum*

S. No.	Name of the compound and pubchem ID	TPSA	Solubility (*ESOL*)	GI absorption	Log S value (all)	BBB permeant	Drug likeliness	Bioavailability score	Lipinski rule	H- Bond	LogPo/W (consensus)
1.	Benzyl benzoate	26.30 Å	1.27e-02 mg/ml; 5.98e-05 mol/l	High	-4.22	Yes	Yes	0.55	Yes; 0 violation	A-2 D-0	3.25
2.	Ferulic acid	66.76 Å²	1.49e+00 mg/ml; 7.68e-03 mol/l	High	-2.52	Yes	Yes	0.85	Yes; 0 violation	A-4 D-2	1.32
3.	Caffeic acid	77.76 Å²	2.32e+00 mg/ml; 1.29e-02 mol/l	High	-2.38	No	Yes	0.56	Yes; 0 violation	A-4 D-3	0.93
4.	Gallic acid	37.30 Å²	2.23e-02 mg/ml; 1.08e-04 mol/l	High	-3.97	Yes	Yes	0.85	Yes; 0 violation	A-2 D-1	3.00
5.	Cinnzeylanol	130.61 Å²	8.91e+00 mg/ml; 2.32e-02 mol/l	High	-1.43	No	Yes	0.55	Yes; 1 violation: NHorOH>5	A-7 D-6	0.31
6.	α-Humulene	0.00Å²	2.17e-02 mg/ml; 1.06e-04 mol/l	Low	-4.27	No	Yes	0.55	Yes; 1 violation: MLOGP>4.15	A-0 D-0	4.26
7.	Caryophyllene oxide	12.53 Å²	7.84e-02 mg/ml; 3.56e-04 mol/l	High	-3.51	Yes	--- Yes; 0 violationes	0.55	--- Yes; 0 violation	A-1 D-0	3.68

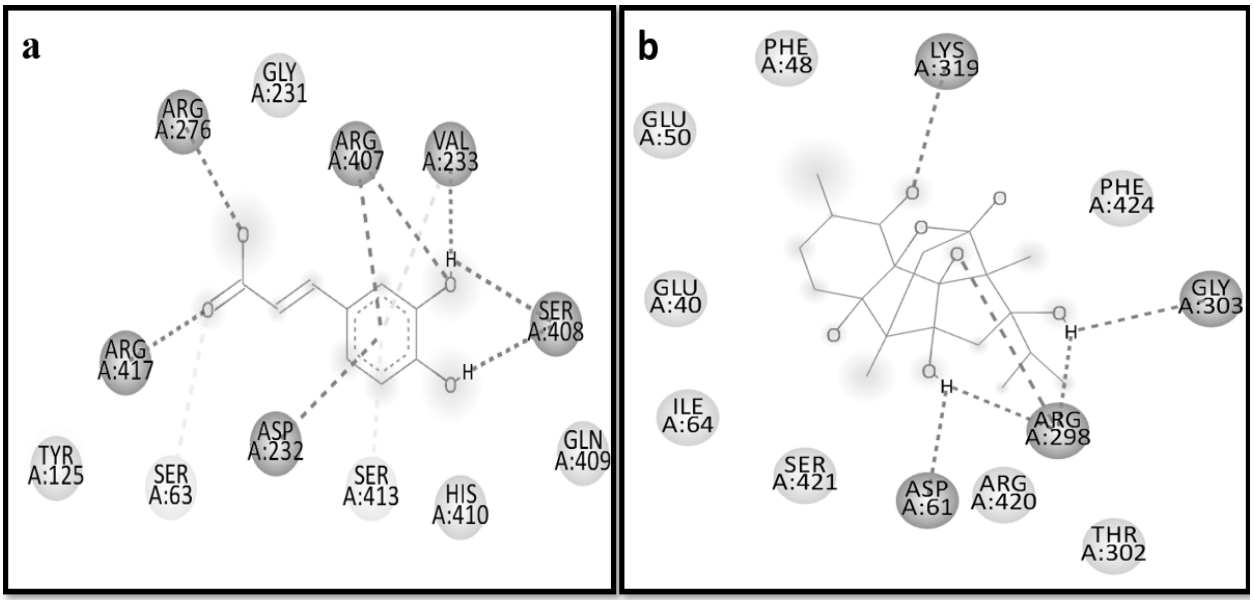

Fig. 5. 2D representation of interaction with RyR2 n-terminal. (a) Caffeic acid bonding interaction with RyR2 n-terminal (Conventional H-bonding: ARG276, ARG407, VAL233, SER408 and ARG417) and (b) Cinnzeylanol bonding interaction with RyR2 n-terminal (Conventional H-binding Arg298, Gly303, Lys319 and Asp61).

need for chemical synthesis and experimental screening, thereby reducing laboratory waste, solvent use and energy consumption. This computational workflow supported environmentally sustainable drug-discovery practices, which were particularly relevant when evaluating plant-derived molecules for large-scale pharmaceutical interest.

ADMET analysis, drug likeness, cLogp, solubility and molecular weight analysis revealed that caffeic acid with molecular weight 180.16 g/mol and Cinnzelanol with molecular weight 133.19 g/mol showed 0.83 and 0.77 overall drug score with favourable clogp value, solubility " 2.56, drug likeness score 1.9 as shortlisted based on the potential interactions with the n-terminal RyR2 target protein. Based on the drug likeness, cLogp value, solubility, molecular weight, Lipinski rule, drug score and toxicity risks, of the phytochemical overall frequency to qualify as a drug candidate is shown in Table 4.

Among all tested compounds, cinnzeylanol exhibited the strongest binding affinity ("7.8 kcal/mol) and formed multiple key interactions with residues Arg298, Gly303, Asp61 and Lys319 within the RyR2 N-terminal region. These residues are known to contribute to RyR2 stability. Strong binding at these positions indicates that cinnzeylanol may stabilise the receptor conformation and reduce aberrant calcium release, a major contributor to ventricular heart arrhythmia.

CONCLUSION

The findings from the docking-based screening and pharmacokinetic analysis indicated that cinnzelanol, a phytochemical from *C. verum*. forms strong and stable interactions with key residues in the N-terminal region of RyR2 (Arg298, Gly303, Lys319 and Asp61), suggesting it as a potential lead compound for modulating pathogenic pathways involved in ventricular heart arrhythmia. Further, it can be verified through *in vitro* and *in vivo* studies.

ACKNOWLEDGEMENT

The authors sincerely acknowledge Dr. Ajay Kumar Mahato, Staff Scientist and Head, Lab of Genome Informatics, Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad, for his valuable support and guidance in the analysis of this study.

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