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INSILICO APPROACH ON SCREENING THE PHYTOCONSTITUENTS OF *TINOSPORA CORDIFOLIA* IN INHIBITION OF CGAS-STING MEDIATED ATHEROSCLEROSIS

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ABSTRACT

Ischemic heart disease (IHD) being a leading global cause of mortality, primarily due to atherosclerosis and thrombus formation in coronary arteries. Atherosclerosis is a chronic immunoinflammatory condition characterized by lipid accumulation and plaque formation due to risk factors such as smoking, hypertension, diabetes, andlife style changes. Recent insights shown that the cyclic GMP-AMP synthase (cGAS)–Stimulator of Interferon Genes (STING) pathway have being a pivotal role in initiating inflammatory responses that contribute to plaque formation. *Tinospora cordifolia*, a herb widely used in Indian System of Medicine, is known for its diverse pharmacological properties including anti-inflammatory, antioxidant, and immunomodulatory effects. This study investigates the potential phytoconstituents of *T. cordifolia* to inhibit STING-mediated inflammatory signaling involved in atherosclerosis. Using molecular docking techniques, various bioactive compounds from *T. cordifolia* were screened against the STING protein (PDB ID: 4KSY). The docking results demonstrate strong binding affinities of selected phytoconstituents to key amino acid residues of STING. These finding suggesting a novel phytochemical therapeutic agent for the prevention and management of atherosclerosis.

KEYWORDS: Atherosclerosis, Stimulator of Interferon Genes (STING), *Tinospora cordifolia*, Docking study.

1. INTRODUCTION

Ischemic heart disease is the second leading cause of death globally.[1] Various Ischemic heart disease include angina (temporary pain), arrhythmias (irregular heart beat), myocardial infarction (permanent heart muscle damage) and heart failure (loss of muscle activity). The root cause for these heart diseases is reduced blood supply to the heart muscles due to the blockage of coronary arteries by atherosclerosis and thrombus.[2,3]

Atherosclerosis (AS) is an inflammatory disease of the arteries associated with immune response. AS is characterized by the accumulation of lipids, fibrous elements and cellular debris in the inflamed blood vessels.[4]Risk factors such as smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity and certain pathogenic infections like chlamydia will accelerate the process atherosclerotic plaque formation in the coronary arteries.[5,6]

Cyclic GMP-AMP synthase (cGAS) is an activator for Stimulator of Interferon gene (STING) which is also responsible for atherosclerosis plaque formation. In normal physiological condition, Cyclic GMP-AMP synthase (cGAS) remains in an inactive state. Cellular damage due to risk factors will trigger cGAS mediated STING pathway. Activation of STING gene associated with the coronary arteries produces the inflammatory response which leads to accumulation of foam cell and lipids forms atherosclerotic plaque.[7,8,9]

*Tinospora*genus comprise of approximately 34 species distributed over the tropical and subtropical regions of Asia, Australia, and Africa.[10,11] *Tinospora cordifolia*, a significant herb in Indian System of medicine recognized for its bioactive components and numerous therapeutic properties, in comparison to other species of *Tinospora*. The herb is commonly used to treat jaundice, rheumatism, urinary diseases, skin conditions, anemia, inflammation, allergic condition, radioprotective properties and also it possessanticancer, antidiabetic, analgesic, immunomodulatory, antioxidant, antiulcer, antibacterial, antipyretic, and nephroprotective.[10,12,13]

Current study focus on identifying the active herbal constituents of *Tinospora cordifolia* in inhibition of STING mediated inflammatory response involved in atherosclerosis using molecular docking. Various active constituents of *Tinospora cordifolia* was docked against STING target (PDB ID: 4KSY) and studied for their atherosclerotic inhibitory activity by blocking the inflammatory response, a root cause of atherosclerosis. Docking study reveals that phytoconstituents has a prominent inhibition on STING by binding with the active amino acid and blocking its stimulatory response.

2. MATERIALS AND METHODS

2.1 cGAS –STING mechanism in atherosclerosis

cGAS is activated by double stranded DNA released from dying cells, DNA viruses or bacteria and damaged mitochondrial DNA. Activation of cGAS will stimulates the innate immune response (inflammation) by trigering the STING present in endoplasmic reticulum of the cell. In general STING is activated by cyclic GMP-AMP, a secondary messenger synthesised by cyclic GMP-AMP synthase (cGAS). Activated STING migrates from the endoplasmic reticulum to golgiapparatusand bind with TBK1. After binding TBK1 phosphorylate the STING and forms complex which inturn stimulates the inflammatory response. This ends with accumulation of fats over the inflammed region (coronary artery) and forms atherosclerotic plaque, there by affects the blood flow. The complete cGAS –STING pathway is given in the (Figure- 1).[7,14,15,16]

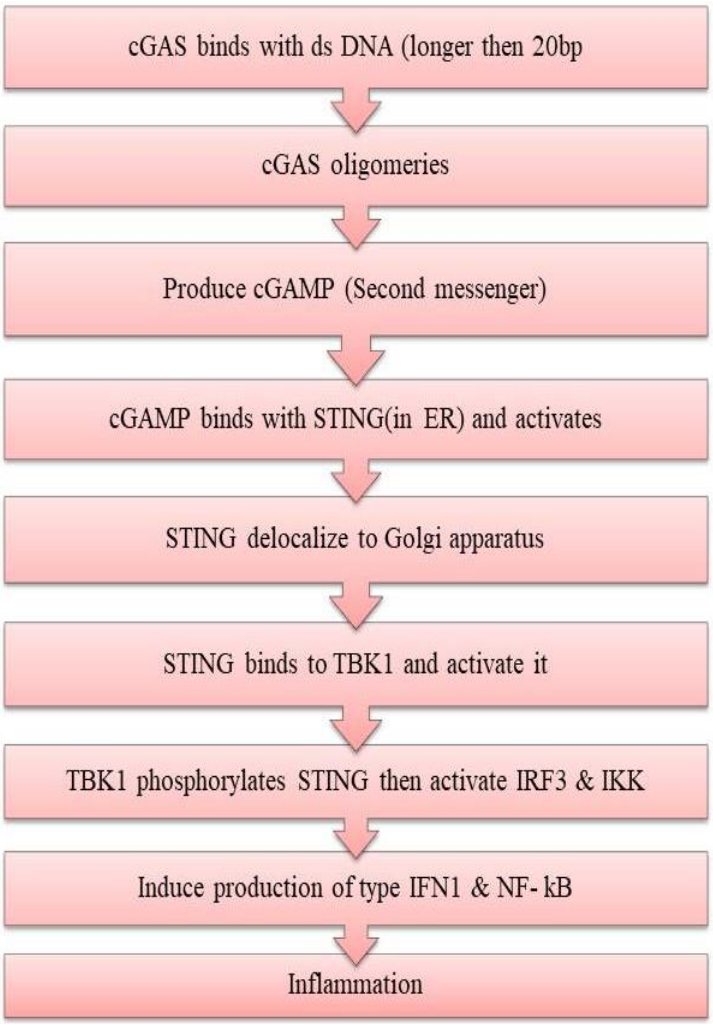


Figure 1: Role of STING in atherosclerosis (cGAS – Cyclic guanosine monophosphate-adenosine monophosphate synthase, ER- endoplasmic reticulum, TBK1 – TANK binding kinase1, IRF3- Interferon regulatory factor 3, IKK- IκB kinase, IFN1-Type 1 interferon, NF-kB – nuclear factor kappa B).

2.2 Plant profile

Species: *Tinospora cordifolia*

Kingdom: Plantae

Family: Menispermaceae

Group: Angiosperms

Common name: Gulbel

Synonymous names: Tinospora tomentosa, Tinospora malabarica, Tinospora cardifolia, Tinospora sinensis, Menispermum cordifolium

2.3 Data sources

In this study, active phytochemicals of *Tinospora cordifolia*were obtained from IMPPAT 2.0 a phytochemical database.[17,21]

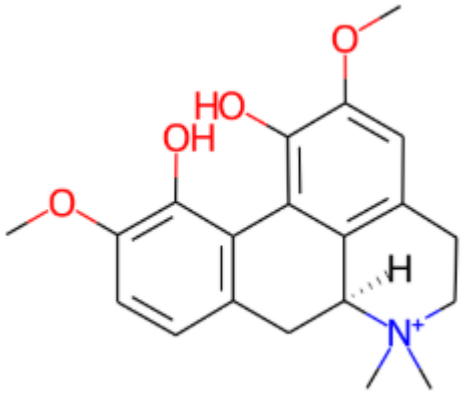
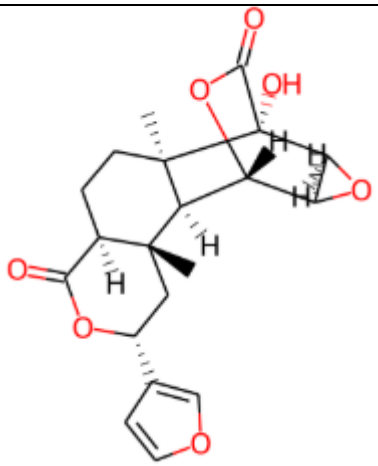
2.4 Preparation of Ligand

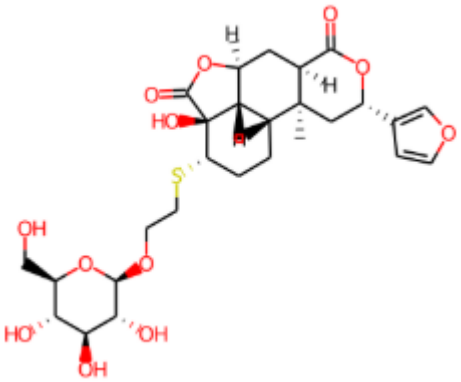
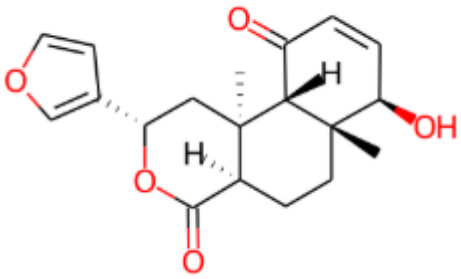
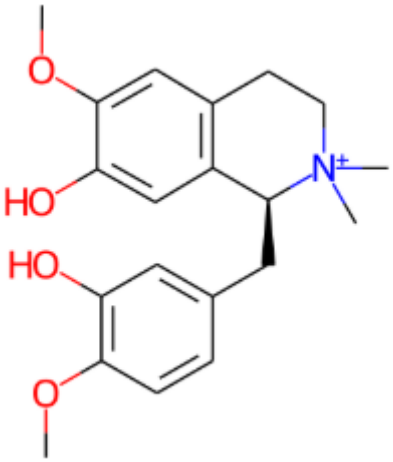
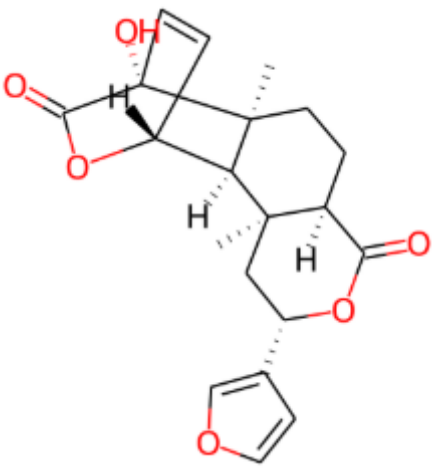
Biologically active phytochemicals present in *Tinospora cordifolia* were identified and selected for further analysis. Their chemical structures were retrieved from IMPPAT 2.0, a curated database of phytochemicals from Indian medicinal plants. Details of the selected phytochemicals are provided in Table-1, and their chemical structures used for docking are shown in Table-2. The phytoconstituents were downloaded in 3D PDB format from IMPPAT and converted to PDBQT format for docking purposes.

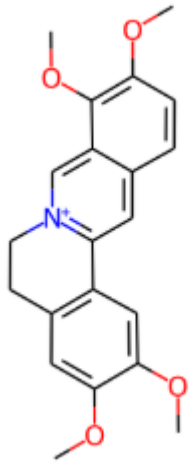
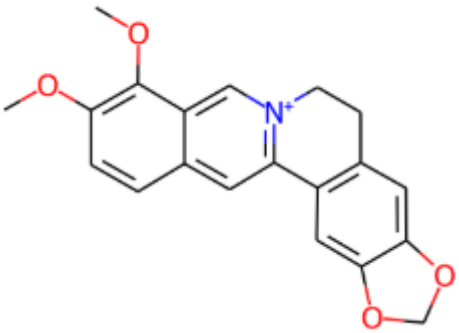
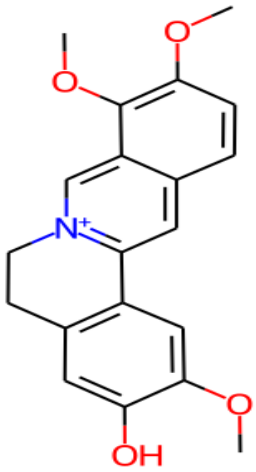
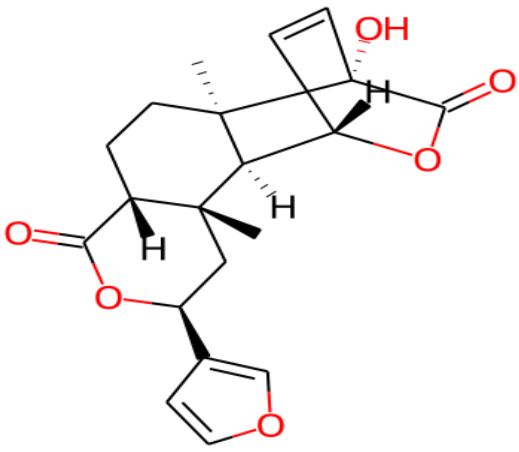
Table -1: Phytochemicals of *Tinospora cordifolia.*

S. No	Phytochemical name	IMPPAT ID	Synonymous chemical names
1.	Magnoflorine	IMPHY008905	Escholine, Escholine (Magnoflorine), Magno-Florine, Magnoflorine, Thalictrin, Thalictrine
2.	Palmarin	IMPHY011716	Palmarin, Tinosporide, Tinosporine
3.	Cordifolide A	IMPHY001347	Cordifolide
4.	Tinosponone	IMPHY001506	Tinosponone, Tinosporon
5.	Tembetarine	IMPHY005103	Tembetarine
6.	Tinosporin	IMPHY011836	Tinosporin
7.	Palmatine	IMPHY005330	Berbericinine, Gindarinine, Palmatine, Palmitine
8.	Berberine	IMPHY005665	Berbericine, Berberine, Umbellatine
9.	Jatrorrhizine	IMPHY007190	Jateorrhizine, Jatrorhizine, Jatrorrhizine
10.	Columbin	IMPHY011813	Unii-Kki91p85ge, Columbin.

Table 2: Chemical structure of selected phytochemicals of *Tinospora cordifolia* for molecular screening.

S. No	Phytochemical name	Phytochemical structure
1.	Magnoflorine	
2.	Palmarin	

3.	Cordifolide A	
4.	Tinosponone	
5.	Tembetarine	
6.	Tinosporin	

7.	Palmatine	
8.	Berberine	
9.	Jatrorrhizine	
10.	Columbin	

2.5 Preparation of protein

The STING protein structure complexes with Cyclic GMP-AMP (cGAMP) with a **PDB ID: 4KSY** was downloaded from the RCSB Protein Data Bank in PDB format. Before analysis or docking, the charge assignment, solvation parameters and fragmental volumes to the protein was done using the Autodock Tool 4 (ADT) . The protein molecule was further optimized using Autodock Tool for the molecular docking.

2.6 Docking studies

Molecular screening of the selected phytoconstituent was conducted using PyRx software, which is commonly used for docking the multiple ligands against the single target. During docking, ligands were treated as flexible, while the protein was kept rigid. Grid parameter configuration files were generated using the AutoGrid engine in PyRx. The software also helped to identify the active site amino acids involved in ligand interactions. Docking results with a positional root-mean-square deviation (RMSD) of less than 1.0 Å were considered ideal and clustered for analysis of favorable binding. The ligand with the most negative binding energy was deemed to have the highest binding affinity.[18,19,20]

The active site of STING (PDB ID: 4KSY) was identified based on information from the literature, Discovery Studio and the Protein Data Bank (PDB). To ensure accurate docking, the correct amino acid residues defining the target protein's binding site were selected for grid box configuration in PyRx. The center coordinates of the grid box used in this study were set at X: 35.7485, Y: 2.2525, and Z: -19.8946.the phytochemicals of *Tinospora cordifolia* was allowed to docked with the STING protein in which the dimension of the grid box is X:35.5576Å,Y:29.6831 Å, Z:36.9530 Å.

2.7 Prediction of ADME properties

The selected phytochemical compounds were exported in SMILES format to the SwissADME and pkCSM web servers for the prediction of toxicity and bioavailability. SwissADME and pkCSM are freely available online tools used to predict the pharmacokinetic properties and drug-likeness of small molecules. The predicted ADME (Absorption, Distribution, Metabolism, and Excretion) profiles of the phytochemicals are presented in Table-3.

Table 3: Predicted ADME properties of phytochemicals.

S. No	Phytochemical name	Lipinski's rule of 5	Bioavailability score	Blood Brain Barrier permeation	Gastrointestinal absorption
1.	Magnoflorine	Passed	0.55	Yes	High
2.	Palmarin	Passed	0.55	No	High
3.	Cordifolide A	Failed	0.17	No	Low
4.	Tinosponone	Passed	0.55	Yes	High
5.	Tembetarine	Passed	0.55	Yes	High
6.	Tinosporin	Passed	0.55	No	High
7.	Palmatine	Passed	0.55	Yes	High
8.	Berberine	Passed	0.55	Yes	High
9.	Jatrorrhizine	Passed	0.55	Yes	High
10.	Columbin	Passed	0.55	No	High

3. RESULT AND DISCUSSION

Atherosclerosis (AS) is a chronic inflammatory disease of the arteries, closely associated with immune system activation and dysregulated immune responses. STING mediated inflammatory response in the blood vessels can end in formation of atherosclerosis Our study was focused on identifying a potential phytochemical therapeutic agent for the treatment of STING mediated atherosclerosis using computational method.

The drug-likeness properties of the selected phytochemicals were predicted using SwissADME and the pkCSM web servers. The theoretical predictions indicate that all the phytoconstituents (except Cordifolide A) comply with Lipinski's rule of five, exhibit high gastrointestinal absorption and possess good bioavailability scores. Additionally, the phytochemicals Magnoflorine, Tinosponone, Tembetarine, Palmatine, Berberine, and Jatrorrhizine are predicted to have the ability to cross the blood–brain barrier.

Docking predicts the mode of interaction between a target protein and a small ligand for an established binding site. Binding energy suggests the affinity of a specific ligand and strength by which a compound interacts with and binds to the pocket of a target protein. A compound with a lower binding energy is preferred as a possible drug candidate.

The potential effects of the phytochemical compounds on the STING protein with PDB ID: 4KSY (Figure-2) is evaluated by molecular docking, performed using the PyRx virtual screening tool. Various phytoconstituents from *Tinosporacordifolia*, a widely used Indian medicinal plant, were screened to select the most promising compound. The selected phytoconstituents was docked against the STING protein (PDB ID: 4KSY) demonstrated favorable binding affinities with the target binding pocket.

In order to understand the effect of phytochemical compounds on STING, molecular docking of selected phytochemicals against STING was performed using PyRx virtual screening tool (Table-4) The target interacting amino acid to which cGAMP binds are ARG 238 and THR 263. Cordifolide A, palmarin and berberine exhibited most favoured binding affinity of -9.7,-8.9 and -8.5 Kcal/mol respectively.

Cordifolide A exhibits a highly promising binding affinity (-9.7 Kcal/mol) toward the target protein, interacting with amino acid residues ARG238, SER241 and TYR167 (Figure-3). However, its predicted ADME properties indicate violations of drug-likeness criteria. In contrast, Palmarin and Berberine demonstrate strong binding affinities (-8.9 and -8.5 Kcal/mol respectively) with ARG238 and TYR167 (Figure-4, 5). It also has shown a favorable drug-likeness profile. Jatrorrhizine and Columbin also display good binding affinities (-8.4 Kcal/mol). Notably, Jatrorrhizine formed a hydrophobic interactions with TYR167, whereas Columbinformed hydrogen bonds with ARG238 (Figure-6,7). Palmatine and Tinosponone exhibits the binding affinity (8.2 Kcal/mol) interacted hydrophobically and formed hydrogen bond with TYR 167 and ARG 238 amino acid residue of target protein respectively (Figure-8,9).

The molecular docking analysis in the present study showed the inhibition potential of selected phytoconstituents, ranked by binding affinity (ΔG); Cordifolide A > Palmarin > berberine >Jatrorrhizine and Columbin > Tinosponone and Palmatine >Tinosporin > Tembetarine >Magnoflorine.

Table 4: Molecular docking analysis of phytochemicals against STING (PDB ID: 4KSY).

S. No	Phytochemical name	Binding affinity (Kcal/mol)	No. of bonds	Bond distance (Å)	Bond category	Interacting amino acid residue
1.	Magnoflorine	-7.4	3	3.20159	Hydrogen	VAL 239
				3.39082	Hydrogen	SER 241
				4.19176	Hydrophobic	TYR I67
2.	Palmarin	-8.9	3	2.41037	Hydrogen	ARG 238
				2.08824	Hydrogen	ARG 238
				3.8582	Hydrophobic	TYR I67
3.	Cordifolide A	-9.7	4	2.61706	Hydrogen Bond	ARG 238
				1.82549	Hydrogen Bond	ARG 238

				3.12206	Hydrogen	SER 241
				3.91367	Hydrophobic	TYR 167
4.	Tinosponone	-8.2	3	2.71644	Hydrogen	ARG 238
				1.89718	Hydrogen	ARG 238
				2.88611	Hydrogen	THR 263
5.	Tembetarine	-7.9	3	3.49788	Hydrogen	VAL 239
				3.61879	Hydrogen	SER 241
				4.01685	Hydrophobic	TYR 167
6.	Tinosporin	-8.1	4	2.65093	Hydrogen	ARG 238
				2.12374	Hydrogen	ARG 238
				3.38178	Hydrogen	SER 241
				3.27917	Hydrogen	SER 241
7.	Palmatine	-8.2	2	5.06555	Hydrophobic	TYR 167
				4.80838	Hydrophobic	TYR 167
8.	Berberine	-8.5	2	2.51379	Hydrogen	ARG 238
				4.5077	Hydrophobic	TYR I67
9.	Jatrorrhizine	-8.4	2	4.36491	Hydrophobic	TYR I67
				5.67457	Hydrophobic	TYR I67
10.	Columbin	-8.4	2	2.15965	Hydrogen	ARG 238
				1.82064	Hydrogen	ARG 238

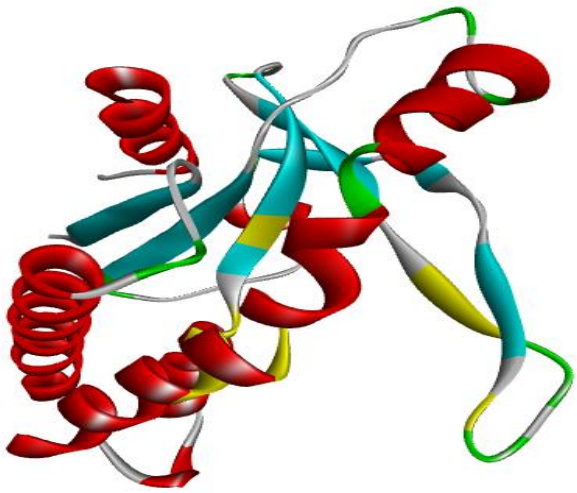


Figure 2: Crystal structure of STING protein with PDB ID: 4KSY.

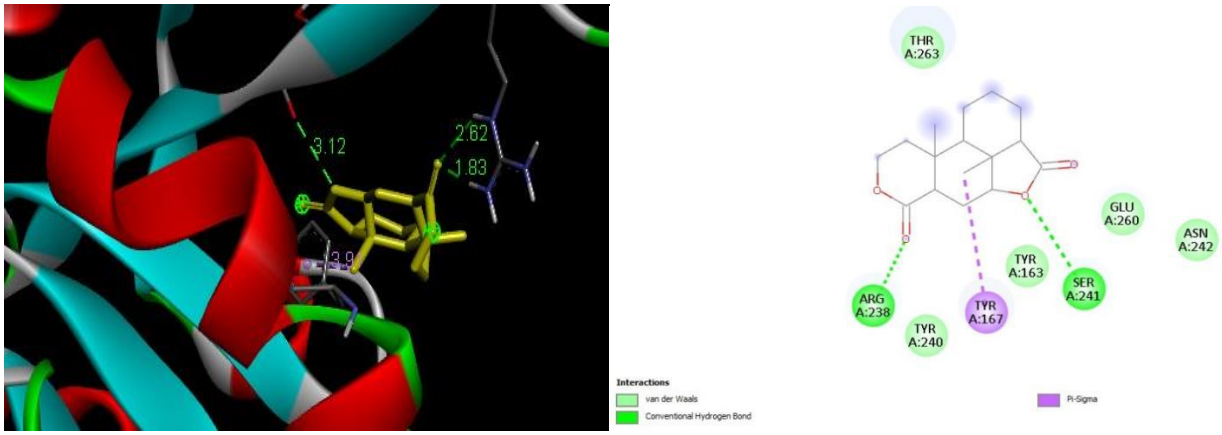


Figure 3: Molecular docking analysis between 4KSY and Cordifolide A showing interaction between the active site residues of the protein and ligand.

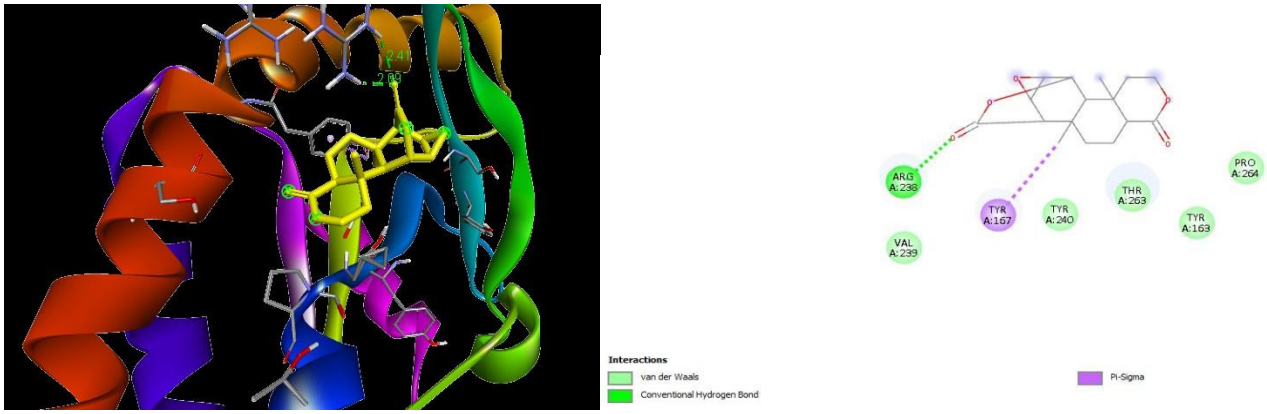


Figure 4: Molecular docking analysis between 4KSY and Palmarin showing interaction between the active site residues of the protein and ligand.

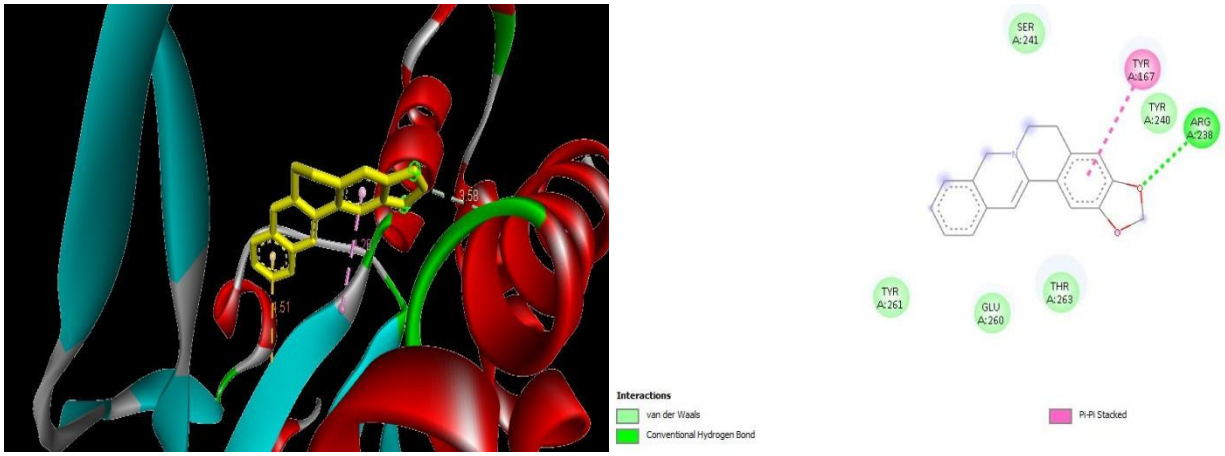


Figure 5: Molecular docking analysis between 4KSY and Berberin showing interaction between the active site residues of the protein and ligand.

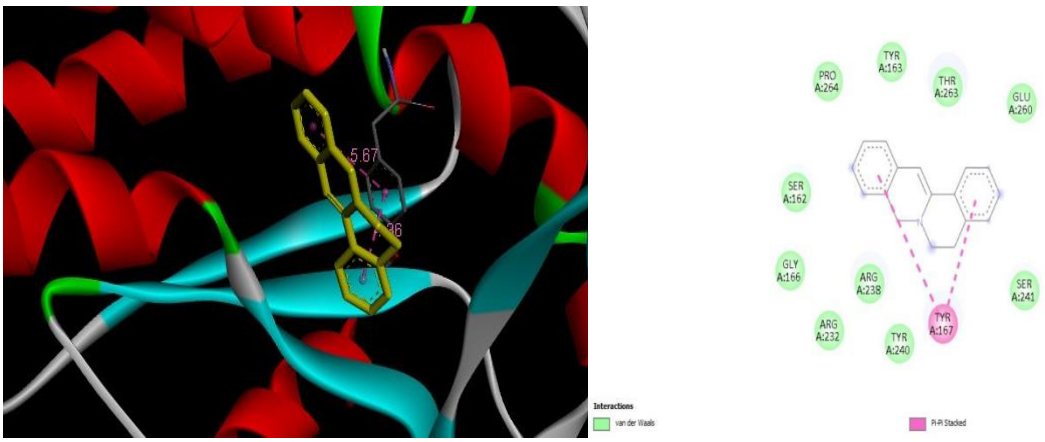


Figure 6: Molecular docking analysis between 4KSY and Jatrorrhizine showing interaction between the active site residues of the protein and ligand.

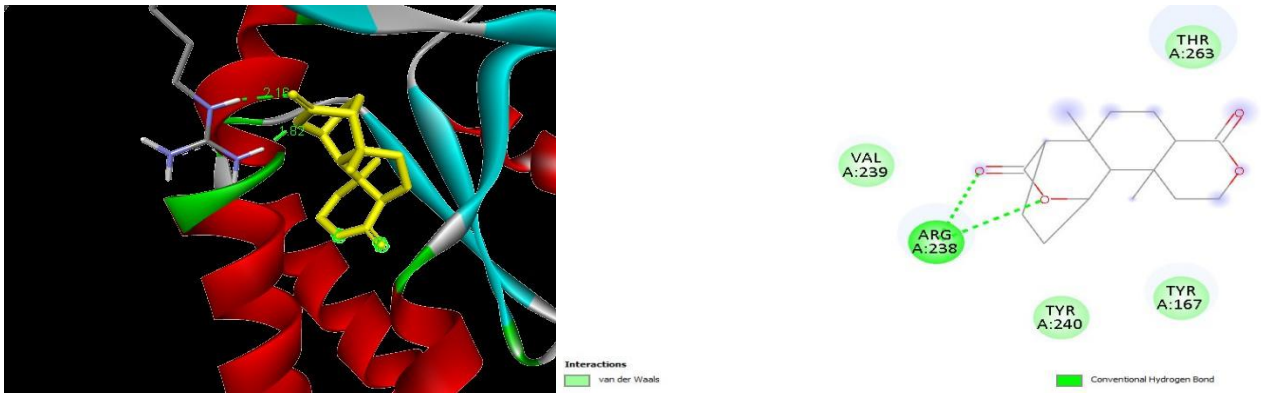


Figure 7: Molecular docking analysis between 4KSY and Columbin showing interaction between the active site residues of the protein and ligand.

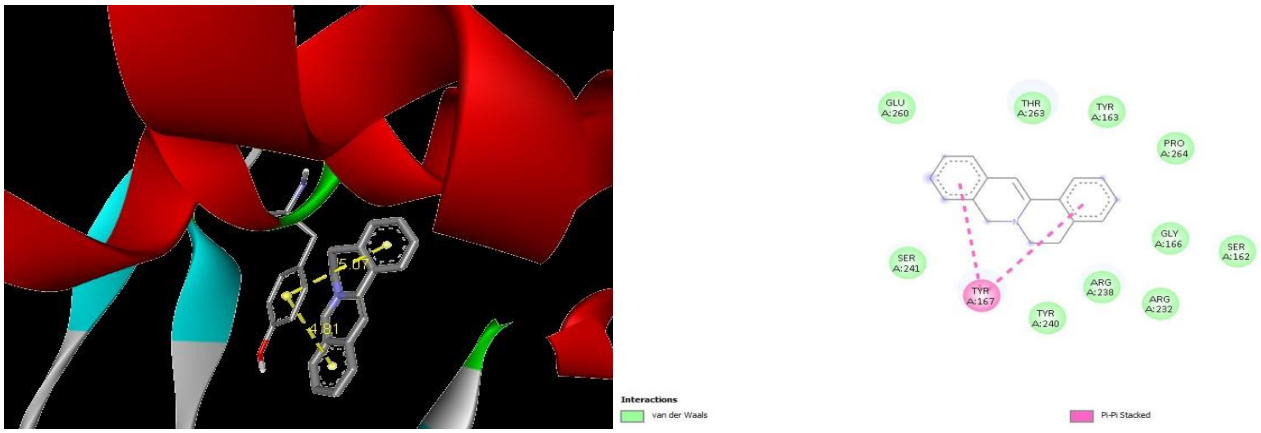


Figure 8: Molecular docking analysis between 4KSY and Palmatine showing interaction between the active site residues of the protein and ligand.

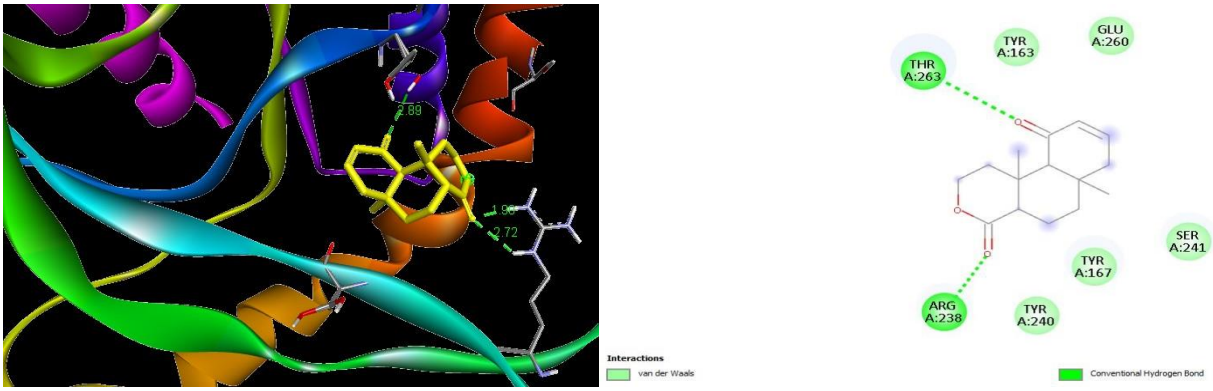


Figure 9: Molecular docking analysis between 4KSY and Tinosponone showing interaction between the active site residues of the protein and ligand.

4. CONCLUSION

In this study, PyRx and Autodock-Vina softwares were used to identify potent Phytochemical inhibitors against STING protein which play crucial role in inflammation mediated atherosclerosis. It is identified that Palmarin, berberin, Jatrorrhizine, Columbin, Tinosponone and Palmatine have most appropriate inhibition against STING Protein by binding to the binding pocket of cGAMP. There by inhibit the formation of inflammation mediated atherosclerosis, a

root cause of various ischemic heart disease. These phytochemicals will also comply with the drug-likeness property. STING inhibition will also prevent the immune mediated inflammation related illness. The findings suggest the potential phytochemical inhibitors against STING protein, which can be further explored to test the phytochemicals for invitro and invivo screening to make a well improved therapeutic agent.

REFERENCES

Statistic report:

1. World health statistics 2025: monitoring health for the SDGs, Sustainable Development Goals. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Journals:

2. Rebekka Vibjerg Jensen, Marie VognstoftHjortbak and Hans Erik Bøtker 2020 Ischemic Heart Disease: An Update, Seminars in Nuclear Medicine. 195-207, DOI:10.1053/j.semnuclmed.2020.02.007
3. Donghoon Choi, Ki-Chul Hwang, Kuen-Yong Lee and Yong-Hee Kim 2009 Ischemic heart diseases: Current treatments and future, Journal of Controlled Release, 2009; 140(3): 194-202, DOI:10.1016/j.jconrel.2009.06.016.
4. Falk, E., Pathogenesis of Atherosclerosis. *JACC*, 2006; 47: DOI:10.1016/j.jacc.2005.09.068.
5. Knoflach M, Kiechl S, Penz D, Zangerle A, Schmidauer C and Rossmann A, et al, Cardiovascular risk factors and atherosclerosis in young women: atherosclerosis risk factors in female youngsters (ARFY study). Stroke, 2009; 40: 1063–9. DOI: 10.1161/STROKEAHA.108.525675.
6. Poznyak AV, Sadykhov NK, Kartuesov AG, Borisov EE, Melnichenko AA and Grechko AV, et al., Hypertension as a risk factor for atherosclerosis: Cardiovascular risk assessment. Front Cardiovasc Med., 2022; 9: 959285, DOI: 10.3389/fcvm.2022.959285.
7. An C, Li Z, Chen Y, Huang S, Yang F, Hu Y, Xu T and Zhang C, Ge S., The cGAS-STING pathway in cardiovascular diseases: from basic research to clinical perspectives. Cell Biosci, 2024; 14(1): 58, DOI: 10.1186/s13578-024-01242-4.
8. Yu X and Pan S., Role and Mechanism of cGAS-STING Pathway in Cardiovascular System. Rev Cardiovasc Med, 2024; 25(4): 135, DOI: 10.31083/j.rcm2504135.
9. Wan X, Tian J, Hao P, Zhou K, Zhang J, Zhou Y, Ge C and Song X, cGAS-STING Pathway Performance in the Vulnerable Atherosclerotic Plaque. Aging Dis., 2022; 1606-1614, DOI: 10.14336/AD.2022.0417.
10. Anu Chaudhary, Rina Das, Kiran Mehta and Dinesh Kumar Mehta 2024 Indian herb *Tinosporacordifolia* and *Tinospora* species: Phytochemical and therapeutic application DOI: https://doi.org/10.1016/j.heliyon.2024.e31229
11. P.S. Udayan, A.K. Pradeep and I. Balachandran. A new species of *tinospora* (*Menispermaceae*) from South India Edinb. J. Bot., 77-80.
12. Priyanka Sharma a, Bharat P. Dwivedee a, Dheeraj Bisht b, Ashutosh K. Dash a and Deepak Kumar; The chemical constituents and diverse pharmacological importance of *Tinosporacordifolia*, Heliyon. e02437.
13. Charu Saxena, and Geeta Rawat, "Tinospora Cordifolia (Giloy) - Therapeutic Uses and Importance: A Review". *Current Research in Pharmaceutical Sciences*, 2019; DOI:10.24092/CRPS.2019.090302.
14. Xie, S., Su, E., Song, X., Xue, J., Yu, P., Zhang, B., Liu, M and Jiang, H., GSDME in Endothelial Cells: Inducing Vascular Inflammation and Atherosclerosis via Mitochondrial Damage and STING Pathway Activation. *Biomedicines*, 2023; 2579, DOI: 10.3390/biomedicines11092579.

15. Weixin Li, Zhuqi Huang, YueLuo, Yaqian Cui, MingjiangXu, Wu Luo, Gaojun Wu and Guang Liang, Tetrandrine alleviates atherosclerosis via inhibition of STING-TBK1 pathway and inflammation in macrophages, International Immunopharmacology, 2023; 1567-5769: 110139. DOI: 10.1016/j.intimp.2023.110139.
16. Mou, J., Chen, Y and Zhu, X. *et al*, Emerging role of the cGAS-STING pathway in cardiovascular diseases: biologic function, mechanisms and targeted therapy, 2025; 218: DOI:10.1186/s10020-025-01273-8
17. K. Mohanraj, B. Shanmugun, R.P. Vivel-ananth, R.P. Bharath Chand, S.R. Aparna, P. Mangalapandi and A. Samal, "IMPAAT: A curated database of Indian Medicinal Plants, Phytochemistry, And Therapeutics." Sci rep., 2018, DOI: https://doi.org/10.1038/s41598-018-22631-z
18. G. Morris, R. Huey and W. Lindstrom, et al, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J. Comput. Chem, 2009; DOI: 10.1002/jcc.21256
19. N.M. O'Boyle, M. Banck and C.A. James, et al., Open Babel: An Open chemical toolbox. J. Cheminform, 2011; DOI: 10.1186/1758-2946-3-33
20. S. Dallakyan and A.J. Olson, "Small-molecule library screening by docking with PyRx." Methods mol boil, 2015; DOI:10.1007/978-1-4939-2269-7_19

Website:

21. IMPPAT | IMPPAT: Indian Medicinal Plants, Phytochemistry And Therapeutics.