Metabolomics of *Cucumis Sativus* Phytochemicals And *in-Silico* Exploration of Their Cardioprotective Effects Through Network Pharmacology And Molecular Docking Simulation Studies

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ABSTRACT: ***Plants belonging to cucurbitaceae family have been utilized in both traditional medicine and culinary traditions since time immemorial. The aim of this study was to perform a detailed phytochemical metabolomics of Cucumis sativus fruit methanol and chloroform extracts using GCMS. This study was also focused on to identify the probable drug targets for phytochemicals of Cucumis sativus and to hypothesize the mode of drug action through simulation of drug target interactions using molecular docking approach. This research revealed representative peaks of 10 potential phytochemicals in chloroform extract and 07 potential phytochemicals in methanol extract. Protein that interact with the***

phytochemicals were identified using the SEA-database, which revealed 264 target protein interactions against 07 phytochemicals of methanol extract and 581 targets against 10 phytochemicals of chloroform extract. Among them 253 interacting protein targets were found to be common. Using STRINGDB, a network of these genes was created. The protein interactome network was analysed by utilizing Cytoscape and key bottle-neck protein PTGS2 was identified. KEGG database was surveyed to study PTGS2 pathways mainly for conferring the involvement of the key target proteins that play a significant role in several important pathways associated to cardiovascular diseases (CVD) mainly in oxytocin signalling pathway, the arachidonic acid metabolism pathway, the VEGF signalling pathway, the TNF signalling pathway, the Nf-Kb signalling pathway, the MAPK signalling pathway, and the Interleukin-17 signalling pathway. Domain analysis and secondary structural analysis of target protein PTGS2 (3HS2) were performed. Furthermore, in-silico pharmacokinetic analysis of compounds was performed using SwissADME, which indicated that all molecules possessed drug likeliness by embarking Lipinski rule of 5 with 0-violations. Molecular docking simulation studies using PyRx showed that all the compounds possessed potential interactions with target protein PTGS2. Among these compounds, di-isooctyl phthalate showed highest affinity towards PTGS2 with binding energy (-6.5 kJ/mol). Likewise, methyl palmitate shows least affinity with binding energy (-4.8kJ/mol). We conclude that PTGS2 can be a potential target for the treatment of CVDs and dibutyl phthalate can be considered as the potential lead molecule for drug development of therapy against CVDs.

Keywords: ***Cucumis sativus*****; PTGS2; GCMS; Network pharmacology; Molecular docking; Cardiovascular diseases.**

I. INTRODUCTION

Cardiovascular disease (CVD) continues to be an important concern both globally and locally. The rise in CVD prevalence across the world is due to risk factors which include smoking, high blood pressure, obesity and diabetes as well as infectious diseases and malnutrition posed in developing countries [1,2]. Elderly individuals suffering from major cardiovascular events tend to experience much greater negative consequences from these events. These outcomes are more common among such individuals and include death and decreased functional ability [2].

The lack of adequate healthcare infrastructure and scarce resources in developing countries serves as a catalyst for enabling CVD. In addition to the traditional risk factors that exist in these nations, there are also environmental concerns such as infectious diseases [1]. Both mild and acute CVD are linked with greater cognitive decline and disability [3,4]. Effective prevention and management of diabetes is important in reducing complications because it significantly increases the risk for stroke and CVD. Those suffering from diabetes face a CVD risk which is more than 3 times that of non-diabetic individuals [4]. Despite the enormous burden of CVD, adopting lifestyle changes and managing risk factors such as diabetes and metabolic syndrome remain imperative. Unfortunately, disparities in adherence to prescribed lifestyles and healthcare access, especially among the elderly and those living in developing countries, experience significant challenges.

Cucumber, or *Cucumis sativus*, is well known for its medicinal value, especially concerning the CVD, with antioxidant effects, and through control of blood pressure. Here, we explore the relevant study and analyze the biochemical mechanisms underlying these benefits. Cardiovascular diseases are often associated with chronic inflammation. *C. sativus* is known to reduce pro-inflammatory cytokines such as IL-6 and IL-1β, thus showing some anti-inflammatory activity. This is due to the enhancement of anti-inflammatory mechanism pathways and the increase of IL-10 secretion [6,7]. *C. sativus* seemed to intervene against vascular remodeling by decreasing expression of transforming growth factor-beta (TGF-β) and other pro-fibrotic factors. *C. sativus* also seems to have protective effects against liver and kidney damage, which are common in hypertensive patients [5]. Studies show that *C. sativus* performs better in promoting antioxidant enzymes such as SOD and GPx, and reducing malondialdehyde (MDA)—a lipid peroxidation marker. *C. sativus* extract has been demonstrated to alleviate oxidative stress and protect cardiac tissues in models of cadmium-induced toxicity where the protective effects are most striking [7,9]. The significance of Angiotensin II (Ang II) is readily apparent within the context of the RAAS Angiotensin – Renin – Aldosterone System, as Ang II is integral to blood pressure control. Evidence indicates that *Cucumis sativus* has the ability to conceal Ang II induced hypertension through the up regulation of the Akt pathway which results in NO production and vasodilation. This anti-inflammatory action and reduction of vascular remodeling supports the previously mentioned findings [5,8]. Several clinical studies have corroborated the effects of cucumber juice on

hypertension. Consumption of cucumber juice has been shown to reduce both systolic and diastolic blood pressure in hypertensive patients. Enhanced endothelial functions along with decreased oxidative stress are believed to be primary factors driving these improvements [10].

Through a thorough grasp of how medications interact across intricate biological systems, network pharmacology offers a revolutionary approach to drug design. Rather than using the conventional “one drug, one target” approach, this approach uses a “multi-target, multi-effect” paradigm, which has proven especially successful for complicated disorders. The function of network pharmacology is examined below in relation to the three crucial phases of drug development: clinical trials, lead modeling, and target identification. Biological networks, including metabolic, gene regulatory, and protein-protein interaction (PPI) networks, are constructed and analysed using network pharmacology. These networks aid in the identification of disease-related genes, proteins, and pathways that may be targets for future medications [12,13].

Network pharmacology has revolutionized drug designing by offering a systems biology-level view of pharmacological activities. By examining biological networks, forecasting drug-target interactions, and improving clinical trial procedures, this strategy can hasten drug discovery and enhance therapeutic results [14]. The importance of network pharmacology in changing the pharmaceutical industry will only increase with the development of computational and artificial intelligence technologies.

Molecular modeling simulates and depicts the behavior of molecules, ions, and particles in biological system. It helps predict molecular modeling and interactions by combining concepts from physics, chemistry, and computer science, which makes it easier to create new materials and medications. This approach has grown more potent with the development of computational technology, allowing for in-depth analyses and predictions of molecular systems. The uses and importance of molecular modeling in various fields will be covered in detail in this overview. Molecular modeling is essential to drug design because it allows scientists to predict how compounds will act in biological systems, which expedites the drug development process [15,16]. It helps clarify molecular interactions, which are essential for creating effective pharmaceuticals [16].

This research was focused on exploring the phytochemical metabolome of *C. sativus* fruit chloroform and methanol extracts through GCMS analysis. Further identify the probable drug targets for phytochemicals of *C. sativus* and also hypothesize the mode of drug action of the phytochemicals through molecular docking simulation of drug-target.

II. METHODS AND METHODOLOGY

A. Phytochemical extraction:

Reagents: All chemicals used in the experiments were purchased from Merck and Loba chemies pvt. ltd.

Plant material: The fresh fruits of *C. sativus* were procured from farmers at Vijayapura, Karnataka, India in January 2025. The plant material was identified by Prof. Kotresh, Department of Botany, Karnatak University, Dharwad.

Extraction and isolation: Fresh fruits of *C. sativus* (1kg), after washing and removing the seeds, were crushed using a commercial juicer. *C. sativus* was extracted with methanol and chloroform at 60°C three times (5l each). After removal of the solvent under reduced pressure, a residue was obtained. The dried powder extract was subjected to GC-MS and further analysis [17,18].

GCMS Analysis: Shimadzu used GC-MS QP 2010 to perform GC-MS analysis on the samples that were extracted from the fresh fruit of the *C. sativus* plant. 01mg of the extract sample was combined with 01ml of ethanol as a solvent to prepare the sample for GC-MS analysis. The equipment had a split mode injector that was used to inject the sample into the Zebron ZB-FFAP column fused with silica. The column had 60 m × 0.25 mm dimensions and a 0.25 μm film thickness for separations. As a carrier gas, helium flowed at a rate of 1ml/min. With a split ratio of 1:50, the sample was introduced in a split mode at a rate of 1 μl/min. A constant injection temperature of 250°C was maintained. Other requirements for GC-MS operation include an ion source temperature of 200°C, an interface temperature of 280°C, and a pressure of 53.5 kPa. After maintaining the column oven temperature at 50°C for one minute, it was raised steadily at a rate of 10°C per minute until it reached 280°C, where it remained for two minutes. The range width of the GC-MS scan spectra was 40–700 m/z. SwissADME was used to analyze the pharmacokinetics of the discovered molecules in order to determine their drugliness [14,19].

B. Target identification:

The molecular formulas, names, structures, journal citations, biological activity, physical and chemical properties, patents, and safety and toxicity data of phytochemicals isolated from *C. sativus* were investigated using PubChem (https://pubchem.ncbi.nlm.nih.gov/) [20]. Target genes were thoroughly searched across the SEA database (https://sea.bkslab.org/) using canonical SMILES from PubChem. These discovered genes were then utilised to build networks) [21].

C. Common target determination and Network construction:

VENNY 2.1.0 was used to identify common targets across methanol and chloroform extracts (https://bioinfogp.cnb.csic.es/tools/venny/). The information was then loaded into the STRING database (https://string-db.org/) in

order to create a network between the target genes. These networks were also utilized to comprehend how they interacted with cardiovascular illnesses [22].

D. Network visualization and PPI Analysis:

Complex biological data, such as networks and pathways, were visualised, analysed, and interpreted using Cytoscape. This study also used Cytoscape to investigate the protein-protein interactions and molecular interaction networks that are commonly seen in genomics, systems biology, and bioinformatics. Cytoscape is also widely used in metabolomics and network pharmacology to visualise and analyse networks, such as phytochemicals, plant metabolites, and their interactions with biological systems [13]. Cytoscape_v3.10.3 was utilized to further analyze the links and interactions between the target genes that were mapped in STRINGDB. The top related hub genes/biomarkers were identified using the cytoHubba plugin [21]

E. Enrichment Analysis using the database for annotation and integrated discovery:

KEGG (Kyoto Encyclopaedia of Genes and Genomes) pathways allow for the systematic and comprehensive representation and analysis of cellular functions, gene-protein-small-molecule interactions, and their connections to diseases, pharmaceutical effects, and other biological processes. In addition to studying the relationship between projected protein targets and CVD, we employed KEGG for pathway enrichment analysis and gene/protein functional annotation. Six overlapping targets were subjected to additional Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis [24].

F. Molecular Docking

In Spatial Data File (SDF) format, the two-dimensional (2D) structures of important active phytochemicals were obtained from the NCBI PubChem online database (https://pubchem.ncbi.nlm.nih.gov). Three-dimensional (3D) structures were created in PDB format using BIOVIA Discovery Studio Visualiser 2021, which also added a force field. The crystal structure of PTGS2 (Prostaglandin Converting Enzyme 2), the target for CVD, was obtained from the Protein Data Bank (https://www.rcsb.org/). The crystal structure complex's ligands and water molecules were eliminated, and the BIOVIA Discovery Studio Visualiser 2021 program was used to visualise the results [25]. Target protein molecular docking with therapeutic compounds and virtual screening were conducted using PyRx software version 0.8. Proteins and important active phytochemical analogues were then converted to pdbqt format using PyRx software v0.8 after key active phytochemicals in PDB format were submitted [24]. Docking was performed on the target protein and all of the phytochemicals. Using BIOVIA Discovery Studio Visualiser, the docked complexes were then examined to ascertain the compounds' and targets' binding capacities. Less than zero binding energy was taken into

account. It is generally acknowledged that the likelihood of binding increasing as the ligand and receptor binding configuration energy score falls.

III. RESULTS

A. *Phytochemical Extraction:* The yields of the chloroform and methanol extracts were 7.5g and 10g respectively for 01kg of *C. sativus* fresh fruit material. Metabolomics based phytochemical profiling revealed 09 molecules in chloroform extract and 07 molecules in methanol extract.

B. *GCMS Analysis***:** The GCMS analysis of both methanol extract and chloroform extract from *Cucumis sativus* reported presence of number of compounds. 09 compounds, that included Pyranone, Dibutyl phalate, Phthalic acid, Glyceryl arachidate, Glycidyl palmitate, Decanoic acid, Octyl phthalate, Diisooctyl phthalate and Phthalatic acid from methanol extract and 07 compounds that included Pyranone , Decanoic acid, Methyl stearate, Methyl tetradecanoate, Hydroxymethyl furfural, Methyl palmitate and Dodecanoic acid were identified from chloroform extract. Out of 16 compounds, 02 compounds found common among both the extracts. The GC chromatogram of chloroform extract (Fig.1.1.) and methanol extract (Fig.1.2.) are given below.

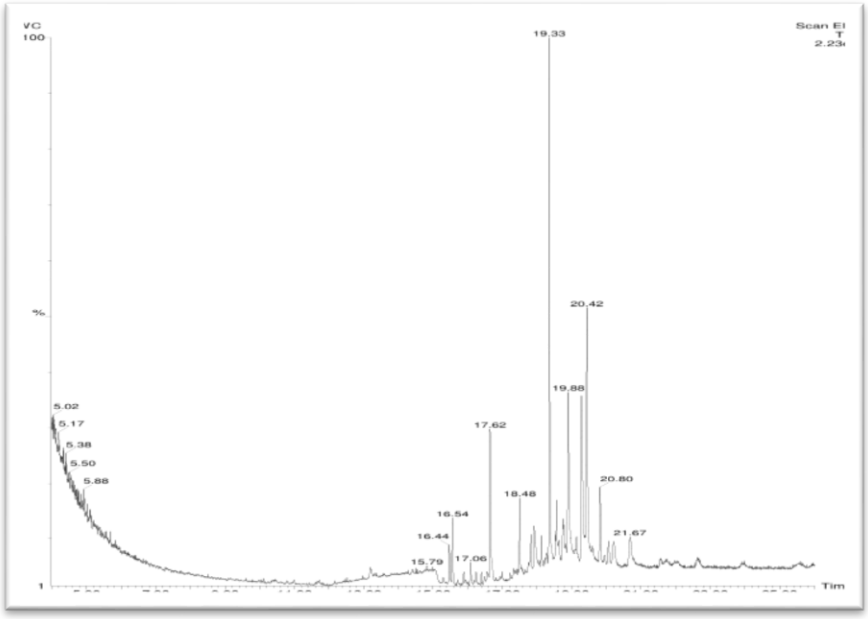

Fig.1.1. **GC chromatogram of *Cucumis sativus* chloroform extract**

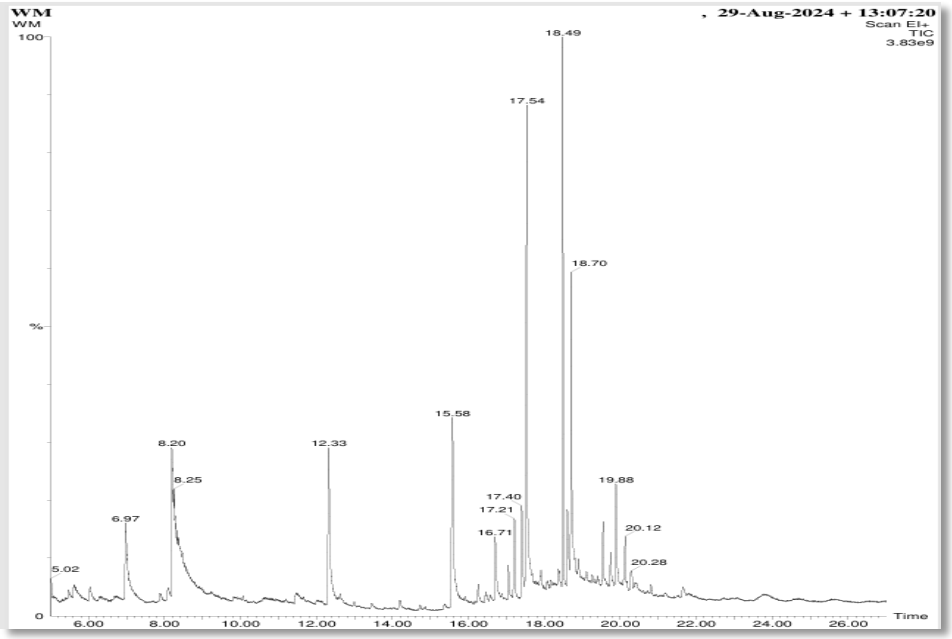

Fig.1.2. **GC chromatogram of *Cucumis sativus* Methanol extract**

All the phytochemicals were subjected to pharmacokinetic properties to analyze the Druglikiness of each analog based on the Lipinski rule using SWISSADME software. Parameters like GI absorption, BBB permeant, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, and Log Kp were considered for analysis. All the analogs of cucurbitacin acquiesce to Lipinski's rule of 5 with one violation (MW>500). Standard Logkp value ranges from-10.92cm/s to -2.08cm/s. Pyranone shows least Log-Kp value ie., -7.01cm/s, which indicates skin permeability of Pyranone is the lowest among all the molecules, whereas, Glyceryl arachidate shows the highest log-kp values ie., -2.62cm/s indicating more skin permeability. The druglikeliness profile and pharmacokinetic profile of the compounds are listed in Table.1.

C. *Target identification*: Finding and comprehending possible targets is essential in drug discovery since they serve as the basis for creating potent treatments. Modifying these targets, which are usually molecules or biological pathways that are important in disease processes, can aid in the treatment or alleviation of the condition. The canonical smiles of all the molecules were downloaded from PubChem. The target proteins were identified from SEA database using canonical smiles. 264 target proteins were identified from methanol extract whereas, 581 proteins were identified from chloroform extract (Fig.2.1). Total number of common proteins for methanol phytochemicals are 128 (Fig.2.2). Total number of common proteins for chloroform phytochemicals was 133 and common proteins between methanol and chloroform

extracts were 253. Among all the proteins in the network under study, there are 05 common interacting proteins viz., PAM, CES2, CES1, CDC25B and EPHX1.

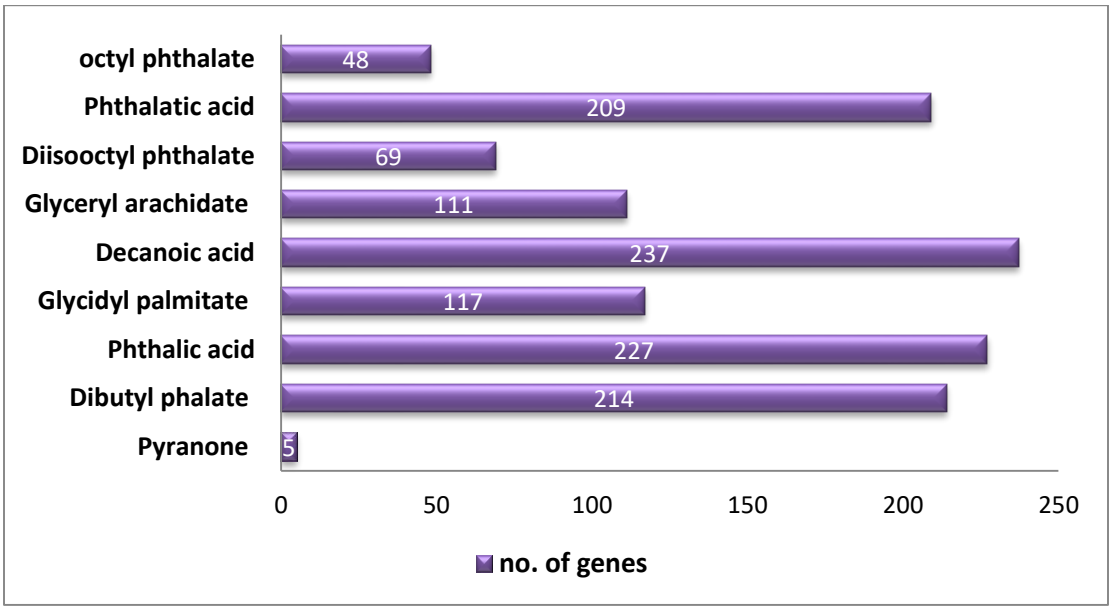

Fig.2.1 Number of proteins identified from chloroform extract

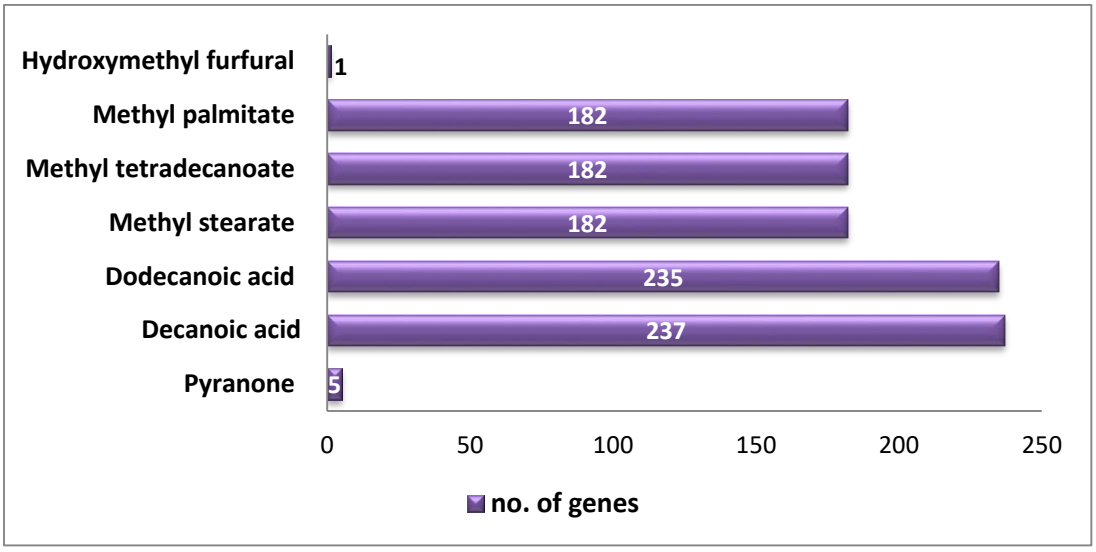

Fig.2.2 Number of proteins identified from methanol extract

D. *Network construction and PPI analysis of target proteins*: Genes from SEA database were allowed for network construction to analyze the network among all the genes. Fig.2.1. shows network among all the proteins identified from methanol extracted phytochemicals. Fig.2.2. indicated network formed among proteins from chloroform extract phytochemicals.

Table.1 ADME properties of Phytochemicals

Sl. No.	Phytochemical name	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (skin permeation) (cm/s)	Lipinski rule 0 violation MW>500
1	Pyranone	High	Yes	No	No	No	No	No	No	-7.01	Yes
2	Dibutyl phalate	High	Yes	No	Yes	Yes	No	No	No	-4.80	Yes
3	Phthalic acid	High	No	No	No	No	No	No	No	-6.80	Yes
4	Decanoic acid	High	Yes	No	No	No	No	No	No	-4.45	Yes
5	Dodecanoic acid	High	Yes	No	No	No	No	No	No	-4.54	Yes
6	Methyl palmitate	High	Yes	No	Yes	No	No	No	No	-2.71	Yes
7	Methyl tetradecanoate	High	Yes	No	Yes	No	No	No	No	-3.23	Yes(1)
8	Hydroxymethyl furfural	High	No	No	No	No	No	No	No	-7.48	Yes
9	Glycidyl palmitate	High	Yes	No	Yes	No	Yes	No	No	-3.09	Yes
10	Glyceryl arachidate	High	No	No	Yes	No	No	No	No	-2.62	Yes
11	Diisooctyl phthalate	High	No	No	No	No	No	No	No	-2.71	Yes(1)
12	Phthalatic acid	High	Yes	No	Yes	Yes	No	No	No	-4.80	Yes
13	Octyl phthalate	High	Yes	No	No	No	No	No	No	-3.52	Yes
14	Methyl stearate	High	Yes	No	Yes	No	No	No	No	-308	Yes

Fig. 2.1. Network of protein interactome from Methanol extract

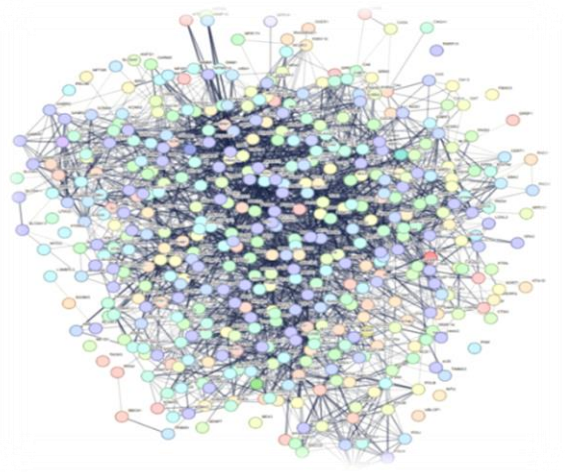

Fig.2.2. Network of protein interactome from Chloroform extract

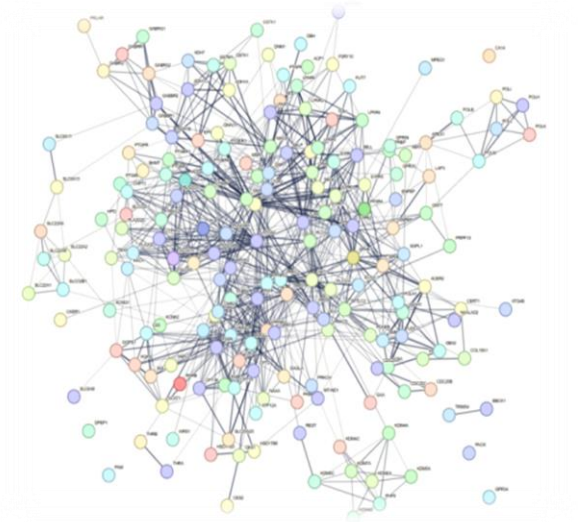

Fig.2.3. Network of intersecting proteins

The network formed between the proteins interacting with the methanol extract and chloroform extract phytochemicals is depicted in the Fig.2.3. Bottle neck protein PTGS2 (Prostaglandin endoperoxide Synthatase2) (Fig.3) was identified after analyzing the network using Cytoscape tool which shares common interaction among all the proteins. Further, Pathways of the bottle neck protein was studied.

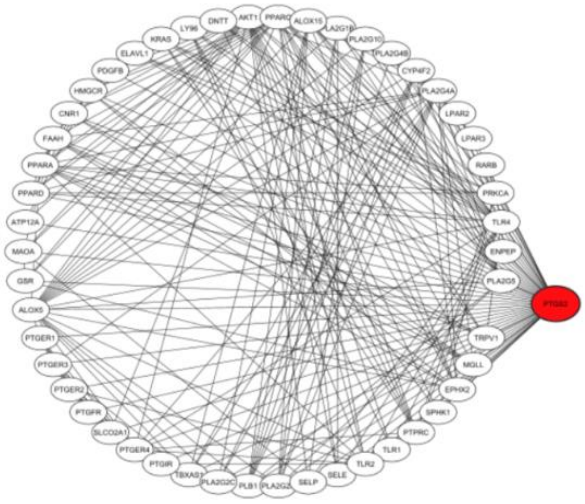

Fig.3. PTGS2 Bottle neck protein

E. *Pathway enrichment analysis:* Analysis of the PTGS2 involved in pathways was carried out by KEGG software. KEGG displayed PTGS2 in 07 pathways referred to as CVD. The pathways were arachidonic acid metabolism pathway, VEGF signaling pathway, NFKB signaling pathway, Oxytocin signaling pathway, TNF signaling pathway and Interleukin-17 signaling pathway. Location of the bottle neck protein PTGS2 was endoplasmic reticulum, membrane, microsome and nucleus extracted from Uniprot.

F. *Molecular Docking***:** Molecular docking was performed between 14 molecules extracted from *C. sativus* and target protein PTGS2 using PyRx software. The outcomes of docking were encapsulated in the table.3. The molecule's affinity for the target protein increases with decreasing binding energy. The findings of the molecular docking revealed all 14 molecules can bind to the target proteins. As showcased in the table.4.

Table.4 Molecular Docking results of phytochemicals from *C. sativus* fruit against PTGS2 target protein

Sl. No.	**LIGAND**	**BINDING ENERGY**
1	Pyranone	-5.5
2	Dibutyl phalate	-6.4
3	Phthalic acid	-5.4
4	Decanoic acid	-5.2
5	Dodecanoic acid	-5.1
6	Methyl palmitate	-5.9
7	Methyl tetradecanoate	-6.7

8	Hydroxymethyl furfural	-5.5
9	Glyceryl arachidate	-5.6
10	Glycidyl palmitate	-5.3
11	Diisooctyl phthalate	-7.0
12	Phthalatic acid	-6.2
13	Methyl stearate	-5.2
14	Octyl phthalate	-6.6

Among all the molecules, di-isooctyl phthalate appeared to have excellent binding affinity with PTGS2 (energy score = -7.0kJ/mol). However, other analogs show moderate binding affinity. Thus, we can conclude that, Di-isooctyl phalate can be considered as potential lead molecules for the treatment against Cardiovascular Diseases (Fig.4).

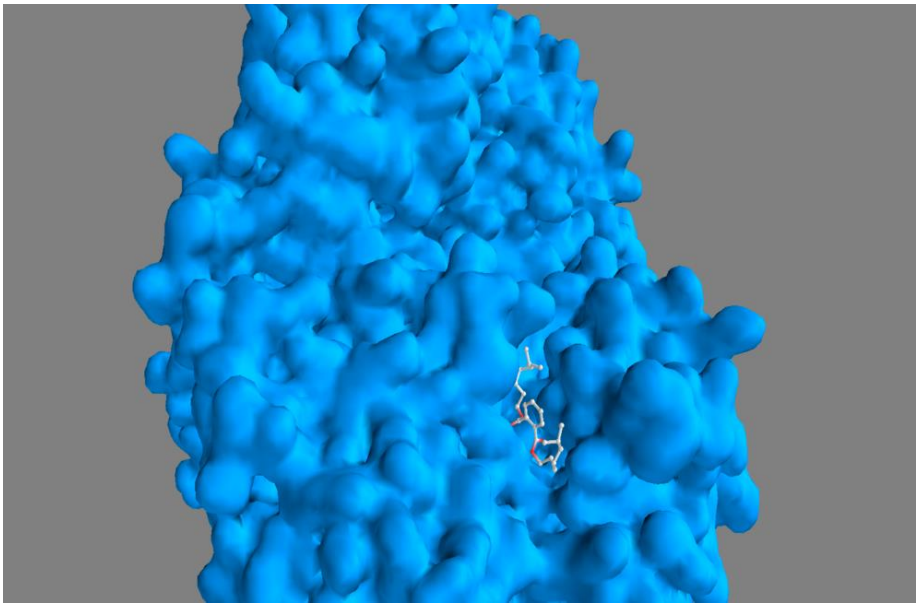

Fig.4 **Diisooctyl phthalate** with least binding energy of **-7.0kJ/mol** showing highest affinity towards PTGS2.

IV. Discussion

According to the WHO survey, cardiovascular diseases continue to have the highest death rate globally, while cancer is ranked second. The death rate for CVD has not changed despite the introduction of numerous medicines (WHO factsheets, 11 June 2021). A study that developed a severity score for 213,088 people with coronary heart disease (CHD) based on 20 clinical indicators found that a 41% increase in the risk of dying from all causes was linked to every unit rise in score [26]. The Genetic SYNTAX Score (GESS) experiment improved diagnostic accuracy and might have decreased the necessity for invasive procedures by employing

machine learning to predict the severity of CAD using genetic markers [27]. In the modern treatment of cardiovascular diseases (CVDs), a range of pharmacological and interventional strategies are employed to reduce morbidity and death. Recent advancements in medicine delivery techniques and therapeutic approaches have improved patient outcomes and treatment efficacy. Even though CVD is a potentially fatal and treatable condition, it is still underdiagnosed and undertreated despite increased awareness. ITGAL is the gene that interacts with cucurbitacin analogues the most out of all the genes that have been found, according to pathway enrichment analysis. The gene PTGS2, often referred to as COX-2 (cyclooxygenase-2), encodes an enzyme that produces prostaglandins, which are implicated in fever, pain, and inflammation [28].

It is an inducible type of cyclooxygenase, which means that certain stimuli, especially those associated with inflammation and injury, boost its expression [29]. By blocking the action of the enzyme, nonsteroidal anti-inflammatory medications (NSAIDs) can lower fever, discomfort, and inflammation by targeting PTGS2. An important factor in the onset and advancement of cardiovascular conditions like atherosclerosis is inflammation. According to [30], PTGS2 is elevated at inflammatory locations and may be involved in the inflammatory response in blood vessels. There is a complex link between cardiovascular disease and PTGS2. COX-2 plays a part in preserving blood vessel function and may occasionally have protective benefits, even though it can also increase inflammation and contribute to the development of plaque. Brodykinin, a peptide linked to pain, swelling, and inflammation, stimulates the arachidonic acid metabolism pathway. PLA2 activates and releases arachidonic acid from phospholipids in the cell membrane when receptors receive the signals. Many enzymes, such as COX2, LOX2, and others, contribute to the transformation of arachidonic acid into bioactive substances, such as prostanoids, through the expression of PTGS2. The pathway significantly affects cardiovascular biology, cancer, and inflammation [31]. As a result, when VEGF attaches to the receptor, it activates endothelial VEGFRs and sets off kinase cascades involving RAS and MAPK. Furthermore, phospholipase gamma is activated by the calcium signalling pathway using Ca+ ions for a number of cellular processes, including the production of PGI via the expression of PTGS2, which is produced in various blood vessels. The main purposes of this pathway are blood vessel formation and vascular permeability [31,33]. The Nfkb Signalling Pathway uses a canonical channel to receive signals from growth hormones, viruses, and bacteria. This mostly affects inflammation and encourages cell survival while also preventing apoptosis through a number of cycles, such as calcium signalling, T-cell receptor signaling, and B-cell receptor signaling pathways. The unwanted proteins are protolyzed by ubiquitin when PTGS2 is expressed. Blocking NF-κB signaling may be used to treat inflammatory diseases and cancers [34,35]. Protease inhibitors and particular IKK inhibitors are among the inhibitors included. The oxytocin signaling pathway promotes the proliferation and differentiation of cardiomyocytes through the production of PTGS2, the gene encoding COX2. OXT signals are sent by the hypothalamus. When a guanine nucleotide binding protein transmits a later signal, kinases act as a mediator. Other pathways are involved, including MAPK signaling and the arachidonic acid metabolism signaling pathway. Prostaglandin synthesis

increases as a result of oxytocin's stimulation of the MAPK pathway [36, 38]. When the TNF signaling pathway is triggered, PTGS2 is increased. The pro-inflammatory cytokine TNF attaches itself to its receptor and then starts a signaling cascade that finally causes transcription factors like NF-κB to be activated [37, 38]. Then, active NF-κB enters the nucleus and binds to the promoter region of the PTGS2 gene, increasing transcription and generating more COX-2 protein. Prostaglandins, which are potent inflammatory mediators that result in pain, fever, and tissue swelling, are produced by the enzyme COX-2 [38]. Within the signaling pathway of Interleukin-17, IL-17 binds to its receptor complex on the cell surface, which is typically composed of IL-17RA and IL-17RD. Upon binding, the adaptor protein Act1 is attracted to the receptor complex. TRAF6 (tumour necrosis factor receptor-associated factor 6) is one of the signaling molecules that Act1 interacts with to activate NF-κB [41]. Once within the nucleus, active NF-κB attaches itself to the promoter region of the PTGS2 gene and initiates transcription. Increased PTGS2 expression increases the production of prostaglandins, such as PGE2, which worsens inflammation. After examining each of these routes, we may infer that PTGS2 influences cardiovascular illnesses either directly or indirectly through COX2 expression [39]. By activating COX2, the investigation of these pathways clarifies PTGS2's active involvement in cardiovascular disorders, including atherosclerosis. According to the results of molecular docking, diisooctyl phalate has the strongest affinity for PTGS2. Therefore, we may conclude that phytochemicals isolated from *C. sativus* may be the potential therapeutic agents for management of CVDs based on network pharmacological and molecular modeling data.

V. Conclusion

We have successfully investigated the primary active phytochemicals and molecular processes of *C. sativus* that are involved in the treatment of CVD. This study identified 14 significant active phytochemicals of *C. sativus*, including phthalic acid, glyceryl arachidate, glycidyl palmitate, octyl phthalate, diisooctyl phthalate, phthalatic acid, methyl stearate, methyl tetradecanoate, hydroxymethyl furfural, methyl palmitate, phthalic acid, pyranone, and phthalic acid, using a range of databases. The locations, chemical functions, and biological processes of these targets were recorded.

According to our research, the cardioprotective effects of phytochemicals of *C. sativus* fruit are likely to be mediated by a number of underlying pathways arachidonic acid metabolism pathway, VEGF signaling pathway, NFKB signaling pathway, Oxytocin signaling pathway, TNF signaling pathway and Interleukin-17 signaling pathway etc. Our results support the hypothesis that the direct or indirect collaborative impacts of bottle neck protein (PTGS2) and multi-pathway activities may contribute to the anti-CVD effects of *C. sativus.* Molecular docking evidences the potential phytochemicals of *C. sativus* can potentially interact with the key protein PTGS2 associated with the pathogenesis of CVD. The compound with the highest binding affinity against PTGS2 was diisooctyl phalate. Despite the need for experimental validation, the findings of this study offer insights for further investigation into

the cardioprotective phytochemicals and mechanisms linked to the bioactivity of Cucurbitaceae family and form the basis for the development of modern cardioprotective drugs based on metabolomics and network pharmacology studies of phytochemicals from the Cucurbitaceae family.

VI. REFERENCES

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