MOLECULAR MECHANISM OF ALOE VERA CONSTITUENTS IN THE TREATMENT OF DIABETEC CARDIOMYOPATHY BASED ON NETWORK PHARMACOLOGY AND MOLECULAR DOCKING

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ABSTRACT

The study aimed to elucidate the effect of Constituents of Aloe Vera (*Aloe barbadensis miller)* in the treatment of diabetic cardiomyopathy in rats and to decipher the molecular mechanism of phytoconstituents via the utilization of gene set enrichment analysis, network pharmacology, compound target pathway network coupled with in silico docking study. First, we utilized Gene Cards Application to get the targets related to the Diabetic Cardiomyopathy (DCM) and intersected with targets of the Aloe Vera plant constituents which we got from the Dr. Duke's Phytochemical and Ethanobotanical Database. Aloe vera constituents such barbaloin, aloesin, aloenin, etc. Like 51 constituents we got. We got drug likeness by using Swiss target prediction software. Pubchem Database were used to get chemical structures of Plant constituents. Through screening and analysis, 51 active ingredients and 7086 target genes belonging to DCM were obtained. The reliability of the core targets was evaluated using molecular docking technology. Key targets of constituents and DCM were acquired by overlapping the above targets via the Venn diagram.The GO and KEGG pathways involved in the targets were analyzed by using the Gene Codis database and Shiny GO. The protein interactions network was constructed using the STRING database. The targets network of active components of the Aloe vera was constructed by using Cytoscape 3.6.0 software. The compound target pathway network analysis was done by using Centiscape, one of the app presents in cyoscape. Autodock Vina software was used to verify the molecular docking of Aloe vera constituents and key targets.The targets such as AKT-1, TNF, MMP9, CASP3, TP53, HSP90AA1, EGFR, etc. may play a crucial role. These targets are involved in PI3K/AKT signaling pathway, cell growth, survival, proliferation, apoptosis, cell cycle arrest, inflammation, and extracellular matrix modelling. The docking results indicated that the binding with the TNF showed the highest binding energy. Based on the network pharmacology, the characteristics of multicomponent, multitarget, and multipathway of Aloe vera constituents were discussed, which provided a scientific basis for explaining the mechanism.in DCM and new ideas for further research.

Keywords: Network pharmacology, Diabetic cardiomyopathy, Drug likeness, Gene Ontology, PPI, CTPN, Molecular docking.

Introduction-

Diabetic Cardiomyopathy (DCM) is one of the major symptoms of Diabetes mellitus which causes sudden heart failure in the diabetic patients. DCM is mainly characterized by the structural and functional abnormalities related to heart in the diabetic patients without any cardiovascular diseases like coronary artery disease, hypertension, etc. [1]. They can be distinguished from hypertensive heart disease, atherosclerotic heart disease of the coronary arteries, and other heart diseases. In the type 2 diabetes mellitus patients, the increased blood sugar level can lead to the deposition of the fat and myocardial fibrosis which mainly leads to the myocardial cell apoptosis, dysfunction of the heart muscles, which can leads to the sudden heart failure due to the over ischemic injury [2]. Its main clinical symptoms include congestive heart failure and angina. In severe cases, this can lead to reduced ventricular compliance, reduced cardiac function, and congestive heart failure [3]. In current senerio, there is no any treatment available for the treatment of DCM. Some studies on the animal models were found several mechanisms which have been involved in the pathogenesis of the DCM such as calcium signaling,changes in myocardial structure, deposition of fibrous tissue, myocardial fibrosis, cell apoptosis,etc.[4]. Some clinical studies have shown that the prevalence of heart failure in diabetic patients ranges from 19 to 26% [5]. The IDF Diabetes Map,10thedition says that the global diabetes prevalence is 540 million in 2021, which will rise by 12.2% upto 780 million by 2045 [6]. Which indirectly indicated that there is much more population will suffer from DCM, causing heavy burden on global health. Medications used against heart failure such as ACEI, Beta blockers, SGLT2i,etc. Are able to improve clinical symptoms of DCM, but rate of morbidity and mortality is increasing day by day [7].A growing number of studies have shown that diverse mechanisms are involved in diabetes-associated cardiac dysfunction, including systemic insulin resistance, oxidative stress, inflammation, activation of the renin angiotensin aldosterone system, and dysregulation of the immune system[8].

Aloe Vera (Aloe barbadensis miller) belonging to family liliaceae family. Aloe Vera is well known for its multiple health and nutritional benefits. It is used as food, drinks, and cosmetics, etc. It contains various compounds, including anthraquinones, anthrones, chromones, alkaloids, and flavonoids, which exhibit anti-tyrosinase, anti-cancer, and anti-diabetic effects [9]. *Aloe vera* is proven to have effect on metabolic disorders such as diabetes mellitus having ability to control glucose and lipid levels in body. In this study we mainly focuses on the molecular mechanism. In that we used network pharmacology molecular docking approch to find out the molecular mechanism of diabetic cardiomyopathy.

Network pharmacology is an emerging field that integrates systems biology with polypharmacology, molecular network data, bioinformatics, and computer simulations. This approach is well-suited for analyzing multitargeted drugs, making network pharmacology methods a valuable tool for investigating the intricate mechanisms of action of compounds [10]. The objective of network pharmacology is to provide a comprehensive perspective on the relationship between drugs, their target proteins, and the diseases they affect. This

perspective is derived from either high-throughput screening analysis or network analytical techniques, which are used for target prediction or mechanism analysis [11]. Network pharmacology is an emerging field that integrates systems biology, pharmacology, and computational biology to understand the complex mechanisms of drug action. It shifts the traditional "one drug, one target" paradigm to a more holistic approach, recognizing that drugs often interact with multiple targets within biological networks [12].

GeneCards (https://www.genecards.org/) is a comprehensive and user-friendly database that provides a wealth of information on human genes. It integrates data from various sources, including genomic, proteomic, transcriptomic, genetic, and functional information, offering a one-stop shop for researchers to explore the intricacies of human genes. This invaluable resource is widely used in the biological and biomedical fields, aiding in understanding disease mechanisms, drug discovery, and personalized medicine [13]. Dr. Duke's Phytochemical and Ethnobotanical Databases [https://phytochem.nal.usda.gov/] is a valuable online resource developed by James A. Duke at the USDA. It offers a comprehensive collection of information on plants, their chemical constituents, and their traditional uses [14]. PubChem (https://pubchem.ncbi.nlm.nih.gov/), a comprehensive chemical information resource, is a valuable tool for researchers and scientists. It provides access to a vast database of chemical substances, including their structures, properties, and biological activities [15]. SwissTargetPrediction is a web-based tool for predicting the potential protein targets of small molecules. It utilizes a combination of 2D and 3D similarity measures to identify potential targets based on their similarity to known ligands[16]. GeneCodis is a powerful web-based tool designed for functional enrichment analysis of gene lists. It integrates diverse biological information to identify significant functional modules and pathways associated with the input genes. By utilizing GeneCodis, researchers can gain valuable insights into the biological processes underlying complex phenotypes and diseases [17]. STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) is a database of known and predicted protein-protein interactions. It provides a comprehensive overview of protein interactions, including physical and functional associations, across various organisms. By leveraging STRING, researchers can explore protein networks, identify potential drug targets, and gain insights into cellular processes [18].

Materials and Methodology

Pharmacokinetic properties prediction- The chemical structural formulas for were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Drug likeness and physicochemical properties were then studied using SwissADME (http://www.swissadme.ch/), which was employed to evaluate the ADME properties of the compounds.

Prediction of target genes related to DCM- A list of 7086 genes related to diabetic cardiomyopathy. This list can be sourced from various databases like GeneCards, PubMed, or specific research papers. The GeneCards API provides programmatic access to the database, allowing you to retrieve detailed information about each gene. Gene cards provides gene symbol and full name,gene description and function, associated diseases and phenotypes, protein information (e.g., protein domains, interactions),gene expression patterns and pathways and networks involved. We searched for the diabetic cardiomyopathy and we got 7086 genes related to diabetic cardiomyopathy by using GeneCards database [19].

Finding the chemical constituents of Aloe Vera- To identify potential bioactive compounds in aloe vera, we consulted Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/). This comprehensive database provided information on the phytochemical constituents of aloe vera, including anthraquinones, polysaccharides, and phenolic compounds. These compounds have been reported to possess various pharmacological properties, such as antioxidant, anti-inflammatory, and wound-healing activities. We extracted 50 constituents from this database. By leveraging this valuable resource, we were able to gain insights into the potential therapeutic benefits of aloe vera and guide our subsequent experimental investigations[20].

Gene ontology and KEGG enrichment pathway- To identify the biological processes, molecular functions, and cellular components associated with the genes implicated in diabetic cardiomyopathy, we performed Gene Ontology (GO) enrichment analysis using GeneCodis 4 ((https://genecodis.genyo.es/). This powerful bioinformatics tool enables the identification of over represented GO terms within a gene list, providing insights into the underlying biological mechanisms. By analyzing the significantly enriched GO terms, we were able to gain a deeper understanding of the cellular and molecular processes involved in the pathogenesis of diabetic cardiomyopathy [21].

Assessing Drug-likeness of Aloe vera constituents- To identify potential drug-like compounds within aloe vera, we first consulted Dr. Duke's Phytochemical and Ethnobotanical Databases to identify its primary bioactive constituents. Subsequently, we retrieved 3D structures of these compounds from PubChem and molecular modeling software. To assess their drug-likeness, we employed SwissADME to predict properties such as Lipinski's Rule of Five compliance, ADME characteristics, and toxicity risk. Additionally, we used Molsoft to calculate further physicochemical properties. By filtering compounds based on these criteria and considering their known bioactivities, we selected promising candidates for further investigation [22]. Virtual screening techniques, such as molecular docking and pharmacophore modeling, were then employed to predict their binding affinities to target proteins involved in diabetic cardiomyopathy. This comprehensive approach, leveraging computational tools and databases, allows for the efficient identification of potential drug leads from natural sources like aloe vera [23].

PPI network and Node centrality measurement- Protein-Protein Interaction (PPI) networks, visualized using tools like Cytoscape, provide insights into cellular processes. Nodes in these networks represent proteins, and edges represent interactions between them. Node centrality measures, such as degree centrality and betweenness centrality, help identify crucial proteins within the network. A node with high degree centrality has numerous connections, while a node with high betweenness centrality lies on many shortest paths between other nodes, indicating its importance in information flow [24].

Compound target pathway network- To display the above results more vividly, compound-target (C-T) network and target-pathway (T-P) network diagrams were constructed. These network diagrams were drawn using Cytoscape version 3.6.1, which can graphically display

and edit the network. Compound-Target-Pathway (CTP) networks provide a comprehensive view of the molecular interactions between drugs, their targets, and the biological pathways they influence. Cytoscape, a powerful bioinformatics software, can be used to visualize and analyze these complex networks. By mapping compounds, their targets, and the pathways they regulate, CTP networks help we understand the mechanisms of drug action, identify potential drug targets, and predict side effects [25].

Molecular docking- Molecular docking is a computational technique used to predict the preferred orientation of one molecule to a second when bound to each other to form a stable complex. PyRx is a user-friendly open-source software that integrates various molecular docking tools, including AutoDock Vina, to perform virtual screening and drug discovery. By using PyRx, we can efficiently screen large compound libraries against target proteins to identify potential drug candidates [26]. The SDF files of the 3D structures of the core components were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The components were energy-minimized with the aid of Open Babel software and exported as "pdbqt" files. The crystal structures of the core target proteins were downloaded from the PDB database (http://www.rcsb.org/) and dehydrated, hydrogenated, charged, and exported as "pdbqt" files. Docking of compounds and target proteins was performed using Auto Dock Vina to obtain binding energies, and some of the 3D docking results were displayed using the PyRx software.

Name	URL
Pubchem	https://pubchem. ncbi.nlm.nih.gov/
Dr. Duke's Phytochemical and Ethnobotanical Databases	https://phytochem.nal.usda.gov/
GeneCodis 4	https://genecodis.genyo.es
shiny GO 0.77	http://bioinformatics.sdstate.edu/go/
SwissADME	http://www.swissadme.ch/
Swiss Target Prediction	www.swisstargetprediction.ch
GeneCard data-base	https://www.genecards.org/
Venn diagram tool	http://bioinformatics.psb.ugent.be/webtools/Venn/
String	https://string-db.org/
Cytoscape 3.9.1	https://cytoscape.org/
PyRx	https://pyrx.sourceforge.io/

Table No. 1 Databases and Software

Results and Discussion-

The pharmacokinetic properties and toxicity prediction

The structural information of top 5 chemical constituents of *Aloe vera* having highest drug likeness was obtained from PubChem. and relevant ADME information was obtained from SwissADME. SwissADME predicted the pharmacokinetics, including the topological polar surface area and Lipinski's rule of 5. The results showed that chemical constituents complied with Lipinski's rule of 5 and were predicted to have good drug-likeness. The results demonstrated that chemical constituents of aloe vera showed no observable toxicity.

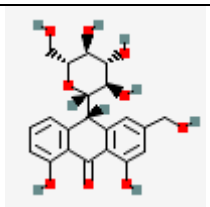
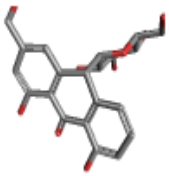
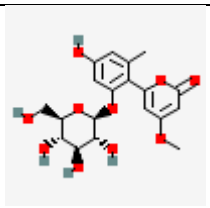
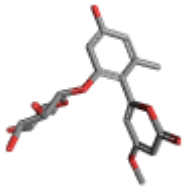
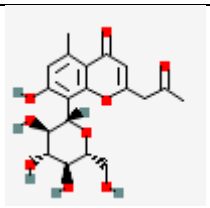
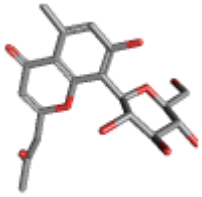
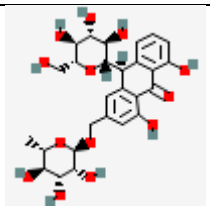
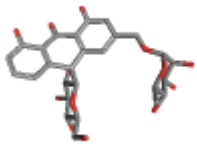
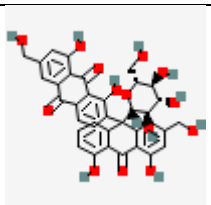
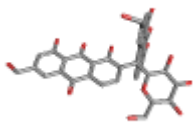
Chemical constituent	2D structure	3D sttructure
Barbaloin		
Aloenin		
Aloesin		
Aloinoside A		
Elgonica Dimer A		

Table 2.- Chemical constituents with there 2D and 3D structures.

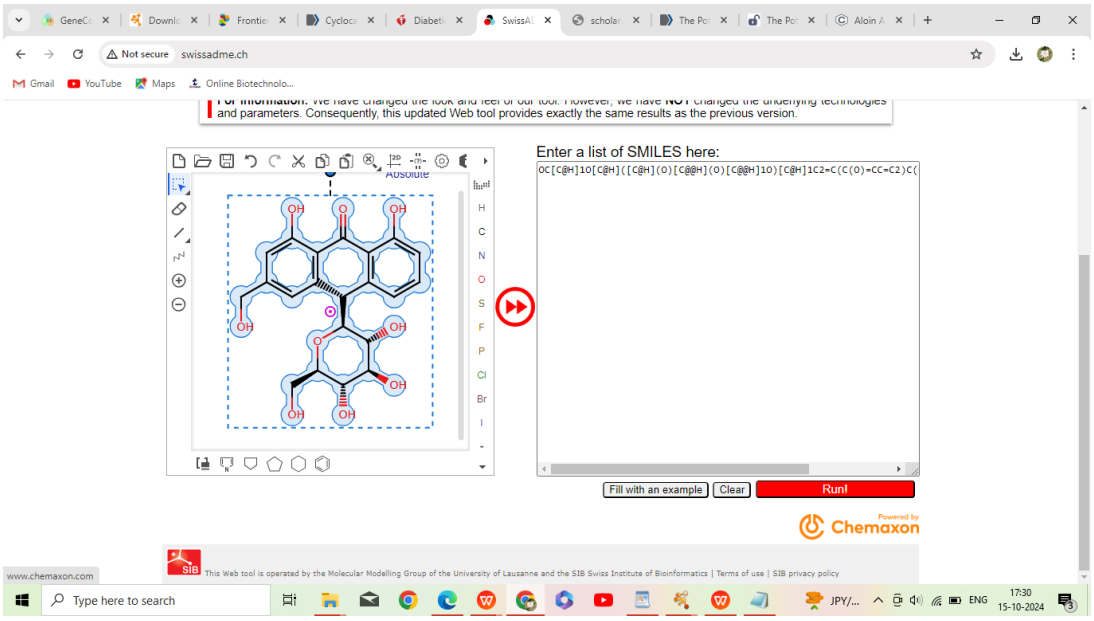


Fig 1. SwissADME.

Screening of targets of Aloe vera against Diabetic cardiomyopathy- To identify the aloe vera constituents-associated targets, 500 targets were collected from SwissTargets, respectively. Additionally, 7086 disease-related targets were obtained from GeneCard, DrugBank, TTD, OMIM, and PharmGBK. Based on these results, we identified 210 targets of aloe vera constituents against DCM .

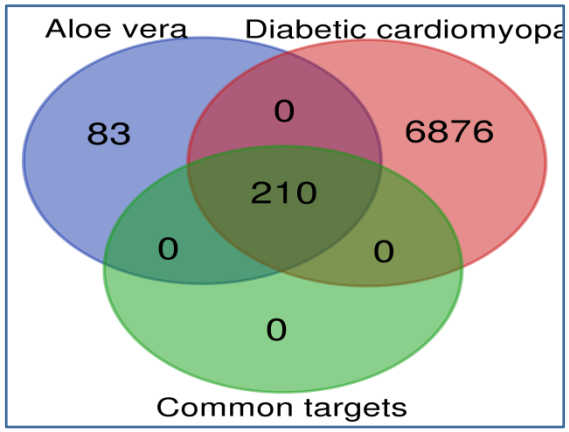


Fig. 2 venn Diagram to find common targets of Diabetic Cardiomyopathy

GO and KEGG enrichment Pathway- 7086 genes were extracted from GeneCards were took in the GeneCodis 4. Bar Graph is obtained. This bar graph displays the significantly enriched GO terms, with each bar representing a specific GO term. The height of the bar indicates the significance of the enrichment, often represented by a p-value or adjusted p-value. GO terms are categorized into three main groups: biological process, molecular function, and cellular component.

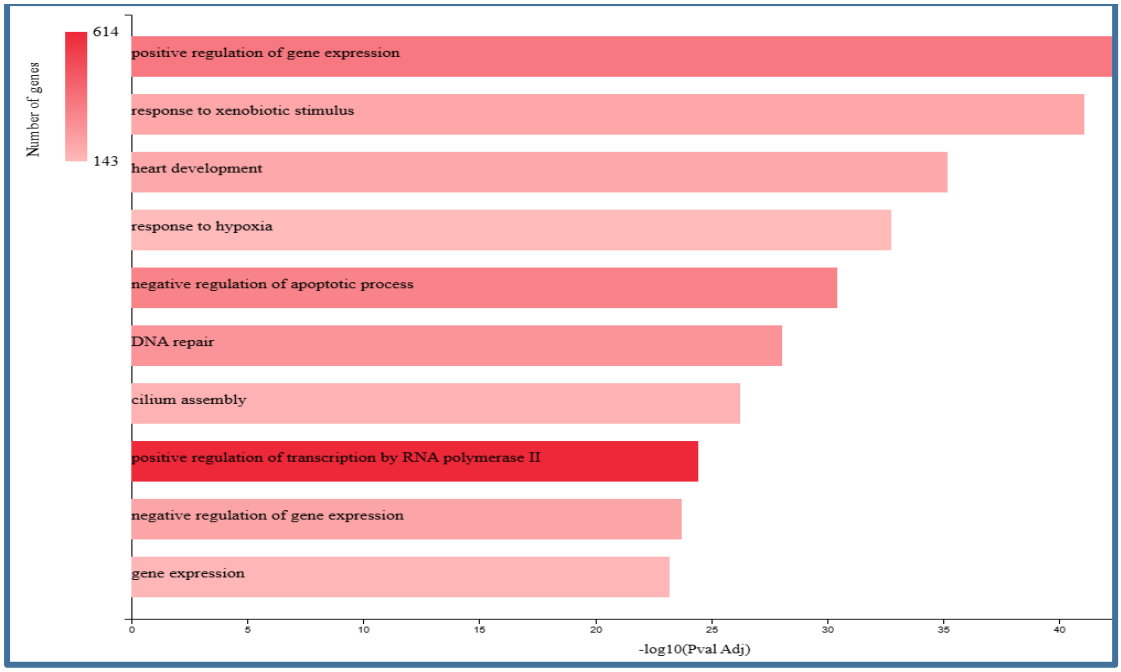


Fig. 3 Bar graph of GO and KEGG enrichment pathway.

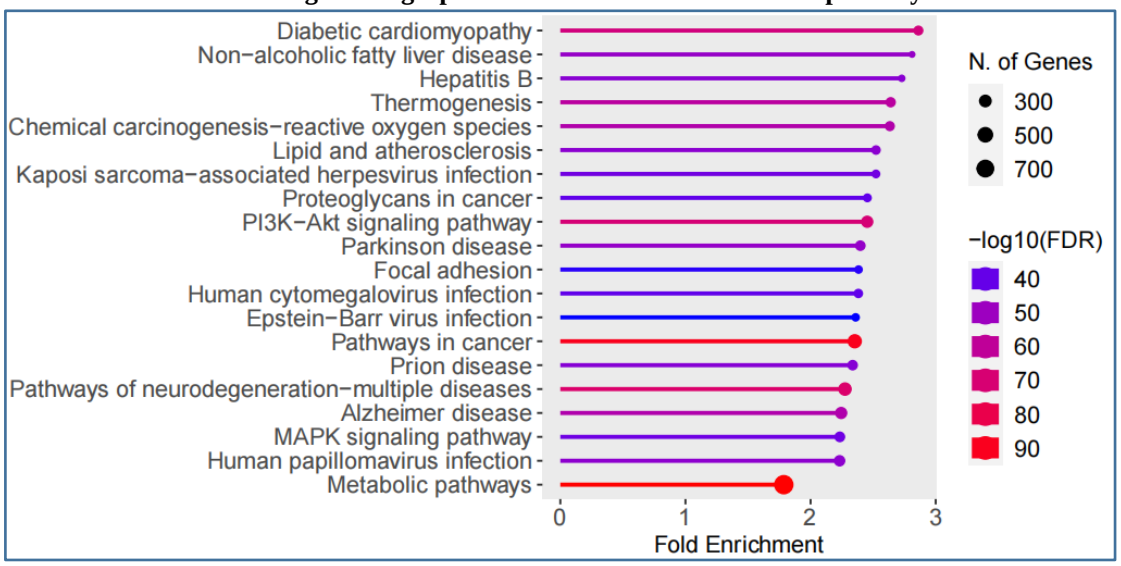


Fig. 4 Fold enrichment we extracted from shiny GO 0.77

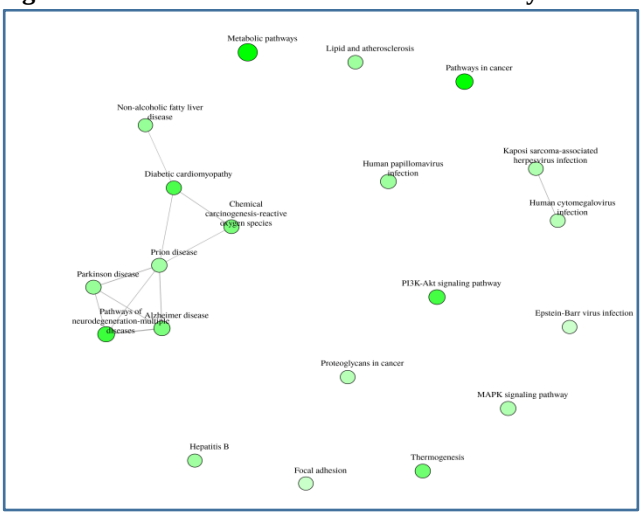


Fig. 5 Interactive enrichment network we extracted from shiny GO 0.77

PPI network of top 50 genes-

The protein-protein interaction network is visualized by string database.The 50 common target from KEGG enrichment analysis after removal of duplicate that taken for string analysis the degree of that targets taken.That degree analysis highlighting pathways in Fig.3.The top 10 targets based on their degree are taken and analysed by using cytoscape.

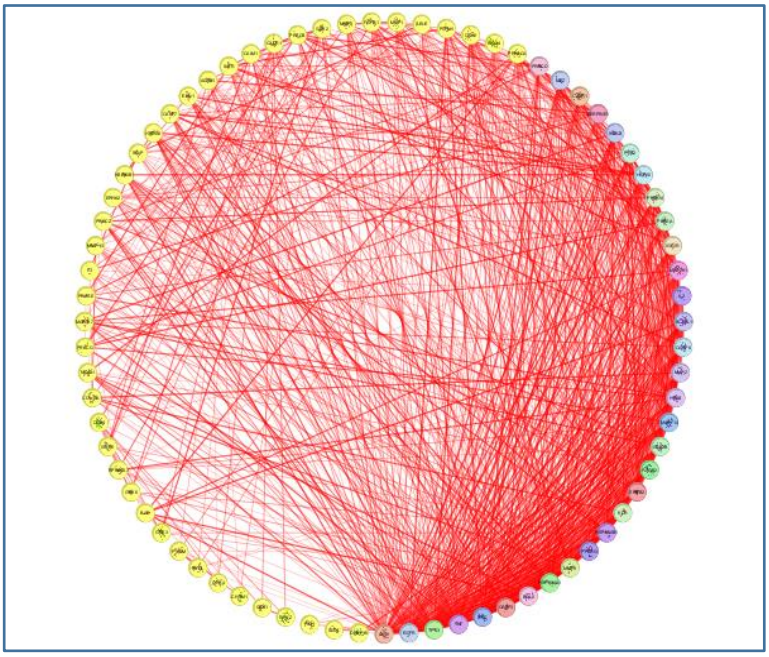


Fig. 6 PPI network of top 50 genes which are found in GO study constructed using STRING and Cytoscape Software. This network provides a visual representation of the interactions between these genes, highlighting potential pathways and mechanisms involved in these processes.

Degree and Betweenness Assessment-

Target	Degree
AKT1	9
TNF	8
MMP9	6
CASP3	6
TP53	6
HSP90AA1	4
EGFR	4
SRC	3
SRC1	3
PPARG	2

Table no. 3- Degree of the top 10 targets of DCM which are involved in the most of the pathways of DCM.

Constituents of Aloe Vera	Degree
Aloinoside	6
aloedin	5
aloenin	4
Elgonica Dimer A	4
Barbaloin	3

Table 4.- Degree of the top 5 chemical constituenmts of Aloe vera plant.

Compound Target Pathway Network (CTPN)-

The Compound target pathway is observed by using cytoscape software.In that 10 (AKT1, TNF, MMP0, CASP3, TP53, HSPOAA1, EGFR, SRC, SRC1, PPARG) target is interacted with ellagic acid and pathways involving the disease network shown in Fig 4.

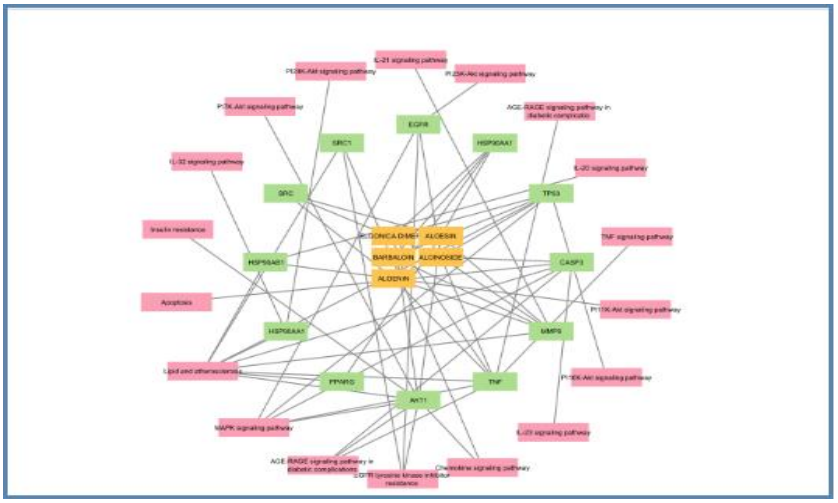


Fig. 7. Compound Target Pathway network of Aloe Vera constituents with top 10 genes involved in a Diabetic Cardiomyopathy.

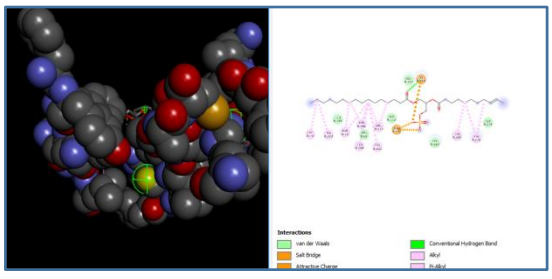
Molecular Docking-

The core 5 ligands targets of Aloe vera and 10 core targets of DCM were selected for molecular docking. The results are shown in Figure 4. It is generally accepted that compounds bind spontaneously to target proteins at binding energies less than 0, the compound binds spontaneously to the target protein; less than -5.0 kJ/mol the two are well bound; less than -7.0 kJ/mol, they have strong binding activity. It can be seen that the binding energies of the core targets and the core components are all less than or equal to 0, with good binding activity. Among them, aloesin had the lowest binding energy to the target sites, and the four lowest targets were used for visualization.

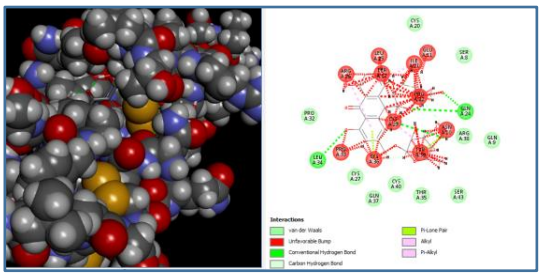
Constituents	Target	Binding affinity
Barbaloin	AKT1	-6.8
Barbaloin	TNF	-6.4
Barbaloin	CASP3	-7.6
Barbaloin	HSP90AA1	-6.4
Barbaloin	EGFR	-7.6
Aloesin	AKT1	-6.4
Aloesin	TNF	-6.3
Aloesin	CASP3	-7.0
Aloesin	HSP90AA1	-6.4
Aloesin	EGFR	-7.8
Aloenin	AKT1	-6.3
Aloenin	TNF	-6.5
Aloenin	CASP3	-7.5
Aloenin	HSP90AA1	-6.2
Aloenin	EGFR	-7.2
Elgonica Dimer A	AKT1	-11.1
Elgonica Dimer A	TNF	-12.3
Elgonica Dimer A	CASP3	-13.3
Elgonica Dimer A	HSP90AA1	-11.2
Elgonica Dimer A	EGFR	-14.0
Aloinoside A	AKT1	-7.0
Aloinoside A	TNF	-6.3
Aloinoside A	CASP3	-8.0
Aloinoside A	HSP90AA1	-8.2
Aloinoside A	EGFR	-8.0

Alloinoside A

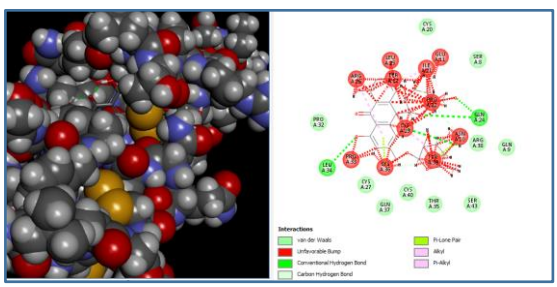
AKT-1



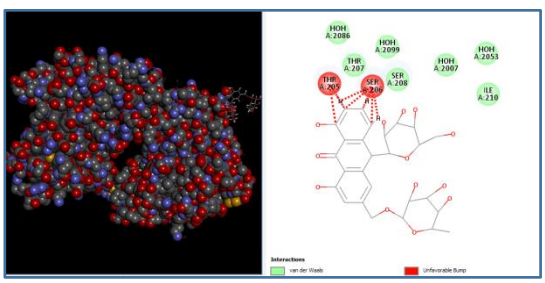
TNF



CASP3

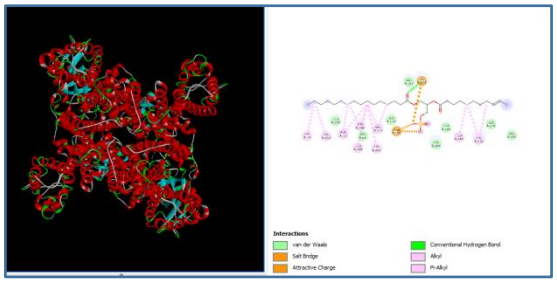


EGFR

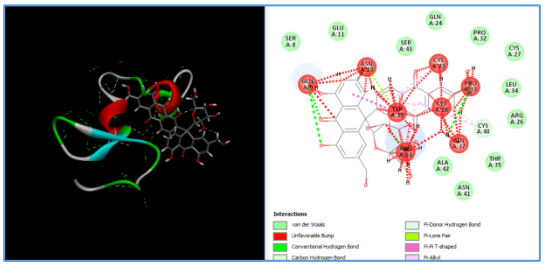


Elgonica dimer A

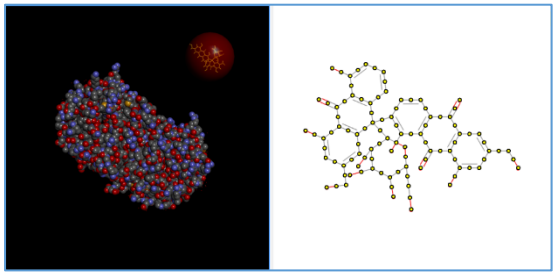
AKT-1



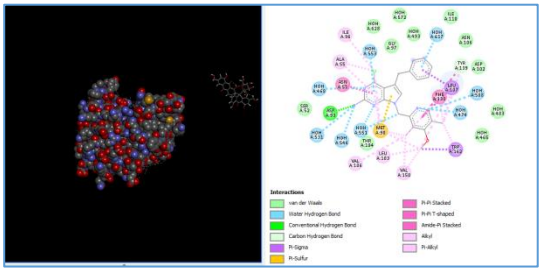
TNF



CASP3

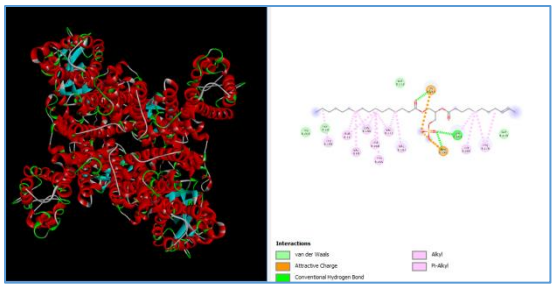


EGFR

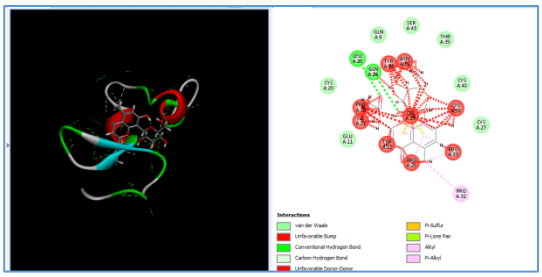


Aloesin

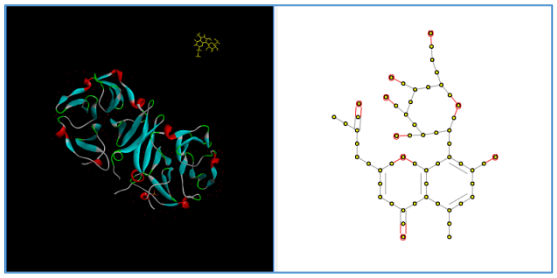
AKT-1



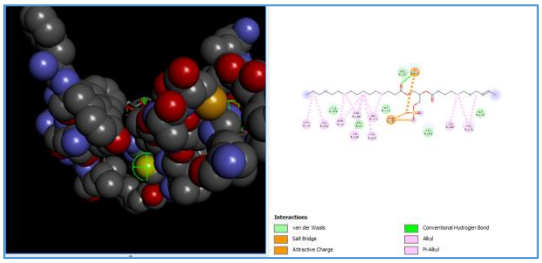
TNF



CASP3

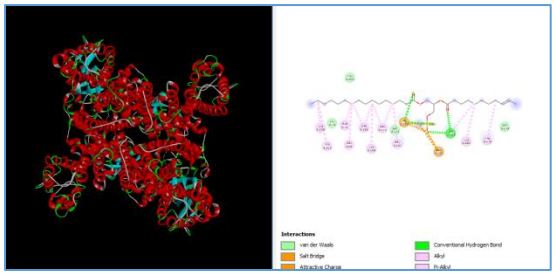


EGFR



Aloenin

AKT-1



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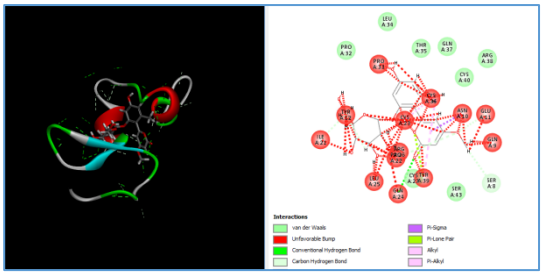

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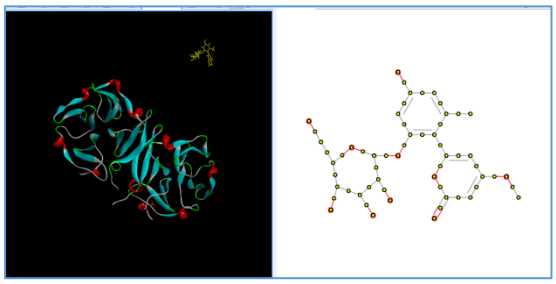
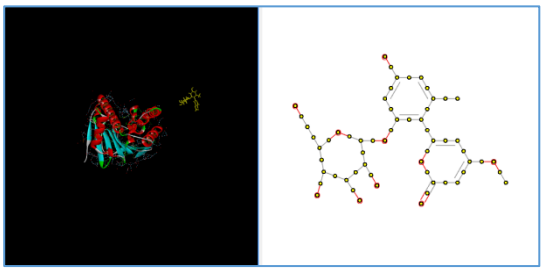
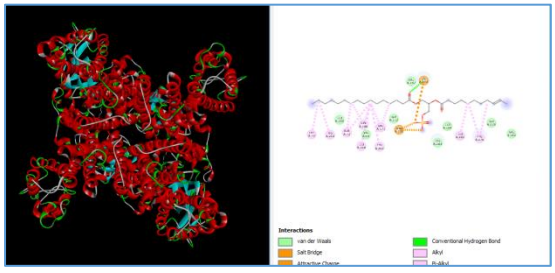


EGFR



Barbaloin

AKT-1



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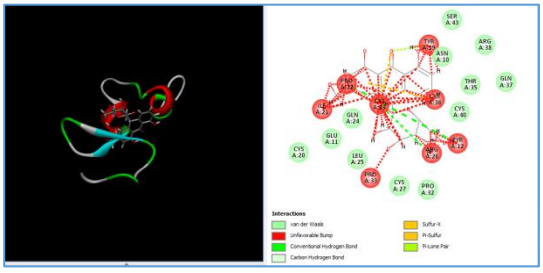

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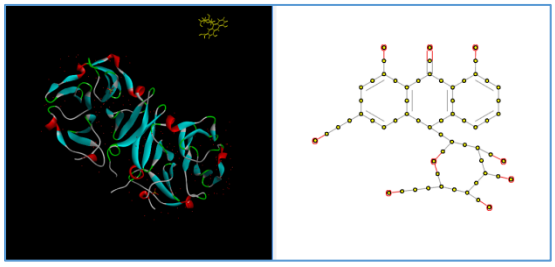
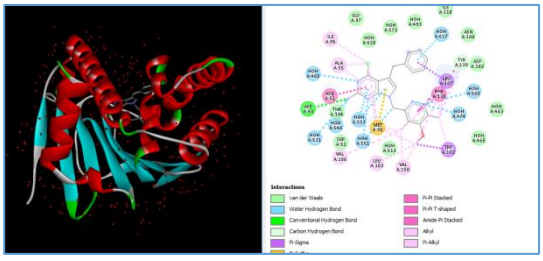


EGFR



Discussion-

This study employed network pharmacology to investigate the potential therapeutic effects of Aloe vera constituents in diabetic cardiomyopathy (DCM). The findings suggest that Aloe vera may exert its beneficial effects through a multi-component, multi-target, and multi-pathway approach.

Pharmacokinetic Properties and Drug Likeness: The analysis using SwissADME indicated that the top five identified Aloe vera constituents (barbaloin, aloenin, aloesin, elgonica dimer A, and aloinoside A) complied with Lipinski's Rule of Five, suggesting

promising drug-like properties. Additionally, the predicted ADME characteristics suggested good absorption and distribution potential. The lack of predicted observable toxicity further strengthens their potential as therapeutic candidates.

GO and KEGG Enrichment Pathway Analysis: The results from GeneCodis revealed significant enrichment of GO terms and KEGG pathways associated with DCM pathogenesis. These enriched terms included biological processes like cell death, inflammatory response, and extracellular matrix remodeling, all of which are known contributors to DCM development. Similarly, enriched KEGG pathways included PI3K-Akt signaling pathway, TNF signaling pathway, and ECM-receptor interaction, further highlighting the potential mechanisms of action for Aloe vera constituents.

PPI Network Analysis: The protein-protein interaction (PPI) network analysis identified key target genes potentially involved in the therapeutic effects of Aloe vera. The analysis using STRING and Cytoscape revealed a network of interacting proteins, with AKT1, TNF, MMP9, CASP3, TP53, HSP90AA1, EGFR, SRC, SRC1, and PPARG emerging as the top 10 based on their degree centrality. These central targets suggest their crucial roles in the underlying mechanisms of DCM and potential points of intervention by Aloe vera constituents.

Compound Target Pathway Network (CTPN): The CTP network constructed using Cytoscape visualized the interactions between the top 10 target genes and the Aloe vera constituents. This network provided valuable insights into the multi-target and multi-pathway nature of Aloe vera's therapeutic effects. Interestingly, ellagic acid, a component of Aloe vera, interacted with several key target genes involved in DCM pathways. This finding suggests that ellagic acid might be a significant contributor to the overall therapeutic effect.

Molecular Docking Analysis: The molecular docking simulations provided further evidence for the potential binding interactions between the core Aloe vera constituents and the identified target proteins. The binding energies obtained were generally favorable, suggesting good binding affinity between the constituents and the targets. Notably, elgonica dimer A displayed the strongest binding energies across all five target proteins, indicating its potential for further investigation.

Conclusion

This study successfully employed network pharmacology to elucidate the potential mechanisms by which Aloe vera constituents might exert beneficial effects in diabetic cardiomyopathy. The findings suggest that these constituents act through a multi-component, multi-target, and multi-pathway approach, potentially influencing key signaling pathways and cellular processes involved in DCM development. The identified target genes and the predicted binding interactions with Aloe vera constituents provide a valuable starting point for further research. Future in vitro and in vivo studies are warranted to validate the in silico findings and explore the therapeutic potential of Aloe vera constituents in DCM treatment.

This study acknowledges certain limitations. The in silico nature of the investigation necessitates further experimental validation through in vitro and in vivo studies. Additionally, the study focused on a limited number of Aloe vera constituents. Further research could explore a wider range of constituents to gain a more comprehensive understanding of the plant's therapeutic potential.

Overall, this study presents a promising approach to investigating the therapeutic effects of natural products like Aloe vera in complex diseases like diabetic cardiomyopathy. By employing network pharmacology and computational tools, researchers can gain valuable insights into the underlying mechanisms of action and identify potential drug candidates for further development.

Results-

In Pharmacokinetic Properties and Toxicity Prediction the top 5 constituents of Aloe vera (Barbaloin, Aloenin, Aloesin, Aloinoside A, and Elgonica Dimer A) comply with Lipinski's Rule of Five, predicting good oral bioavailability and drug-likeness. SwissADME confirmed no observable toxicity for these constituents. In the GO and KEGG Enrichment Pathway Analysis gives the key Findings are Enrichment analysis identified significant biological processes, molecular functions, and cellular components related to diabetic cardiomyopathy (DCM). The pathways were visualized in a bar graph (Figure 3) and interactive network plots (Figures 4 and 5). In the Protein-Protein Interaction (PPI) Network the top 10 targets by degree are AKT1 (9), TNF (8), MMP9, CASP3, TP53 (6 each) show the highest connectivity in the PPI network, suggesting they play critical roles in DCM pathways. In degree analysis of Aloe Vera constituents the top 5 constituents by degree are aloinoside A (6), aloesin (5), aloenin (4), elgonica dimer A (4), and barbaloin (3) indicate significant involvement in DCM-associated pathways. Molecular docking results criteria indicates that binding energy less than -5.0 kJ/mol indicates good binding and binding energy less than -7.0 kJ/mol indicates strong binding. Binding Energies for Core Targets indicates that barbaloin has Strong binding with CASP3 (-7.6) and EGFR (-7.6). aloesin has Strong binding with EGFR (-7.8) and CASP3 (-7.0). aloenin has Strong binding with CASP3 (-7.5) and EGFR (-7.2). elgonica Dimer A has Exceptional binding with EGFR (-14.0), CASP3 (-13.3), TNF (-12.3), and AKT1 (-11.1). Aloinoside A has strong binding with CASP3 (-8.0), EGFR (-8.0), and HSP90AA1 (-8.2). Elgonica Dimer A displayed the strongest binding affinity across all targets, with particularly exceptional results for EGFR and CASP3, making it a promising candidate for therapeutic intervention. Aloesin and aloenoside A also showed high binding affinities to several targets, supporting their potential effectiveness in modulating DCM-related pathways.

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