EXPLORING THE POTANTIAL OF *Ziziphus jujuba* IN ARTERIOSCLEROSIS: A NETWORK PHARMACOLOGY APPROACH

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DEEKSHA PANDEY

(2K22/MSCBIO/17)

Under the supervision of

DR. NAVNEETA BHARADVAJA

Assistant professor

DEPARTMENT OF BIOTECHNOLOGY

DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)

Shahabad Daulatpur, Bawana Road, Delhi- 110042

June, 2024

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Shahabad Daulatpur, Bawana Road, Delhi- 110042

CANDIDATE'S DECLARATION

I Deeksha Pandey hereby certify that the work which is being present in the thesis entitled Exploring the Potential of *Ziziphus jujuba* in Arteriosclerosis: A network pharmacology approach partial fulfillment of the requirements for the award of the Degree of Masters of Science, submitted in the Department of Biotechnology, Delhi Technological University, is an authentic record of my own work carried out during the period from Aug 2023 to March 2024 under the supervision of Dr. Navneeta Bhardvaja

The matters presented in the thesis has not been submitted by me for the award of any other degree of this or any other institute.

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DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Shahabad Daulatpur, Bawana Road, Delhi- 110042

CERTIFICATE

Certified that Deeksha Pandey (2k22/MSCBIO/17) carried out their research work presented in this thesis entitled "**Exploring the potential of *Ziziphus jujube* in Arteriosclerosis: A network pharmacology approach**" for the award of Master of Science from the Department of Biotechnology, Delhi Technological University, Delhi, under my supervision. The thesis embodies results of original work, and studies are carried out by the students herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

Place - New Delhi

Date -

Dr. Navneeta Bharadvaja

Assistant Professor

Department of Biotechnology, DTU

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EXPLORING THE POTANTIAL OF *Ziziphus jujuba* IN ARTERIOSCLEROSIS: A NETWORK PHARMACOLOGY APPROACH

DEEKSHA PANDEY

ABSTRACT

The use of traditional herbal medicines in the medical management of various acute and chronic conditions in the modern world has been enhanced through the integration of the two. The antitherapeutic property of *Ziziphus jujuba* plant, a plant commonly referred to as jujube, is examined in relation to arteriosclerosis, a life-threatening cardiovascular disease. *Ziziphus jujuba*, also known as jujube fruit or ber in India, has long been used for traditional medicine, with the bark of the root used to treat coughs, biliousness, and headaches, and the bark of the stem used to treat boils, dysentery, and diarrhea. The plant exhibits various pharmacological properties as mentioned, which include anti-inflammatory, anti-microbial, anti-cancerous, cardioprotective, nephroprotective, anti-oxidant, gastrointestinal protective property and others. Therefore, we analyzed its bioactive chemicals and protein-target interactions with arteriosclerosis proteins consistently identified by network pharmacology and molecular docking. As by using network pharmacology we can understand complex disease, finding hub genes that are more closely related to the disease and for netter molecular docking results. The outcomes identified several highly effective phytochemicals in ZJ that bind to relevant target genes related to the development of arteriosclerosis. Molecular docking further proved drugs attachment probability to critical proteins including TNF and IL-6. Thus, the results presented in the work show that *Ziziphus jujuba* has high antigeneotic activity and possesses significant anti-arteriosclerotic effects which can serve as the basis for its use in the treatment of cardiological diseases.

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Name of Authors: Anjali Sharma, Deeksha Pandey, Navneeta Bharadvaja*

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LIST OF ABBREVATIONS

1- ZJ – Ziziphus jujube
2- CVD- Cardiovascular Disease
3- NO- Nitric Oxide
4- COX- Cyclooxygenase
5- CI- Critical Ischemia
6- PCSK9- (Proprotein Convertase Subtilisin/Kexin Type 9)
7- IMPPAT- Indian Medicinal Plants, Phytochemistry And Therapeutics.
8- RCSB PDB- Research Collaboratory for Structural Bioinformatics Protein Data Bank
9- OMIM- Online Mendelian Inheritance in Man

CHAPTER 1

INTRODUCTION

1.1 Background

Modern medicine has been complemented with traditional herbal treatment that has recently boosted world health systems by quickly curing many acute and chronic diseases contrary to long conventional treatments with several side effects. Herbal plants are used to cure diseases like diabetes mellitus, cancer, cardiovascular disorders, TB, wound healing, asthma, hypertension, etc. of human being. These natural remedies have been in use for centuries in cured prevention and treatment of human diseases. The continued consideration of these medicines in the present has further expanded their impact on the world's medical and health care systems today. For over a thousand years, various different plant species have been considered important for the syntheses of therapeutic agents, and numerous pharmaceuticals are still derived from natural plant compounds. Herbal medicine has an irreplaceable position in the traditional and advanced branches of medical sciences.

It is significant to note that today about 75% – 80% of the world population, and especially in the developing countries depends on natural products for primary health care by Murugan et al. (2021). This can be due to the cultural acceptability that is improving, compatibility with the human body, and minimal adverse reactions reported on these medications. The world health organization defines traditional medicines, including herbal pharmaceuticals as medicinal techniques that can be traced hundreds of years back to the present time. India has around 45,000 plant species and therefore known as the "Botanical Garden of the World" due to its high production of therapeutic herbs. In rural parts of India about 70% of population is directly dependent on the herbal medicine by Chopra et al. (1986).

Herbal extracts and the derivatives found in plants have the potential to strike and enhance molecular message pathways of hypertension and atherosclerosis – both of which are the major contributor of Cardiovascular diseases (CVD). Consequently, these herbs offer a high level of effectiveness in different fields of natural therapies targeted at improving the cardiovascular system by Shaito (2020). While several plant-based chemicals have cardiovascular preventive properties, the most effective ones include: Flavonoids, terpenoids, saponins, and polysaccharides are some of the bioactive compounds that have been linked to have a positive effect on human health. This makes herbal medicines to focus on molecular matters, providing a broad vision for CVD prevention and treatment, as revealed in this thesis, that herbs are valuable and effective resources in natural medicine. *Ziziphus jujuba* (ZJ), also known as Chinese date or Indian ber, is a highly valued medicinal herb due to its nutritive and pharmacological characteristics, which are primarily linked to phytochemical constituents. It is an indigenous, medium-sized plant from the Rhamnaceae family and very well-known for producing one of the earliest and most useful fruits for Chinese people by by Lu et al. (2021).

It contains about 293 total phytochemical compounds in different plant parts. The phytochemical compounds present in the plant are Vitamin 'C', phenolic, flavonoid, triterpenic acids and polysaccharides. In the past it was taken as a general strengthening aid as well as given because of its aphrodisiac effects; it is also a hypnotic, a sedative, and an anxiolytic by Preeti et al. (2014). In addition, the drug possesses some other pharmacological effects such as exposure of anticancer activity on melanoma cells, antifungal and antibacterial effects, role in the management of ulcers, anti-inflammatory action, improvement of cognitive function, antispasmodic potential, contraceptive ability, hypotensive and antinephritic effect, cardiotonic ability, antioxidants offer, immunomodulation ability and promotion of wound healing. This broad anti-inflammatory profile of *Ziziphus jujuba* further underlines the diverse pharmacological uses of this plant in therapy and medicine, and therefore warrants further research and efforts be directed towards its complete utilization. Juju, a new jujube fruit, not only is consumed globally as a healthy, delicious fruit but also becomes a versatile ingredient for both cooking and medicinal recipes in traditional Chinese medicine formulation. Once they wither, jujube can be used as an ingredient in fruit-food items and tea-based dishes including those used in traditional medicine purposes, as well as cultural ceremonies which the inclusion of delicious tastes and health benefits by Zhu et al. (2024).

According to its extensive literature analysis, it is an important component of traditional medicine with the potential to prevent diseases and improve health. It not only has relevance in the conventional medicine but also in the modern medicine systems. It is still an important one needing more investigation due to the variation in its morphology, rich diversity, numerous pharmacological uses, and strong bioactive compounds. If further research will be initiated regarding the pharmacology and the mode of action of jujube, it

can enhance its application in managing cardiovascular diseases like arteriosclerosis as well as various other diseases, it also eliminates the gap between the practice of traditional health care and advanced techniques.

1.2 Objectives

1. A deep research analysis into the potential of *Ziziphus jujuba* in the treatment of arteriosclerosis. Therapeutic uses, specifically focusing for cardiological pathologies, and other potential activities of the plant that might be considered an important factor for the treatment of arteriosclerosis.

2. Conducting network pharmacology to find out the potential core targets along with the important phytonutrients.

3. Conducting molecular docking of gene targets and potential phytonutrients for evaluating the efficiency of their bindings.

4. Further recommendation for a future study to incorporate further the *Ziziphus jujuba* for treating arteriosclerosis and other cardiovascular diseases.

CHAPTER 2

LITERATURE REVIEW

2.1 *Ziziphus jujuba* and its phytopharmacological uses:

1-Taxonomical Description

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida

Order: Rosales

Family: Rhamnaceae

Genus: Ziziphus

Species: jujuba

2-Biological diversity of the plant

Ziziphus Jujuba is a popular plant species, particularly in northern China, because to its numerous economic and ecological benefits. It is found in tropical and subtropical temperature zones of Europe and Asia, and its range includes India, China, Iran, Russia, the Middle East, and other countries by. Jujube trees are well recognized for their ability to grow in locations with high levels of soil salt and alkalinity by Gao et al. (2013) and hence may be planted in diverse regions of the world including plains, sunny slopes, cliffs and barren hills by Aafi et al. (2022). The archaeological data analysis, together with the discovery of jujube seed fossils by Chinese experts, reveals that jujube has been farmed

in China for the past 8000 years. Jujube has been used in traditional Chinese medicine since time immemorial, or for over 3000 years, and is one of the earliest fruits utilized in treatment. As a result, it can adapt well in varied habitats; it consequently has a high probability of surviving the effects of climate change such as variations in temperature.

This is consistent with historical accounts of the jujube fruit being consumed and possibly sold since ancient times, as mentioned in the Classic of Poetry from the Western Zhou Dynasty (1046-771 BC) by Chen et al. (2017). Nowadays, jujube-based goods can be found all over the world, indicating that this botanical resource is still important and valuable. As a result, jujube's ability to grow in the current climatic change condition, when climate change is still altering the entire world's ecosystems, qualifies this fruit as a component of the world's plant genome and an important addition to plant life by Guanghua et al. (2021).

3-Plant Morphology and phytochemistry

The species has a diverse phenological variation, whereby it can grow as small to medium-sized shrubs, spreading semi-erect or erect trees. Tree heights vary between 3-4 to10–16 meters or more, but trees with a height of 20 meters or more are rare. It is a tree that has many branches and is semi-deciduous in nature by Xinwen et al. (2018) and Preeti et al. (2014).

The outer layer of the stem belongs to *Ziziphus jujuba* is grayish brown or reddish with deep furrows. This shrub or tree has thorns though they may not be present in some species of this plant. The young branches of the tree are densely covered with white hairs, and they are also zigzag; the branches and twigs become erect and flexuous with a dull brown-gray color as they grow older. The fruiting branches are kept on the plant. The leaves are elliptic to ovate or suborbicular with rounded or acuminate apices and often symmetrical bases. It has small serrations at the margins, and three longitudinal veins on the fore wing extends almost to the apex. The upper surface of the leaf is green and glabrous while the lower surface is pale or light yellowish with dense pubescent hairs; sometimes it may be glabrous By Xinwen et al. (2018). The leaves have short petioles (1. 1–5. 8 mm), and there are two types of stipule: one of them hooked and one of them straight in each pair, or both hooked, or both may develop into one spine.

The flowers have sepals which are covered with wool, a disk which is 3mm in diameter and an ovary with two chambers located in the disk. The styles are 2mm long and are connected in the middle where they can be seen. These flowers are not fragrant and have an unpleasant smell, and they grow in clusters or cymes. These cymes can be sessile or have short petioles (1-4 mm), which are also covered with densely matted woolly hairs. The fruit is a smooth, edible drupe that ranges in size from 1 to 2 cm in diameter; oval shaped fruits can grow to be up to 5×3 cm. The outer surface of fruit of *Ziziphus jujube* can either be rough or smooth, ranging from yellow to green to reddish depicting varied state of development. The seed inside the fruit is single and very hard with a rough surface

shapes ranging from round to oval by Xinwen (2018) and Chen and Tsim (2020). The pulp of the fruit is sweet with a low PH (acidic). Many types of substances, including polyphenols, alkaloids, terpenoids, polysaccharides, fatty acids, vitamins, proteins, and organic acids, are present in different parts of the plant in variable amounts.

Table I. Different phytocompounds with their sources of the plant

Phytochemical Class	**Compound(s)**	**Source/Part**	**References**
Alkaloids	Ex- Isoboldine, Mauritine-A, Sativanine-C, Frangufoline (antibacterial), Frangulanine (sedative)	Leaves, Bark, Stem bark, Root bark	Tschesdche et al. (1979), Shah et al. (1985), Ziyaey et al. (1987), Devi et al. (1987), Otsuka et al. (1974)
Glycosides	Ex- Spinosin (2"-O-β-glucosylswertisin)	Seeds (var. spinosa)	Woo et al. (1979)
Saponins	Ex- Jujubosides A, B, A1, B1, C, Ziziphin,	Seeds, Dried leaves	Zeng et al. (1987), Yoshikawa et al. (1997), Mastuda et al. (1999), Kurihara et al. (1988)
Flavonoids	Ex- Swertish, Spinosin, Quercetine 3-O- robinpbioside	Fruit and seeds	Cheng et al. (2000)
Terpenoids	Ex- Zizyberenalic acid	Fruits	Lee et al. (2003), Sang et al. (2004)
Phenolic Compounds	Ex- Betulinic acid	All parts	Pawlowska et al. (2000)

4-Pharmacological Properties

The pant exhibit diverse pharmacological activities like anti-inflammatory activity, anti-aging activity, anti-cancer activity, wound healing activity, cardioprotective activity, neuroprotective activity, antiviral activity, antioxidant activity and others making *Ziziphus jujube* a valuable plant for the treatment of varied range of diseases with high therapeutic potential. Though further studies are still needed for understanding its benefits in detail that can be utilized for future health conditions. various pharmacological properties of the plant are summarized below.

1-Anti-inflammatory Activity:

Leave extract of plant possess anti-inflammatory activity by Kumar et al. (2004) and even several investigations have found that hydroalcoholic extract of plant has promising anti-inflammatory properties in both acute and chronic inflammation paradigms in rats. It accomplishes this by targeting cyclooxygenase (COX), nitric oxide (NO), and histamine by Goyal et al. (2011). It specifically inhibits macrophage NO generation and splenocyte mitogenesis. Among all the 21 chemicals extracted from the plant it was found that the terpenoid acid fraction exhibits the greatest anti-inflammatory effect by Yu et al. (2012).

2-Anti-microbial Activity:

Snakin-Z is a peptide produced from jujube that has extensive antibacterial and antifungal properties and acts best against gram-negative bacteria by Daneshmand et al. (2013). It is therefore obvious that *Ziziphus jujuba* extracts contain antibacterial activities against E. coli and S. aureus, with variations in antibacterial effectiveness amongst extracts. According to a study, ethanol extract of the root part shown to have anti-fungal properties while extract of the root bark part of plant is shown to have antibacterial properties by Saefaraz et al. (2002) and Elmahi et al. (1997).

3-Antioxidant Activity:

Fruits of the plant are known to have reasonably high level of total phenolics and flavonoids, thus, having strong antioxidant properties by Sun et al. (2011). It can more easily be understood in fruits which are specifically grown with environmental stress. Peel of the plant contains more phenolic compounds, flavonoids, anthocyanins than any other part of the plant, as well as the highest antioxidant activity by Esteki and Urooj (2012). Water-soluble polysaccharide fractions containing uronic acid, specifically ZSP3c and ZSP4b, exhibit higher antioxidant activity by Li et al. (2011).

4- Neuroprotective Activity:

Ziziphus jujuba extract protects neurons from glucose-induced cytotoxicity in the PC 12 cellular model, as well as oxidative stress in the hippocampus of rats exposed to ethanol. It has been proven that they minimize apoptotic cell death, ROS production and LPO, and increased GPx activity by Kaeidi et al. (2015) and Taati et al. (2011).

5- Anti-Alzheimer Activity:

Oleamide a pharmacologically important compound was extracted from jujube fruit, it was found that it protects against cholinergic toxicity and also promotes choline acetyl transferase, making it suited for Alzheimer's disease by Heo et al. (2003). Furthermore, Snakin-Z peptide contains antioxidant and anticholinesterase properties that are important in Alzheimer's disease treatment by Zare-Zardini et al. (2013).

6- Cardioprotective Activity-

Jujube peel phenols prevent the effects of isoproterenol and aluminum chloride on cardiac and cerebral tissues while also altering antioxidant enzymes, serum indicators, and blood counts by Cheng et al. (2012).

7- Nephroprotective Activity:

In terms of nephrotoxicity, the current study's findings show that Jujube fruit extract improves histological damages, serum urea, and creatinine concentrations, as well as antioxidant enzyme activities that are reduced by ibuprofen by Awad et al. (2014).

8- Anti-Cancer Activity:

Jujube extracts' (from fruits to aqueous extract) capacity to induce apoptosis and decrease cell growth makes them potentially effective against a variety of cancer cells, including breast, cervical, laryngeal, and hepatoma cells. Its anti-cancer actions are dose-dependent, affecting the tumor cell cycle and inducing cancer cell death at varying stages if jujube ripening. According to some studies, the plant is also considered to be good a source (natural) in the chemotherapy as a chemotherapeutic agent by Hoshyar et al. (2015).

9- Gastrointestinal Protective Activity:

The extract of *Ziziphus jujuba* fruit has been shown to have positive effects for ulcerative colitis, persistent constipation, and colon cancer and also decreases the number of WBCs and platelets by reducing inflammation, thus exhibiting anti-inflammatory properties, normalizes the histomorphology of colon tissue in all studies on humans, and reduces constipation by Periasamv et al. (2015) and Naftali et al. (2008).

5- Medicinal Uses:

Ziziphus jujuba, often known as jujube fruit or ber in India has been widely used for traditional remedies, offering several medicinal effects earlier which includes bark of root used to treat coughs, biliousness, and headaches, whereas the bark of stem used to treat boils, dysentery, and diarrhea by Kritikar and Basu (1994). The leaves have anti-pyretic properties and can help reduce obesity, whereas the fruit can be used as a cooling, digestible, tonic, aphrodisiac, and laxative, as well as to treat biliousness, burning sensation, thirst, vomiting, tuberculosis, and blood diseases by Chopra et al. (1986).

Both the dried and fresh leaves and bark in the powdered form is used to heal wounds while in case of burning wounds a liquid or aqueous paste of the leaves is applied. Each part of plant exhibits large number of pharmacological properties like the seed of jujube fruit treats eyes disorders as well as leucorrhea, some people also juice fresh leaves and blend them with buffalo milk to treat smallpox. *Ziziphus jujuba* fruits include vitamins C, B1 (thiamine), B2 (riboflavin), and bioflavonoids, and consuming one fruit per day provides the daily recommended value of these vitamins as they are present in a very good amount by Kuliey et al. (1974).

2.2 Arteriosclerosis

2.2.1 Overview

Cardiovascular diseases are the major causes of death in the world, according to a report about 17 million deaths or more than that has been occurred in 2017 itself by Roth et al. (2017). Among which a large number of diseases have occurred due to artery wall disorders, including Arteriosclerosis, Monckeberg medial calcific sclerosis, Atherosclerosis. Arteriosclerosis is typically defined as a disease in which fats, cholesterols, and other materials accumulate along the walls of arteries, obstructing the flow of blood affecting arteries in the heart, brain, arms, legs, pelvis, and kidneys, resulting in major health consequences. It is a Greek word with a meaning “hardening of the arteries”. In other words, it is basically the result of oxidation of lipids along with abnormal level of lipid/fat in the blood.

It plays an integral part in microvascular disorders such chronic renal failure, vascular dementia, and Alzheimer's disease by Dagenais et al (2019) and Mitchell (1985). In the developed countries it has been the major cause of mortality and considered as a chronic inflammation, currently become more common. To date, no RCTs have been completed, and several human studies using diverse measuring methodologies and epidemiological characterizations have failed to identify a definitive genetic basis for arterial stiffness by Niiranen et al. (2017).

A condition in which the artery walls harden and thicken, primarily due to the deposition of collagen. This sclerosis, particularly in the aorta, increases the burden on the left ventricle, resulting in hypertrophy, decreased relaxation and filling during diastole, and an increased risk of developing heart failure in the absence of systolic dysfunction. The stiffening also has an effect on normal pressure gradients, and the pulsatile pressures produced by numerous organs, including the brain and kidneys, are unusually high and harmful to microcirculation.

Obesity induces aortic dilatation due to increasing cardiac output with aging, since the aorta diameter naturally expands to support the higher pace. Because of the significant risk associated with aortic arteriosclerosis and the fact that the disease primarily affects middle-aged and older people, the disease's burden in the population is projected to rise if people do not take preventative measures. Even while arterial stiffness with age is natural, it does not have to be, emphasizing the need for more research into what causes it and how to promote healthy vascular aging by Niiranen et al. (2017). Arteriole thickening can be classified into two types: hyaline and hyperplastic arteriolosclerosis by Fishbein and Fishbein (2009). Hyaline arteriolosclerosis is a frequent disease that is linked to hypertension. This illness can affect both the kidneys and the brain. In hypertensive patients, hyaline arteriolosclerosis of the afferent glomerular arteriole causes chronic renal hypoperfusion and glomerulosclerosis, which can lead to chronic kidney failure.

The disease's pathologic alterations in the brain manifest as Charcot-Bouchard microaneurysms, which cause intraparenchymal bleeding and are considered a severe condition in individuals with hypertension. Hyperplastic arteriolosclerosis lowers the Artemisinin lumen by enlarging the arteriole walls by Hill (2008). It also contains numerous smooth muscle blood leading to thrombosisuscle cells and multiple layers of the basement membrane, found in essential hypertensive cases. Arteriosclerosis involves either stable plaque or unstable plaques, stable ones are slower and static as compared to unstable plaque and less complicated too by Jonason and Bergstrom (1987). Thus, mostly the clinical events occur due to the complication in unstable plaques causing thrombosis, infraction, stenosis. Stabilization of plaque can prove to be good treatment if we want have less complications, in turn reducing mortality related to arteriosclerosis. Rupturing of plaques occur through enzymes which are secreted by activated macrophages, as soon as the plaque ruptures it comes in direct contact of blood, ultimately leading to thrombosis. Arteriosclerosis is mainly classified into three classes which are discussed in the table 2.2.

Table II. Classification of Arteriosclerosis

Classes	Description	Factors	Diseases	References
Atherosclerosis	Disease of the elastic and large muscle arteries, characterized by atheroma lesions. Lipids, connective tissues, inflammatory cells, matrix proteins, enzymes, and calcium deposits all contribute to the expansion of the artery intima.	High level of cholesterol, hypertension, smoking, diabetes, obesity, poor diet, physical inactivity	Coronary artery disease, peripheral artery disease, stroke	Gregory et al. (2009), Santos et al. (2021)
Monckeberg Medial Calcific Sclerosis	The calcification process affects the media of large and medium-sized arteries. Only the tunica media is affected, leaving the artery lumen intact. It is a very rare disease usually observed in adults over the age of 50.	Diabetes, genetic predisposition, Age, chronic kidney disease	It might co-exist with atherosclerosis	Gregory et al. (2009)
Arteriosclerosis	Arteriole lesions are tiny artery blood vessels with one or two layers of smooth muscle cells. There are two subtypes: hyaline and hyperplastic. It is typically related with hypertension and diabetes mellitus.	Hypertension, diabetes, aging, genetic factors	Hypertension, nephropathy	Santos et al. (2021)

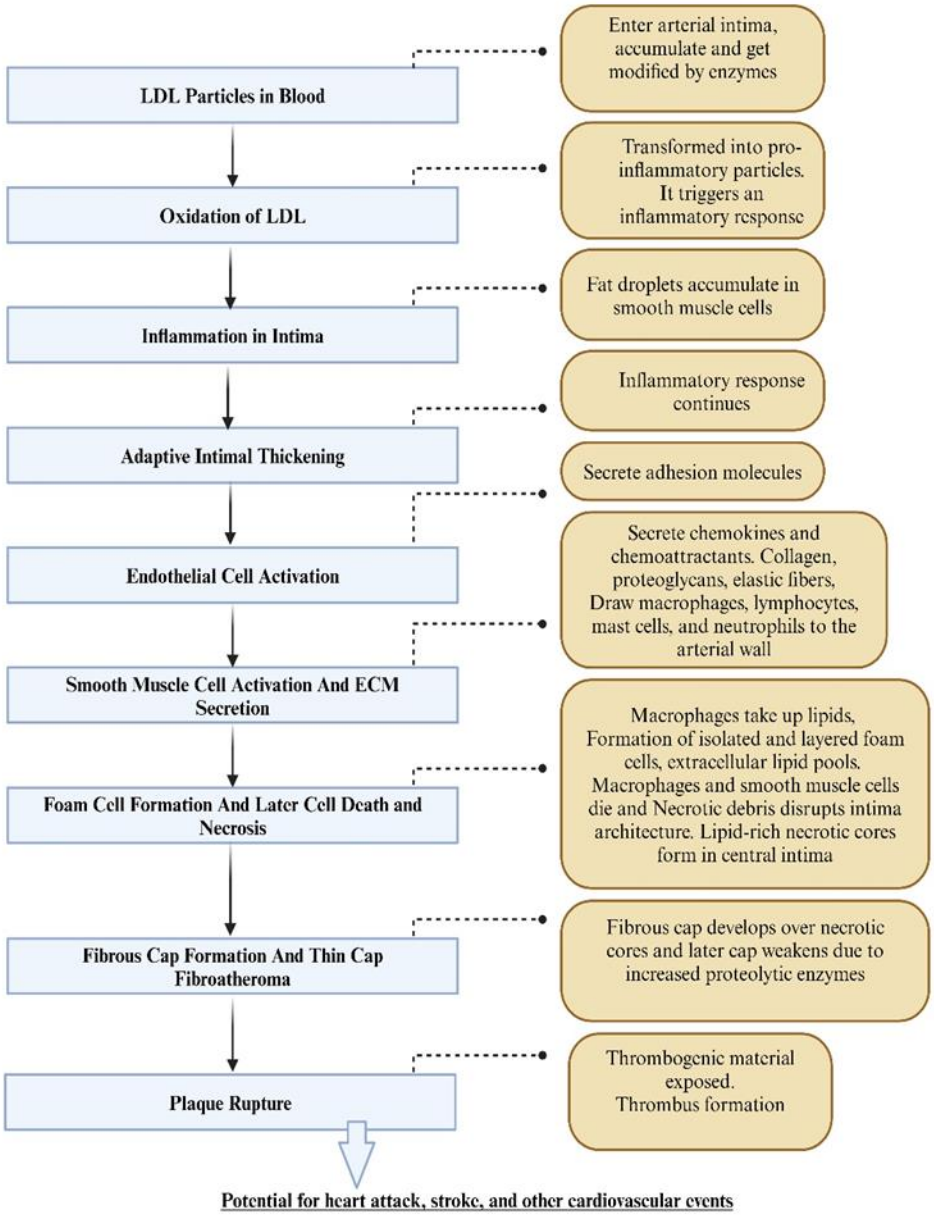


Fig 2.1 Pathway of Arteriosclerosis

2- Symptoms, Diagnosis and Treatment of Arteriosclerosis-

If we talk about the symptoms of it, at first it is asymptomatic, with time when lesions interfere with the movement of blood in the arteries might develop symptoms (the artery is either fully or partially blocked/narrowed limiting the supply of blood to various organs)

and later when plaque grows, lumen of arteries reduces, increasing the tension causing transient ischemic symptoms and a lot more, in serious cases it can cause sudden death by Cannon et al. (2004).

Affecting various location in the body; majorly including heart arteries, brain arteries, arm and leg arteries and kidney arteries causing pain in chest (angina), trouble in speaking and understanding with blurry speech, temporary loss in vision of one eye, mild cramps during walking, hypertension, kidney disorders, dropping of the face from one side that could even point to a stroke etc. Such patients should be evaluated depending upon their genetic history, past, lipid profile, physical examination, glucose level etc. by British National formulary (2014).

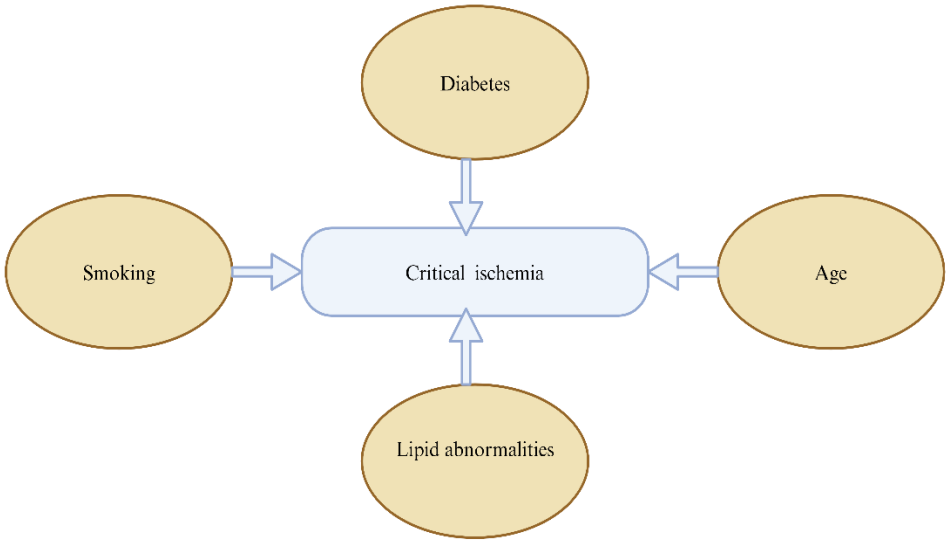


Fig 2.2 Risk factors associated with critical ischemia (CI)

Various approaches have been considered with varying mechanism, each distinct from other along with their potential to treat the disease, their efficiency with varied amount of adverse effects each had.

- Statins- It is considered as the first-line of treatment for both the primary and secondary prevention in cardiovascular diseases. The drug maintains an enzyme called HMG-CoA reductase which is responsible for increasing the uptake of LDL cholesterol in the liver along with decreasing the synthesis of cholesterol. Trials have been done and according to them statin is found to be beneficial in the prevention of coronary events, specifically in high risk patients, but have some adverse effects too Kumar Gupta et al. (2019).

- PCSK9 Inhibitors (Proprotein Convertase Subtilisin/Kexin Type 9)- These drugs are significantly responsible for lowering LDL Cholesterol level. Evolocumab is the monoclonal antibody, a very well studied PKCS9 inhibitor, it has been studied in detail to consider it as a part of combination therapy instead of the monotherapy with better potential to treat the disease Kumar Gupta et al. (2019). Though they have proved to be effective in preventing major cardiovascular event but further more trials are needed to be done to validate their long-term efficiency.

- Fibrates- Based on clinical trials for primary and secondary prevention, it was discovered that fibrates have good therapeutic potential, as they reduce major circumstances that can lead to cardiovascular problems. They have a detrimental effect on glomerular filtrate rate by Kumar Gupta et al. (2019), but statins have been demonstrated to have renal protective characteristics, particularly for those at high risk.

- Cholesterol Absorption Inhibitors- Ezetimibe is the most common and frequently used cholesterol absorption inhibitor, lowering LDL cholesterol by limiting cholesterol absorption in the intestines; nevertheless, statins cut LDL-C more Kumar Gupta et al. (2019). Though there is some evidence that CAI plays a substantial role in decreasing LDL-C levels, it has not been fully demonstrated to be helpful in cardiovascular events. These medications can be used in combination to improve one's efficacy while reducing the detrimental effects of others in the treatment of arteriosclerosis and other cardiovascular disorders.

2.3 Exploring Network Pharmacology for the Treatment of Challenging Diseases like Arteriosclerosis

Basically, network pharmacology is an integration of pharmacology and systems biology where pharmacological actions, targets, and networks are viewed within the framework of a system. This method offers large amount of information regarding the multifaceted diseases, the process of their formation, target drugs for diseased-tissues, and their treatment/ therapies. Disease processes are genotype and phenotypic interactions and the product of multiple molecular interactions.

It enables the establishment and subsequent evaluation of disease-related networks; It identifies and demonstrates relationships between molecules that are associated with the pathophysiology of a disease. Network pharmacology is a link between the disease-associated biological processes derived from omic data, drug-target, and protein-protein interaction. This all-round understanding will assist in the ability to define the exact molecules operating within the disease and the course of signals to manipulate besides the

vital spots to augment. The whole process of network pharmacology done is sequentially presented in the below fig 2.3.

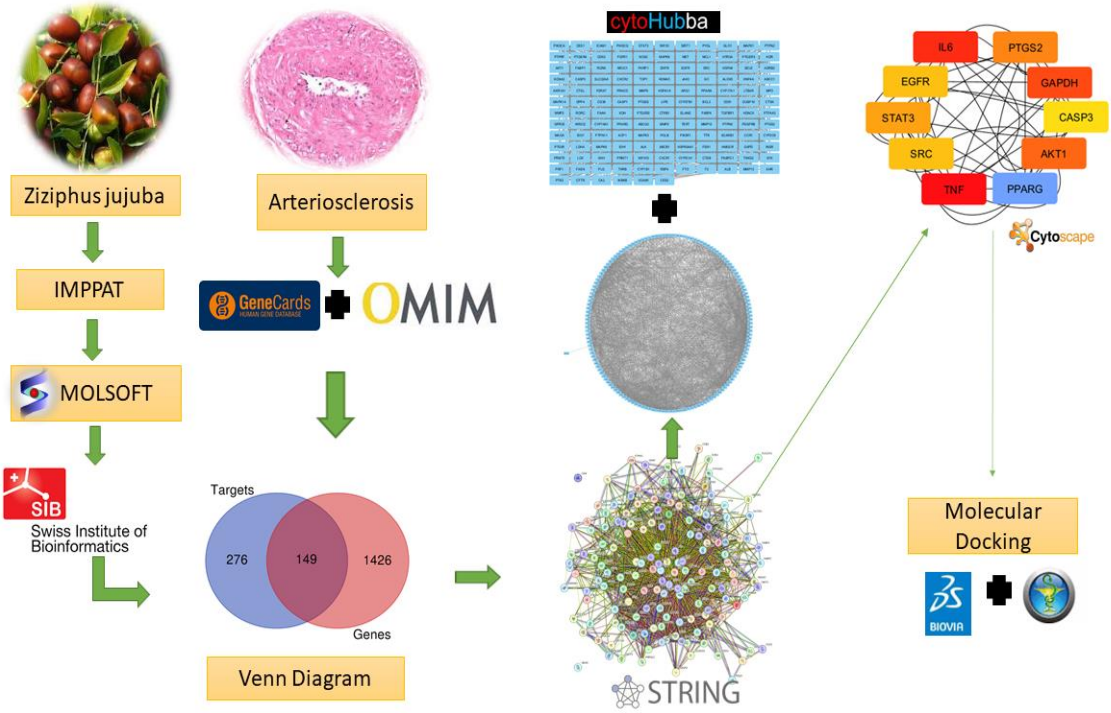


Fig 2.3 The process of network pharmacology

But for the distinction between network pharmacology and systems biology, the latter is a division of the former to some extent. This can assist the therapeutically and genomic data of the Network pharmacology to provide a comprehensive understanding of diseases and effects of therapies at the network level. While proteomics, metabolomics and clinical data can help identify potential biomarkers for arteriosclerosis, there is no robust biomarker set that is State-of-the-art diagnostic for arteriosclerosis. This technique thus enables individualized management of care as every individual's treatment program can be dependent on the individual's genetic roots and the physical arrangement of the topographical structure of the disease. It is worth mentioning that, at least one of the above presented, multi-target and multi-pathway model can be elicited in the context of the disturbance of the multifactorial diseases. Polypharmacology is defined as the attempt to get more than one physiological outcome by a compound that acts at multiple receptors. This is well understood or accepted in network pharmacology.

The complexity of diseases especially chronic illnesses is analyzed in network pharmacology since it is an expansion of pharmacology research. TCP is a systematic approach to the identification of complex multi-targeted drugs or drug synergistic of complex diseases based on drug-target networks. It can facilitate the individualized therapy using model predicted drug responses and combination treatments which are specific to each patient's biological markers and their associated network topology.

The network pharmacology approach interprets the disease mechanisms systematically, aids drug repositioning, locus effective targets, encourages polypharmacology and combination therapy, and forecasts poor prognosis. Drugs derived reactions and particular treatment approaches have shifted the investigation of complicated ailments. There is no doubt that integration of pharmacological, systems biology, and network study has indeed revolutionized disease research. Also, it has the opportunity to enhance the ways for creating new medications themselves. As a result, by using a systemic approach, network pharmacology can improve drug discovery and reveal novel targets and disease pathways. It provides a counterbalance to overly simplified approaches to policy creation and execution. Certain constraints remain in data integration, handling model complexity, and experimentation. However, network pharmacology may aid in the identification of new targets and increasing the chances of discovering successful medications.

CHAPTER 3

MATERIALS AND METHODOLOGY

As it a computational analysis there is no need of materials to be present physically. It is done in a sequential manner by utilizing a number software, step by step for finding potential phytochemical that can be used for the treatment of arteriosclerosis by finding out their efficacy to bind the potential gene target that can cause the disease.

3.1 TOOLS & SOFTWARES

3.1.1 IMPAAT

Its most noteworthy database, IMPPAT (Indian medicinal plant database), contains a wealth of information on phytochemicals found in traditional Indian medicinal plants. This online tool allows you to easily search for natural product-derived pharmaceuticals on this extensive website. IMPPAT has information about 1742 medicinal plants in India, 9596 phytochemicals in 2D and 3D, and 1124 therapeutic uses of these plants, resulting in the plantation of 27074 plant-phytochemical associations and 11514 plant-therapeutic associations by Mohanraj et al. (2018). The upgraded IMPPAT 2.0 has expanded the scope of its database; it now includes the entire picture at the plant part level, such as stems, roots, and leaves, and has a phytochemical database of 17967 without duplication by Vivek-Ananth et al. (2023).

3.1.2 PUBCHEM

The US National Institute of Health (NIH) created and maintains PubChem, an NCBI database in biochemistry. It is favored by researchers, patent agents, students, and millions of other individuals worldwide on a monthly basis. ChemSpider collects data on millions of compounds from over 1,000 sources, including siRNA, miRNA, lipids, carbohydrates, and chemically modified biopolymers 9640 by Kim et al. (2016). It is a massive database organized into numerous groups, including Substance, Compound, BioAssay, Gene, Protein, Taxonomy, Pathway, Cell Line, and Patent. The Substance database provides chemical descriptions supplied by database participants, whereas the Compound database contains information on independent structures formed from Substance. BioAssay primarily deals with activity data derived from assay experiments.

3.1.3 RCSB PDB

Protein Data Bank is a premier database for macromolecular crystal structures that was established at Brookhaven National Laboratories in 1971. At its inception, it only contained the coordinates for seven structures; however, the archive grew to critical mass in the 1980s as data collection methodology improved through crystallography and structures determined by nuclear magnetic resonance (NMR) were added to the Protein Data Bank as more data was shared among the scientific community. Towards 1993, various scientific journals and funding institutions asked that data be submitted to PDB, resulting in a considerable increase of entries by Berman et al. (2000).

The data access techniques evolved away from magnetic media and toward the World Wide Web, improving data availability. Brookhaven operated the PDB until 1998, when the Research Collaboratory for Structural Bioinformatics (RCSB) took over, seeking to improve its use with modern technologies for improved data utilization. The RCSB PDB's readership now includes biologists, chemists, computer scientists, educators, and students. PDB serves as a storehouse for experimentally determined 3D structures of proteins, nucleic acids, and other macromolecules. There are indexing tools that allow users to search the database in a variety of ways, as well as powerful visualization tools that reveal information such as protein secondary structures and binding locations. In addition to structure, the RCSB PDB includes functional annotations that explain the structure's context and relevance, making it a vital database for structural biology, bioinformatics, and drug discovery.

3.1.4 MOLSOFT

Molsoft offers molecular structure prediction-based software products and consulting, using bioinformatics and cheminformatics in the pharmaceutical arena. They provide niche services of computation chemistry & biology for biotech & pharmaceutical organizations. I have reviewed the websites of various software companies and concluded that Molsoft is one of the leading software companies when it comes to technological advancement and the presentation of credible and scientific information. MolSoft was founded in 1994 by Ruben Abagyan and involved in the structure prediction which means that it allows for the visual study of biological molecules on the atomic level. Its technologies help in molecular visualization / construction of protein structures / drug development targets / and virtual molecular libraries screening by Sachapira et al. (1999). Besides, it is applied in protein conformation prediction, protein and peptide design, and chemical information database management. They have developed and employed a highly relevant molecular modeling method named Internal Coordinate Mechanics (ICM). MolSoft's advanced algorithms and rules are applied to tackle various biomedical challenges.

Having mentioned MolSoft, the following gives specific explication of its high-level algorithms and rules used in such obstacles of biomedical science.

- The following picture has been drawn when it comes to the use of molecular structures and data transmission;
- The key development emphasizes improving and verifying the structural models of targeting proteins
- Since the proteins are compact structures of folding, implying that the structures indicating the biologically active ligands, in addition to new sites for allosteric regulation are intricate.
- In what ways does the concept of constantly reviewing and ranking drug targets like PPI interfaces lead to a more plausible framework of drug targeting?
- Molecular virtual screening Millions of compounds out there in the structural data bases Mol docking Flexible molecular docking Molecular scoring which has been used in Molsoft
- Determining residues based on the prior of interface propensity, meaning the positions of a protein amino acids sequence which plays a part in protein-protein contacts
- Protein structures: The following are the benefits of loops in secondary structure and the advancement gained from the present work compared to some of the earlier ones.
- An example of the application of such a paradigm in morphological design is to provide the means of directly declaring the desired morphological form of proteins and then using this form to characterize those proteins that are to assume certain forms.
- In limited and structureless peptide design the major aim is to score and rank the flexible peptide in respect of its corresponding protein.
- Biological activities such as signal transduction, cellular metabolism, immune responses, and developmental processes rely on protein-protein inter actions and peptides that selectively bind certain proteins and control their activity have been described as potential source of starting points to antidote useful for disorders resulting from improper protein-protein interactions.
- importing of some compound libraries, conversion of 2D to 3D, and clustering of the mentioned types

- That is, employing the techniques outlined and discussed in this chapter, it is possible to predict the characteristics of new chemical substances, build QSAR equations, as well as create and interrogate three-dimensional spacer receptors.

- Chemical structure database: As what is an enterprise, it is crucial to create chemical structure databases.

3.1.5 PRO-TOX

Another second-generation technology in pipeline currently is called ProTox-II a robust model employed in toxicity prediction of small molecules. All combined, ProTox-II features molecular similarity, Site-Map pharmacophore, and fragment propensity modeling, and can predict acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, and Tox21 adverse outcomes. Using Tox21, Ames bacterial mutations, HepG2 cytotoxicity, immunotoxicity as typical in-vitro assays, as well as complex in-vivo samples including carcinogenicity and hepatotoxicity, the platform develops its predictive models. As is with its predecessor, ProTox-II comes with a few features that are quite easy to use and can be operated without entering the web-based server with a login; it is for the toxicologists to predict the toxicity of chemicals, for the regulatory agencies, and for researchers in both computational and medicinal chemistry. In case of chemical two-dimensional structure there is an option to get 33 models of toxicity along the toxicity radar chart and a confidence level of toxicity. The other options that is available to the users are information about three similar chemicals that contain toxicity data by Banerjee et al. (2018).

One of the many benefits associated with ProTox-II is the model's ability to aid drug discovery programs and administrative choices. It helps regulatory organizations around the world, including the EMA, FDA, and environmental health protection agencies, examine the safety of chemical goods more quickly. In an environment with various chemicals and their compounds, ProTox-II is a precise in silico tool that aids in the reduction of costly and ethically sensitive animal trials. ProTafx-II improves chemical toxicity evaluation by incorporating toxicology, biostatistics, systems biology, and computer science into existing in vitro techniques. Nonetheless, ProTox-II provides extensive toxicity estimates, although this comes with downsides.

3.1.6 SWISS TARGET PREDICTION

Knowing how small molecules exhibit their bioactivity is important in the drug discovery process and in making decisions for approving or rejecting drug molecules. SwissTargetPrediction meets this need through a GUI based web tool for bioactive compound target prediction. Building on liability, SwissTargetPrediction searches for proteins that have known ligands that are predicted to be similar to the query molecule. While other methods use only 2D or 3D similarity comparisons or compute results for only one species, SwissTargetPrediction combines both 2D and 3D similarity measures and offers the target prediction for five different organisms; therefore, the tool enables

users to compare the target homology and map the predictions between and within the organisms by Gfeller et al. (2014).

SwissTargetPrediction works on the basis of the prediction that bioactive molecules always have the same targets. This is through FP2 fingerprints giving 2D similarity and conformation of molecules for 3D similarity giving Electroshape vectors. In this model, targets are ranked based on similarity values in a logistic regression of the format P(interaction) = 1/(1+e^-z), where interaction values range between 0 and 1. The data set involves five organisms, 280381 compounds interacting with 2686 target proteins where a large number of targets are proteins of human organism. This data set has been obtained from ChEMBL database. Nevertheless, Swiss Target Prediction may encompass some biases, but its prediction accuracy helps targeting identification of the new molecules that contribute to drug discovery and toxicity analysis.

3.1.7 GENECARD

Using the vast strength to envision practically all genomics data that is being generated in today's world of genomics research, GeneCards has been steadily consolidating the strength of human public data for nearly 15 years to generate the comprehensive annotation of all the human genes. Currently GeneCards catalogues developed from data assembly of over 80 online sources as a GC facility for over 73000 human genes under various categories of protein-coding, RNA-encoding non-coding genes genetic loci and much more by Safaran et al. (2010). This new develop of the updated and better version of GeneCards V3 allow the practitioners to have a searching utility and structural change with enhanced framework that appears to have echo with the changing face of biomedical infomancy. New and improved features of GOFUNC in this release are GeneALaCart and GeneDecks; two new Gene-set analysis tools for Micro array queries and Gene-ontology mapping between organisms and their annotations.

In addition, the new advance of GeneCards V3 officials includes much expanded graphical representation, link of the gene related research reagents and a new software tool known as 'Inferred Functionality Score annotation landscape function' all of which guides the wide prevailing knowledge to the researchers regarding the function and interaction of genes. In addition to this, GeneCards offers well-organised and easy-to-navigate web page, concise yet clear gene cards as well as other compelling features that place this organization as the gold standard for directing researchers on the jungle of human genomics.

3.1.8 OMIM

OMIM remains a unique and highly useful catalogue of human genes and genetic disorders to address different needs of all academic and professional sides interested in human genetics. MIM was founded in the early 1960s by Dr. Victor A. McKusick under the name of Mendelian Inheritance in Man, and it became a dynamic electronic source of information collected daily and accessible for free on the Internet. Provided and supported

by the Johns Hopkins University School of Medicine, OMIM provides easy access to the summaries of human genes and phenotypes with phenotypes and genes created by internationally collected literature and global researchers. Combined with the NCBI EntrezMolecular structure, OMIM has links to a large selection of genetic information, such as DNA and protein sequences, related PubMed links, mutation links and databases, and group support from the US National Library of Medicine by Hamosh et al. (2005)). OMIM thus offers concise and accurate information balanced by OMIM-annotated literature that makes it an excellent starting point for any researcher engaged in human genetics.

3.1.9 VENNY 2.0

Venny 2.0 is a multipurpose website with an option for constructing Venn diagrams, which are graphical representations of intersections of sets or groups of objects/genes. Its popularity, as an example of finding similarities and differences between sets, is rather vast ranging from biology to statistics and data analysis. Venny 2.1 offers its users the ability to input the data as lists or sets, and to create the Venn diagrams which can be drawn, manipulated, and annotated interactively; as well as providing the users with the possibility to alter the look of the diagram by changing the colors, the text sizes, and the thickness of the lines. In addition, get operations such as union, intersection and relative complement to other sets and additional analyze the link between these sets by Kaur et al. (2022). After generating Venn diagrams where users can choose simple or advanced option, they can export the final diagrams in the form of PNG image files suitable for presenting, reporting, or publishing, thus Venny 2.1 a useful assistance to the researchers and data miners, who have to use the overlapping data.

3.1.10 CYTOSCAPE

Cytoscape continues to be an important tool in the depiction, evaluation, and network modeling, offering itself as an extendable and open-source platform that connects many groups of network and systems biology and bioinformatics. In detail, the feature set allows users to create easy-to-understand and aesthetically pleasing visual images of networks that share various types of data, including various structures, and provides more flexibility in manipulating layouts, color, and line types to highlight the most important features of existing networks by Dutta and Roy (2020)). Cytoscape provides users with a number of simple plugins that allow them to examine network properties, clusters, motifs, neighborhoods, communities, and centrality calculations in order to clarify structural-functional connectivity.

3.1.11 CYTOSCAPE-CYTOHUBBA

CytoHubba is a plugin coming with Cytoscape that turn out to be handy for analyzing biological networks and identifying the most important and influenced hub or node. CytoHubba comes with numerous algorithms and techniques that provide centrality of nodes and help in ranking the nodes according to their importance in the network by Dashti

et al. (2020). CytoHubba offers various metrics such as node ranking with degree, betweenness, and eigenvector centrality regarding the network connectivity.

CytoHubba allows the user to find the crucial nodes through the hub analysis since these are the elements intertwined most closely which serve as essential connectors of the network. Furthermore, the plug-in offers different approach to calculate score such as edge-based score, neighborhood-based score, as well as centrality-based score. As for advanced settings, CytoHubba offers extra options that let the user change analysis parameters and select the scoring method of the networks. CytoHubba helps in understanding about the topology of the network and decoding about the functional and regulatory aspects of the important entities in the biological systems as it has provision to represent top nodes and their connections making it an essential tool for network biology research.

3.1.12 STRING

STRING-DB stands for search tool for the retrieval of interacting genes/proteins, a tool that is used for visualization of various networks, studying their interactions, in which display of the nodes and their edge is customizable, thus making it user friendly. It has data from various sources which might include literature, experimental results and computational modelling, making a complex network of both predicted and already known proteins through protein protein interactions. The tool provides fun enrichment analysis for understanding their functional context by Kong et al. (2023).

3.1.13 PyRx

PyRx is a drug discovery software that tests virtual molecules against possible therapeutic targets on a computer. Aside from its versatility, it allows medicinal chemists to screen libraries of molecules across several platforms. It is useful from data preparation and job application submission to result assessment time, and so cannot be overlooked in any computer-assisted medicine production by Dallakyan and Olson (2015). PyRx's docking wizard simplifies the complex tasks connected with virtual screening through a user-friendly interface. Furthermore, spreadsheets may be utilized to handle chemical data, and the software contains a powerful visualization engine, which is critical in rational drug design. PyRx is a must-have for every medicinal chemist because it includes all of the characteristics needed for successful research in this field.

3.1.14 OPEN BABBLE

The Open Babel GUI is an efficient bloated coherent application that can significantly help chemical informatics, computational chemistry and molecular modeling individuals. Structural detail Its work with an easy graphical user interface which is constructive to convert all chemical file formats those are available with smiles, Inchi PDB sdf xyz and mol2 format. The GUI is again relatively rich in tools for structure manipulation and

visualization, so that it is convenient to build structures, to optimize and to manipulate them by Suplatov et al. (2020). Also, the Open Babel GUI enables performing various activities in the evaluation of molecular descriptors, including molecular weights, LogP, and topological indexes so as to help in the study of chemical and physical characteristics. They are compatible with several other database platforms like PubChem and ChEMBL; the capability in scripting allows for automation and sophisticated modifications in a field like cheminformatics and molecular modeling.

3.1.15 BIOVIA DISCOVERY STUDIO

BIOVIA development Studio, previously known as Accelrys Discovery Studio, is a suite of computer tools designed specifically for drug development, computational chemistry, and molecular modeling. It includes more advanced capabilities designed primarily for structure-based drug creation, such as protein-ligand interaction analysis, virtual screening, and molecular docking. Furthermore, the platform offers ligand-based drug design, which may be accomplished utilizing tools like as ligand similarity searches, 3D-QSAR, and QSAR modeling approaches by Bisht et al. (2021). The software's pharmacophore modeling tools identify common features in active compounds, while the comprehensive data analysis and visualization tools aid in the examination of their molecular structures and activities.

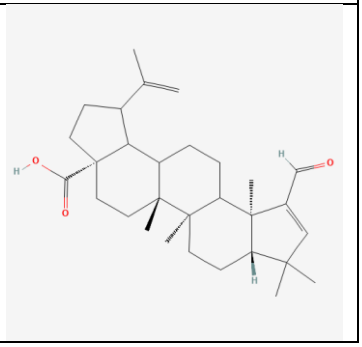
CHAPTER 4

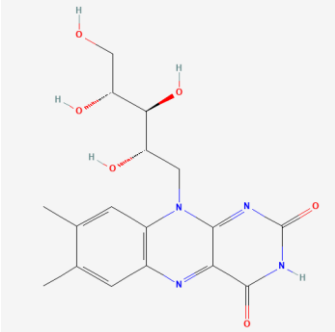
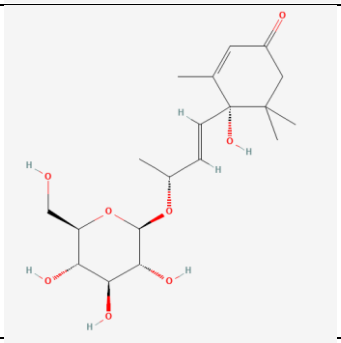
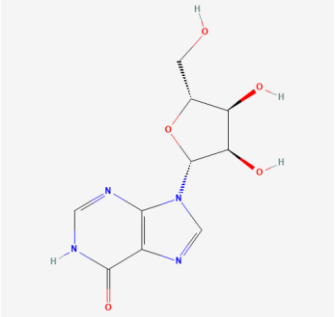
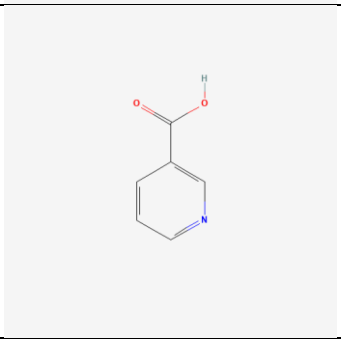
RESULT

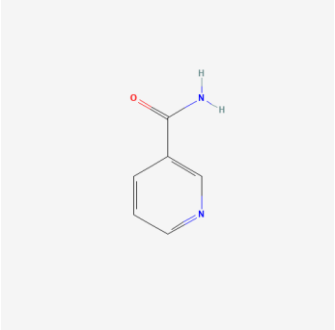
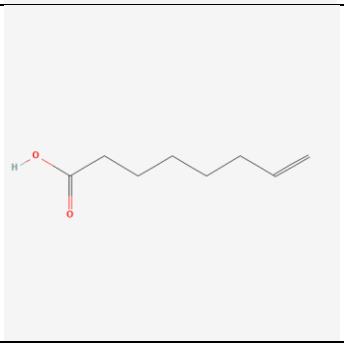
4.1 Identification of bioactive compounds

Total 193 phytochemical were collected from IMPPAT that were present in the plant-*Ziziphus jujube*, first part involves filtering of phytochemical on the base of fruit part only as few studies suggest that fruit part has high potential in cardioprotective activities. Later by utilizing MOLSOFT and PRO-TOX bioactives were filtered on the basis of their drug-likeliness index, their toxicity including carcinogenicity, immunogenicity, mutagenicity and cytotoxicity. Plant exhibiting a positive drug-likeliness with no toxicity, not any one out of all 4 toxicity criteria were selected for the final list of bioactive of the plant for further analysis which are mentioned below in the Table. III

Table III. List of *Ziziphus jujube* fruits' phytochemical compounds

Phytochemical	**Pubchem ID**	**Molecular weight**	**Drug Likeliness**	**Structure**
Zizyberenalic acid	15958448	452.33	0.11	

Riboflavin	493570	376.14	0.62	
Roseoside	9930064	386.19	0.33	
Inosine	135398641	268.08	1.19	
Nicotinic acid	938	123.03	0.30	

Nicotinamide	936	122.05	0.37	
7-Octenoic acid	543977	142.10	0.29	

4.2 Potential gene targets of *Ziziphus jujube's* bioactive compounds

By using the canonical smiles of the plant *Ziziphus jujube* from PUBCHEM database and later the Swiss Target Prediction tool to predict the potential gene targets or protein molecules with which these phytochemicals may interact. It is done by uploading canonical smiles of each plant one by one to the software and as a result a data was generated depicting in total 686 gene target that have potential to interact with the phytochemicals of our plant. STITCH is another software used for gene target prediction for some cases where canonical smiles of that phytochemical was not found at the PUBCHEM, instead the name of phytochemical was directly used to generate potential gene targets

4.3 Identification of differentially expressed genes of Arteriosclerosis

In this we utilize two software OMIM and GENECARD respectively to collect a set of potential gene for arteriosclerosis. Now, combine make a single list of potential gene targets of the disease obtained from both the software, gene symbol in GENECARD and approved symbol from OMIM. As a result of which a total of 1634 gene targets were identified.

4.4 Identification of intersecting gene targets

The common gene targets of the active phytochemical compound of the plant *Ziziphus jujube* which were 686 and the target genes linked to arteriosclerosis were examined by using a software online Venny2.1. There were about 149 gene in total which were find out as a result that overlapped in both the sets of disease gene targets and phytochemical gene targets are considered as potential gene targets for arteriosclerosis. Below the diagrammatic representation of the Venn diagram obtained as a result of the analysis by kaur et al. (2022)

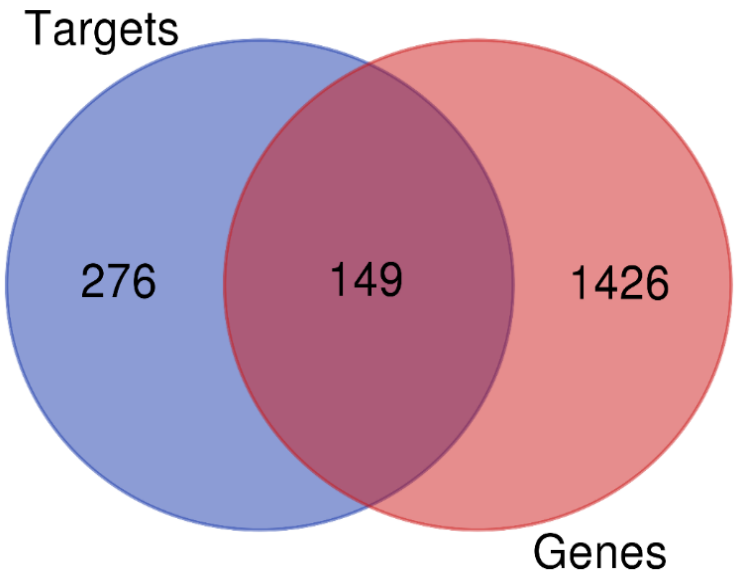


Fig 4.1 Venn diagram showing common gene target between potential phytonutrients and the disease (Arteriosclerosis)

4.5 PPI network analysis

In this network analysis, a total of 149 common target genes obtained as a result from the Venn diagram were used and loaded to string database to develop a protein-protein interaction network. It can be used for mapping networks of interaction on broader range based on their functional and physical relationship. PPI are visualized through string database in fig 3.2 (a). The data downloaded from that network is uploaded in cytoscape to form a grid layout and circular layout (b), (c) respectively. Based on the statistical summary it was found out that, nodes were 147 and edges were 1968 as shown in Fig 3.2 (a). While network's radius, diameter, density, heterogenicity, centralization, average no. of neighbors, clustering coefficients were found to be 2, 4, 0.183, 0.834, 0.550, 26.776, 0.603 respectively.

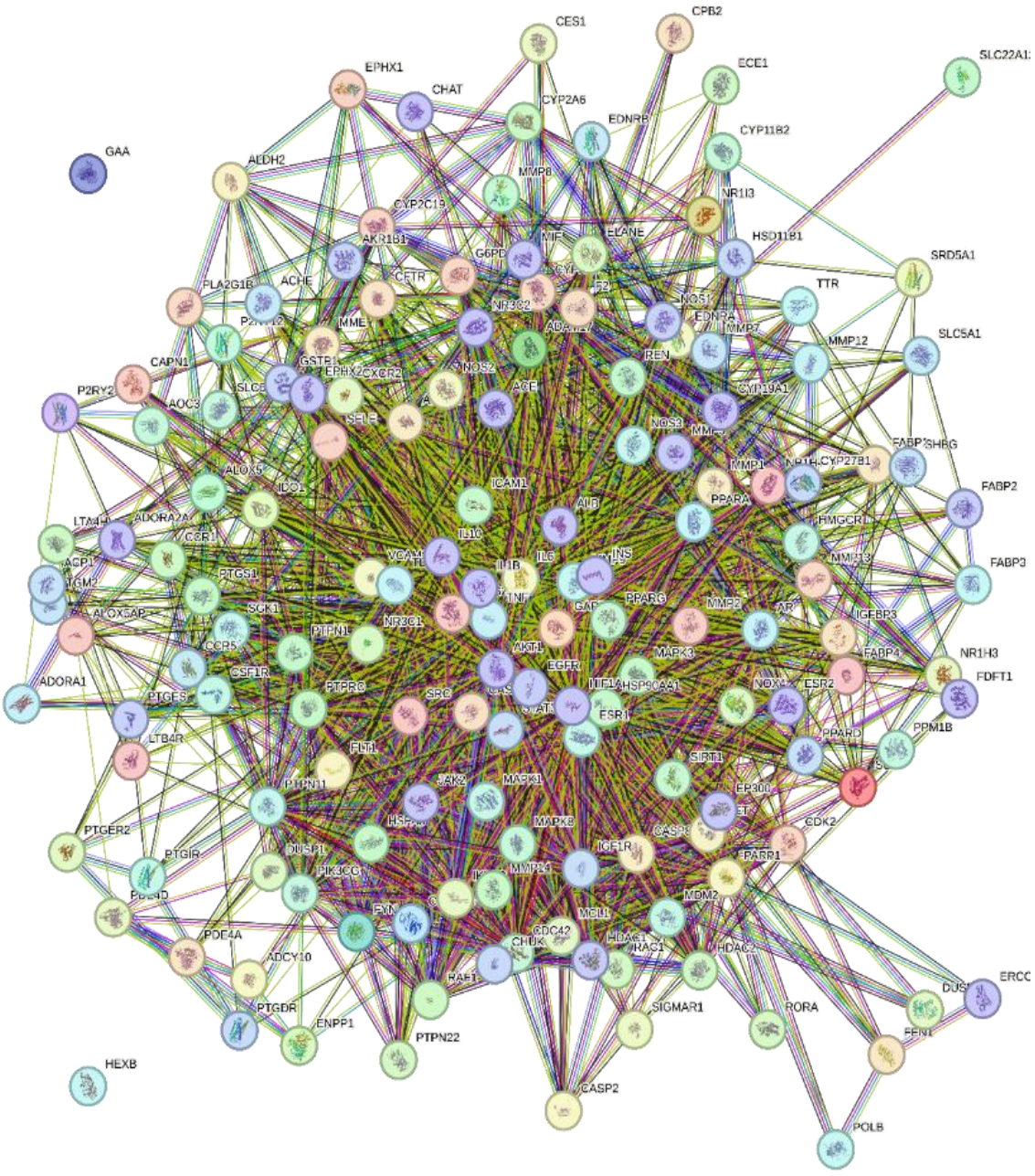
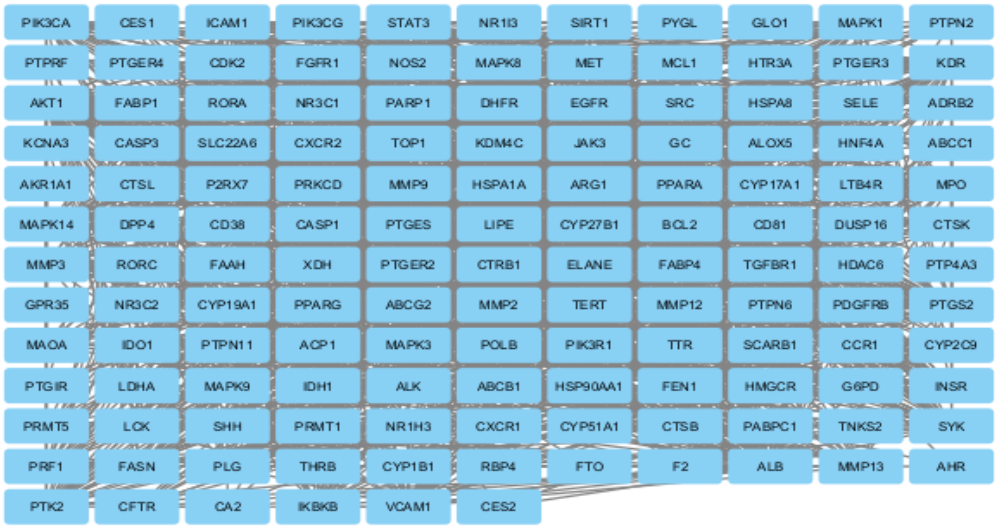
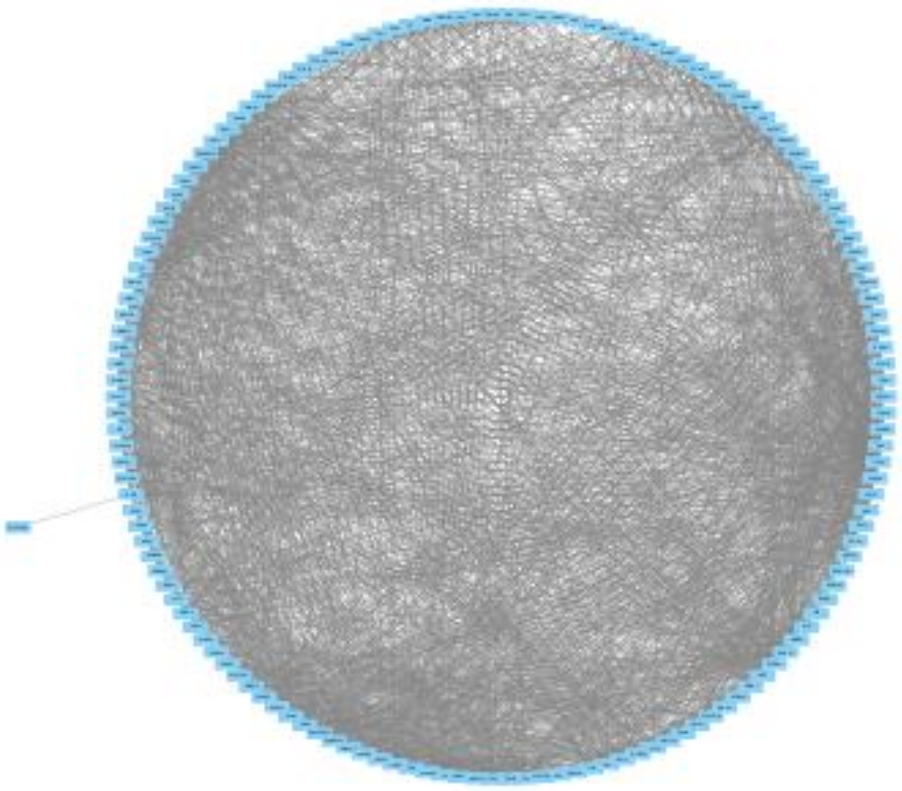


Fig 4.2 String PPI interaction network (a)



(b)



(c)

Fig 4.3 Cluster formed by Cytoscape (b, c)

4.6 Core target Analysis

By the help of a plugin in Cytoscape i.e. Cytohubba core target analysis can be done with the help of that we can easily identify the core targets that might have high potential and efficacy than other targets as shown below in the fig 3.4 These are filtered on the basis of degree, Maximal Clique Centrality, Maximum Neighbor Component and Closeness. As a final result of which we got total 10 core targets.

Table IV Core targets using Cytohubba

Rank	Core Targets	Score
1	TNF	106
2	IL6	104
3	GAPDH	100
4	AKT1	93
5	PTGS2	80
6	STAT3	77
7	SRC	76
8	EGFR	76
9	PPARG	76
10	CASP3	72

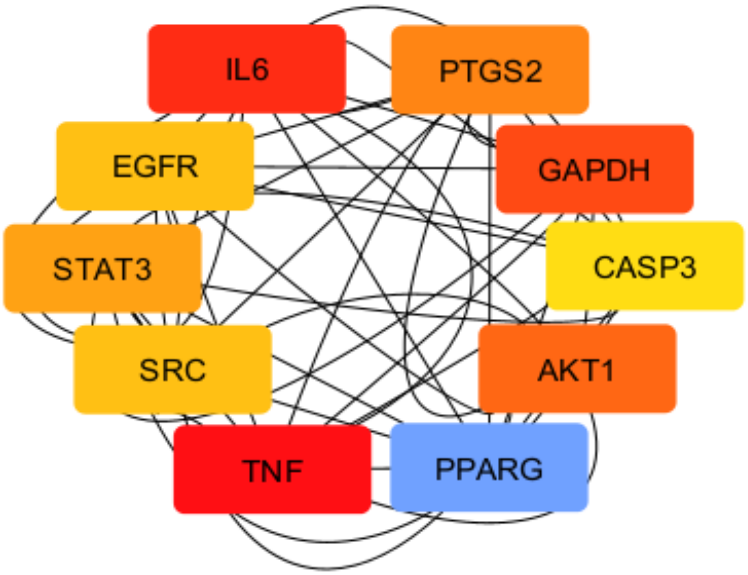


Fig 4.4 Hub genes predicted by Cytohubba

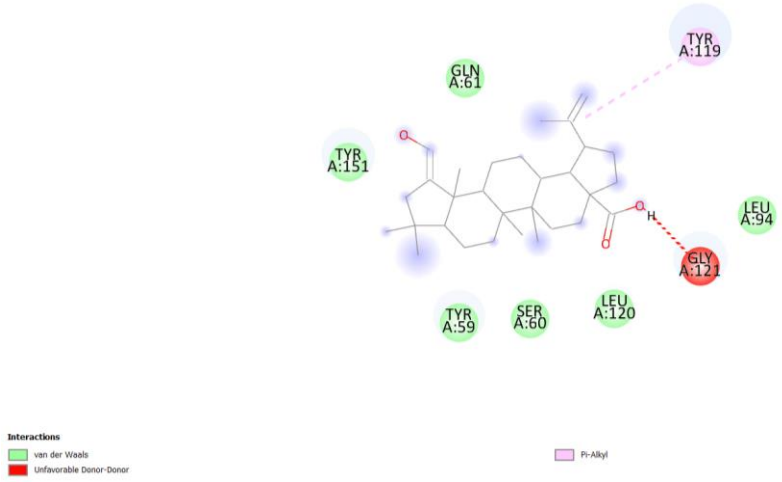
4.7 Molecular Docking

The first step involves the Collection the 3-D structure of 7 phytochemicals of our plant *Ziziphus jujube* found as result of screening process through Drug-likeliness and toxicity in the network pharmacology from PubChem in sdf format (Zizyberenalic acid, Riboflavin, Roseoside, Inosine, Nicotinic acid, Nicotinamide, 7-Octenoic acid). Later collecting the 3-D structure of target ligands (top 2: TNF, IL-6) from Protein Data Bank in pdb format. Ligand macromolecules are prepared using biovia discovery studio by uploading the file to the software. First the presence of active site is checked in the selected structure, then we will remove water molecules and heteroatoms as it causes hindrance and might affect the interactions and final result. Now polar hydrogen atoms are added and the structure is saved in PDB file format. Now loading the prepared target ligand in pyrx, and then click on it to make it macromolecule as a result it will converted to pdbqt format. Now got to open babel and select phytochemical one by one, and minimize all the ligand and convert all in autodock to pdbqt format. As soon as it completes go on vina wizard select all phytocompounds and the macromolecule and move forward. A box around the structure will be generated, now arrange the grid in such way so that active sites are covered inside that box, it is generally to enhance the outcome efficiency. Run vina and a final result will be generated in a tabular format, download the csv file and find out the highest binding affinity out of all phytochemicals and download the structure.

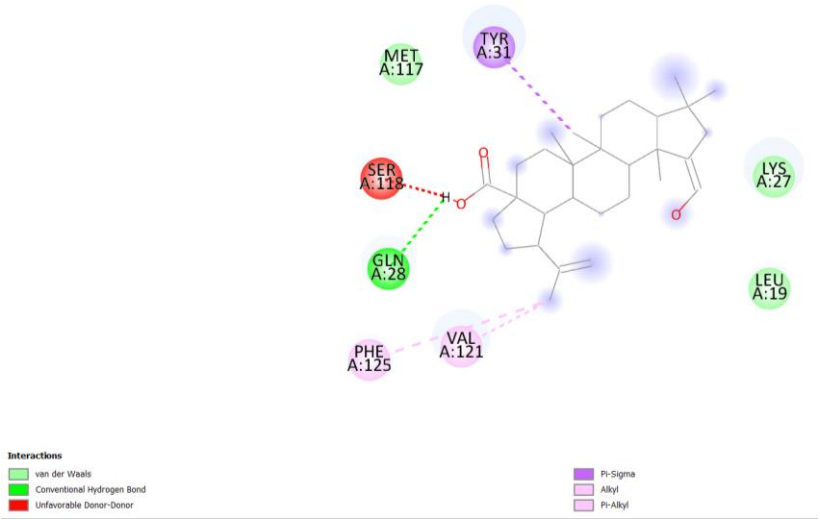
Now, go on biovia again to download the 2-D structure of that, by loading the earlier prepared macromolecule and copying the docked structure, pasting it to the hierarchy side, as a result finally the receptor bunds to it. Go on the receptor ligand interaction and first define receptor and ligand and now download the 2-D structure. Among all the phytochemicals it was found out that Zizybernalic acid has highest affinity with both the hub genes (TNF, IL-6) i.e -7, -6.1. 2-D structures of both the interactions are shown below in fig 3.5

Table V. Binding affinities (kcal/mol) of phytochemicals with both anti-arteriosclerosis genes

Targets	**TNF**	**IL-6**
Zizyberenalic acid	-7.1	-6.1
Riboflavin	-6.4	-5.8
Roseoside	-6.4	-5.7
Inosine	-5.7	-6
Nicotinic acid	-4.6	-4.8
Nicotinamide	-4.2	-4.6
7-Octenoic acid	-4.2	-4.1



(a)



(b)

Fig 4.5 2-D Molecular docking results (a- TNF, b- IL-6)

Discussion

The current study aims to better understand the pharmacological potential of *Ziziphus jujuba* (ZJ) in stabilizing arteriosclerosis by combining network pharmacology with molecular docking research. The use and function of ZJ in cardiovascular illnesses is primarily proven and derived from traditional Chinese medical uses. As a result, based on this consideration, and with the goal of revealing how the bioactive components of ZJ may regulate the genes associated with arteriosclerosis, our study required a broader perspective on the molecular interactions of the targeted genes with the disease-related molecular component. Here the phytochemicals that include vitamins, flavonoids and triterpene acids are many about 293 in total that were downloaded from IMPPAT and the way they have been widely used by Chinese for various medicinal purposes earlier as a traditional herb we cannot neglect their pharmacological prospects. Sure enough, it is quite impressive that even flavonoids, alkaloids, fatty acids, polysaccharides can possess the characteristics of anti-inflammatory agents, antioxidants and cardio-protectors; therefore, the ZJ can be potentially useful for the improvement of the condition of the cardiovascular system. As with time cardiovascular diseases have been increasing world widely making life-threatening condition at worst cases, so there is a need to treat them with lesser or no adverse effect where comes our plant with high future potential. The study identified seven key phytochemicals, among all 293 from different parts of the plant, focusing on fruit part phytochemical which are Zizyberenalic acid, Riboflavin, Roseoside, Inosine, Nicotinic acid, Nicotinamide, 7-Octenoic acid. In addition, the structures of the molecules in screened and the toxic consequences of these substances were analyzed to evaluate their potential as medicines. Furthermore, in accordance with the concept of network pharmacology, we were able to make selections of phytochemical-target with reference to gene targets related to arteriosclerosis of ZJ. Using systematic approach of the current kind we were able to establish the list of 149 genes which may be targeted both by ZJ and may be seen to facilitate arteriosclerosis in one way or another. Particularly, the effective signals consist of TNF, IL-6, GAPDH, AKT1, and PTGS2 which are related to inflammation, oxide stress, and other intra cellular signal transduction related to arteriosclerosis.

In addition, molecular docking was useful in determining the type and site of the ZJ phytochemicals interactions with the core targets of TNF and IL-6. From the docking studies, most of the compounds showed relatively good to fairly good binding affinities that could potentially enable them to act as modulators or inhibitors of those pro-inflammatory cytokines.

CHAPTER 5

CONCLUSION

Based on this research it can be concluded that *Ziziphus jujuba* has some or potential potential value as treatment remedy for arteriosclerosis. Herein, for investigating the specific interaction of ZJ phytochemicals and proteasome-related biological targets involved in arteriosclerosis, the approaches of network pharmacology and molecular docking were employed. The results prove that ZJ used the intervention model which is quite comprehensive that addresses many spheres of patients' lives because cardiovascular diseases can also be quite diverse and severe. Therefore, one can conclude that not only does the synthesis of the traditional herbal therapy and the complex pharmacological interventions fulfill the requirement of the necessity to further modernization of traditional healings but also opens a new horizon of the improvement of effective recovery with the help of herbs. Further research is needed to make them a usable effective medicine; it indicates a safe, effectual, and cheap way of treatment of arteriosclerosis and numerous cardiovascular illnesses.

Proper conduction of clinical trial of ZJ on the arteriosclerosis patients to show how effective it is, potential associated risks and the dosages for medical use. The pharmacokinetics of the compound implies the extent to which the compound is absorbed in the body, how it is distributed and how it is metabolized among the body systems. Therefore, from the various phytochemicals present in ZJ one may wonder if the effectiveness of the drug would be even greater or if it would interfere with the commonly used Arteriosclerosis drugs such as statins or PCSK9 inhibitors.

Develop better compounds to enhance the solubility and stability of the bioactive enhancements and constituents in the products of ZJ to establish the optimum therapeutic value. For next experiments designed in in studies vitro studies, more need to be carried out to determine how ZJ's phytochemicals' targets work and can treat various diseases with evidences.

Other aspects that make ZJ worth further investigation include understanding whether it can be used to treat other diseases of the cardiovascular system in order to reveal other facets of this preparation's therapeutic prospect in the sphere of cardiology.

References

1. A.H. Shah, V.B. Pandey, G. Eckhardt and R. Tschesche: A 13¬membraned cyclopeptide alkaloid from **Ziziphus sativa**. Phytochemistry. 24(11): 2765-2767 (1985)

2. A.M. Pawlowska, F. Camangi, A. Bader and A. Braca. Flavonoids of *Zizyphus jujuba* and *Zizyphus spina-christi* (L) Wild (Rhamnaceae) fruits. Food Chemistry. 112: 858- 862 (2000).

3. Sarfaraz, S. H. Ansari and E. Porchezhian. Antifungal activity of alcoholic extracts of *Ziziphus vulgaris* and *Acacia concinna*. Hamdard Medicus. Bait al-Hikmah, Karachi, Pakistan. 14/15: 42-45 (2002).

4. Awad DS, Ali RM, Mhaidat NM, Shotar AM. *Zizyphus jujuba* protects against ibuprofen-induced nephrotoxicity in rats. Pharm Biol. 2014;52 (2):182–186.

5. A.A. Kuliev and N.K. Guseinova. The content of vitamin C, B1, B2 and E in some fruits. Referativnyi Zhurnal. 2: 69-73 (1974).

6. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank. Nucleic Acids Res. 2000 Jan 1;28(1):235-42.

7. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018 Jul 2;46(W1):W257-W263.

8. British National Formulary. 68th ed. UK: BMJ Group and the Royal Pharmaceutical Society of Great Britain; 2014 September.

9. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, et al. (2004) Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350: 1495-1504.

10. Chen J, Tsim KWK. A Review of Edible Jujube, the *Ziziphus jujuba* Fruit: A Heath Food Supplement for Anemia Prevalence. Front Pharmacol. 2020 Nov 26;11:593655.

11. Cheng D, Zhu CQ, Cao JK, Jiang WB. The protective effects of polyphenols from jujube peel (*Ziziphus jujube Mill*) on isoproterenol-induced myocardial ischemia and aluminum-induced oxidative damage in rats. Food Chem Toxicol. 2012;50(5):1302–1308.

12. Dagenais GR, Leong DP, Rangarajan S et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. Lancet. 2019.

13. Daneshmand F, Zare-Zardini H, Ebrahimi L. Investigation of the antimicrobial activities of Snakin-Z, a new cationic peptide derived from *Zizyphus jujuba* fruits. Nat Prod Res. 2013;27(24):2292–2296.

14. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015;1263:243-50.

15. D. Suplatov, Y. Sharapova, and V. Švedas, "EasyAmber: A comprehensive toolbox to automate the molecular dynamics simulation of proteins," J Bioinform Comput Biol, vol. 18, no. 06, p. 2040011, Dec. 2020, doi: 10.1142/S0219720020400119.

16. Esteki Taraneh and Urooj Asna :Antioxidant components and activity in the peel of *Ziziphus jujuba Mill*, Journal of Pharmacy Research, 5(5):2705-2709 (2012).

17. Ensiye Aafi, Mohammad Reza Shams Ardakani, Mehran Mirabzadeh Ardakani. Jujube (*Ziziphus jujuba Mill*. (Rhamnaceae)): a review on its pharmacological properties and phytochemistry, 2022;7(4):38.

18. Fishbein GA, Fishbein MC. Arteriosclerosis: rethinking the current classification. Arch Pathol Lab Med. 2009;133(8):1309-16.

19. Gao QH, Wu CS, Wang M. The jujube (*Ziziphus jujuba Mill*.) fruit: a review of current knowledge of fruit composition and health benefits. J Agric Food Chem. 2013;61(14): 3351–3363.

20. Gfeller D, Grosdidier A, Wirth M, Daina A, Michielin O, Zoete V. SwissTargetPrediction: a web server for target prediction of bioactive small molecules. Nucleic Acids Res. 2014 Jul;42(Web Server issue):W32-8.

21. Guanghua Zhao, Xinyue Cui, Jiejie Sun, Tingting Li, Qi Wang, Xingzhuang Ye, Baoguo Fan, Analysis of the distribution pattern of Chinese *Ziziphus jujuba* under climate change based on optimized biomod2 and MaxEnt models, Ecological Indicators, Volume 132, 2021, 108256, ISSN 1470-160X.

22. Gong Cheng, Yanjing Bai, Yuying Zhao, Jing Tao, Yi Liu, Guangzhong Tu, Libin Ma, Ning Liao and Xiaojie Xu. Flavonoids from *Ziziphus jujuba* Mill var. spinasa. Tetrahedron. 56: 8915-8920 (2000). 37.A.M. Pawlowska, F. Camangi, A. Bader and A. Braca. Flavonoids of *Zizyphus jujuba* and *Zizyphus spina-christi* (L) Wild (Rhamnaceae) fruits. Food Chemistry. 112: 858- 862 (2000).

23. Goyal R, Sharma PL, Singh M. Possible attenuation of nitric oxide expression in anti-inflammatory effect of *Ziziphus jujuba* in rat. J Nat Med. 2011;65(3–4):514–518.

24. Gregory A. Fishbein, Michael C. Fishbein. Arteriosclerosis: Rethinking the Current Classification, Arch Pathol Lab Med (2009) 133 (8): 1309–1316.

25. Heo HJ, Park YJ, Suh YM, et al. Effects of oleamide on choline acetyltransferase and cognitive activities. Biosci Biotechnol Biochem. 2003;67(6):1284–1291.

26. Hoshyar R, Mohaghegh Z, Torabi N, Abolghasemi A. Antitumor activity of aqueous extract of *Ziziphus jujube* fruit in breast cancer: an in vitro and in vivo study. Asian Pac J Reprod. 2015;4(2):116–122.

27. Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res. 2005 Jan 1;33(Database issue):D514-7.

28. Hill GS. Hypertensive nephrosclerosis. Curr Opin Nephrol Hypertens. 2008;17(3):266-70.

29. H. Otsuka, Y. Ogihara and S. Shibata. Phytochemistry. 2016 (1974).

30. H. Matsuda, T. Murakami, A. Ikebata, J. Yamahara and M. Yoshikawa. Bioactive saponins and glycosides. XIV. Structure elucidation and immunological adjuvant activity of novel protojujubogenin type triterpene bisdesmosides, protojujubosides A, B, and B1, from the seeds of Zizyphus jujuba var. spinosa (Zizyphi spinosi semen). Chemical and Pharmaceutical Bulletin. 47:12-14 (1999).

31. Jianping Chen, Xiaoyan Liu, Zhonggui Li, Airong Qi, Ping Yao, Zhongyu Zhou, Tina T. X. Dong, Karl W. K. Tsim, "A Review of Dietary *Ziziphus jujuba* Fruit (Jujube): Developing Health Food Supplements for Brain Protection", Evidence-Based Complementary and Alternative Medicine, vol. 2017, Article ID 3019568, 10 pages, 2017.

32. Jonason T, Bergstrom R (1987) Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 221: 253-260.

33. J. Kaur et al., “Distinct Gene Expression Profiles of Matched Primary and Metastatic Triple-Negative Breast Cancers,” Cancers (Basel), vol. 14, no. 10, p. 2447, May 2022, doi: 10.3390/cancers14102447.

34. Kaeidi A, Taati M, Hajializadeh Z, Jahandari F, Rashidipour M. Aqueous extract of *Zizyphus jujuba* fruit attenuates glucose induced neurotoxicity in an in vitro model of diabetic neuropathy. Iran J Basic Med Sci. 2015;18(3): 301–306.

35. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker BA, Wang J, Yu B, Zhang J, Bryant SH. PubChem Substance and Compound databases. Nucleic Acids Res. 2016 Jan 4;44(D1):D1202-13.

36. K.R. Kirtikar and B.D. Basu. Indian Medicinal Plants, Vol II, 2nd Edn. (Bishen Sigh Mahendrapal Singh, Dehradun, 1994).

37. Keshav Kumar Gupta. Shair Ali. Ranjodh Singh Sanghera. Pharmacological Options in Atherosclerosis: A Review of the Existing Evidence. Cardiol Ther (2019) 8:5–20.

38. K.M. Nadkarni. Indian Materia Medica, (Popular Prakashan, Bombay, 1986) 1315-1319.

39. L. Zeng, R.Y. Zhang, and X. Wang. Studies on the constituents of Ziziphus spinosus Hu. Acta Pharm Sin. 22: 114-120 (1987).

40. Li JW, Liu YF, Fan LP, Ai LZ, Shan L. Antioxidant activities of polysaccharides from the fruiting bodies of *Zizyphus Jujuba* cv. jinsixiaozao. Carbohydr Polym. 2011;84(1):390–394.

41. Lu Y, Bao T, Mo J, Ni J, Chen W. Research advances in bioactive components and health benefits of jujube (*Ziziphus jujuba* Mill.) fruit. J Zhejiang Univ Sci B. 2021 Jun 15;22(6):431-449.

42. Mitchell GF. Aortic stiffness, pressure and flow pulsatility, and target organ damage. J Appl Physiol (1985). 2018;125:1871–1880.

43. M. Yoshikawa, T. Murakami, A. Ikebata, S. Wakao, N. Murakami, and H. J. Y. Matsuda. Bioactive saponins and glycosides. X. On the constituents of Zizyphi spinosi semen, the seeds of *Ziziphus jujuba* Mill. var. spinosa Hu (1): structures and histamine release-inhibitory effect of jujubosides A1 and C and acetyljujuboside B. Chem Pharm Bull. 45: 1186¬-1192 (1997).

44. Murugan Prasathkumar, Salim Anisha, Chenthamara Dhrisya, Robert Becky, Subramaniam Sadhasivam, Therapeutic and pharmacological efficacy of selective Indian medicinal plants – A review, Phytomedicine Plus, Volume 1, Issue 2, 2021, 100029, ISSN 2667-0313.

45. Mohanraj, K., Karthikeyan, B.S., Vivek-Ananth, R.P. et al. IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry And Therapeutics. Sci Rep **8**, 4329 (2018).

46. M.L. Sang, G.P. Jin, H.L. You, G.L. Cheal, S.M. Byung, H.K. Jung and K.L. Hyeong. Anti- complementary Activity of Triterpenoides from Fruits of *Zizyphus jujuba*. Biol. Pharm. Bull.
47. 27(11): 1883-1886 (2004).

48. M. Elmahi, E.M. Essassi, M. Hamamouchi and J. Hamamouchi.. Study on the antimicrobial and antibilharzia activity of *Ziziphus vulgaris*. Fitoterapia. 68: 34-36 (1997).

49. Naftali T, Feingelernt H, Lesin Y, Rauchwarger A, Konikoff FM. *Ziziphus jujuba* extract for the treatment of chronic idiopathic constipation: a controlled clinical trial. Digestion. 2008;78(4):224–228.

50. N. Bisht, A. N. Sah, S. Bisht, and H. Joshi, "Emerging Need of Today: Significant Utilization of Various Databases and Softwares in Drug Design and Development," Mini Reviews in Medicinal Chemistry, vol. 21, no. 8, pp. 1025–1032, May 2021.

51. Niiranen TJ, Lyass A, Larson MG, Hamburg NM, Benjamin EJ, Mitchell GF, Vasan RS. Prevalence, correlates, and prognosis of healthy vascular aging in a western community-dwelling cohort: the Framingham Heart Study.Hypertension. 2017; 70:267–274.

52. Preeti Preeti, Shalini Tripathi Shalini Tripathi, *Ziziphus jujuba*: a phytopharmacological review, International Journal of Research and Development in Pharmacy and Life Sciences, 2014, Vol. 3, No. 3, 959-966 ref. 58.

53. Preeti et.al, *ZIZIPHUS JUJUBA*: A PHYTOPHARMACOLOGICAL REVIEW, April - May, 2014, Vol. 3, No.3, pp 959-966 ISSN: 2278-0238.

54. Periasamy S, Liu CT, Wu WH, Chien SP, Liu MY. Dietary *Ziziphus jujuba* fruit influence on aberrant crypt formation and blood cells in colitis-associated colorectal cancer in mice. Asian Pac J Cancer Prev. 2015;16(17):7561–7566.

55. R.N. Chopra, S.C. Nayar and I.C. Chopra. Glossary of Indian Medicinal Plants, (Council of Industrial and Scientific Research, New Delhi, 1986).

56. R. Tschesche, A.H. Shah, G. Eckhardt. Sativanine-A and sativanine- B, two new cyclopeptide
57. alkaloids from the bark of *Ziziphus sativa*. Phytochemistry. 18: 9-11 (1979).

58. R. Ziyaev, T. Irgashev, I.A. Israilov, N.D. Abdullaev, M.S. Yunusov and S.Y. Yunusov. Alkaloids of *Ziziphus jujuba*. Structure of iusiphine and iusirine. Khimiya Prirodnykh Soedinenii. 2: 239-243 (1977).

59. Roth GA, Abate D, Abate KH, et al. and the GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88.

60. S. Lee, B. Min, C. Lee, K. Kim and Y. Kho. Cytotoxic triterpenoids from the fruits of Zizyphus jujuba. Planta Medica. 69: 18-21 (2003).

61. Schapira, M., Totrov, M. and Abagyan, R. Prediction of the binding energy for small molecules, peptides and proteins. J Mol Recognit 12, 177-190 (1999).

62. Safran M, Dalah I, Alexander J, Rosen N, Iny Stein T, Shmoish M, Nativ N, Bahir I, Doniger T, Krug H, Sirota-Madi A, Olender T, Golan Y, Stelzer G, Harel A, Lancet D. GeneCards Version 3: the human gene integrator. Database (Oxford). 2010 Aug 5;2010:baq020.

63. Santos VP, Pozzan G, Castelli Júnior V, Caffaro RA. Arteriosclerosis, atherosclerosis, arteriolosclerosis, and Monckeberg medial calcific sclerosis: what is the difference?. J Vasc Bras. 2021;20:e20200211.

64. Shaito A, Thuan DTB, Phu HT, Nguyen THD, Hasan H, Halabi S, Abdelhady S, Nasrallah GK, Eid AH and Pintus G (2020) Herbal Medicine for Cardiovascular Diseases: Efficacy, Mechanisms, and Safety. Front. Pharmacol. 11:422.

65. S. Kumar, M. S. Ganachari, Banappa, V. S. Nagoor: Anti inflammatory activity of *Ziziphus jujuba* Lam leaves extract in rats ,Journal of Natural Remedies, Vol 4/2: 183 – 185 (2004)

66. Sun YF, Liang ZS, Shan CJ, Viernstein H, Unger F. Comprehensive evaluation of natural antioxidants and antioxidant potentials in *Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex HF Chou fruits based on geographical origin by TOPSIS method. Food Chem. 2011;124(4):1612–1619.

67. S. Devi, V.B. Pandey, J.P. Singh and A.H. Shah. Peptide alkaloids from Ziziphus species. Phytochemistry. 26(1): 3374-3375 (1987).

68. S. Dutta and S. Roy, "Complex Network Visualisation Using JavaScript: A Review," 2022, pp. 45–53.

69. S. Dashti, M. Taheri, and S. Ghafouri-Fard, "An in-silico method leads to recognition of hub genes and crucial pathways in survival of patients with breast cancer," Sci Rep, vol. 10, no. 1, p. 18770, Oct. 2020.

70. Taati M, Alirezaei M, Moshkatalsadat MH, et al. Protective effects of *Ziziphus jujuba* fruit extract against ethanol-induced hippocampal oxidative stress and spatial memory impairment in rats. J Med Plants Res. 2011;5(6): 915–921.

71. Vivek-Ananth RP, Mohanraj K, Sahoo AK, Samal A. IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants. ACS Omega. 2023 Feb 23;8(9):8827-8845.

72. W.S. Woo, S.S. Kang, S.H. Shim, H. Wagner, V.M. Chari, O. Seligmann, G. Obermeier: The structure of spinosin (2"-0-betaglucosyiswertisin) from Ziziphus vulgaris var. spinosus (seeds). Phytochemistry. 18(2): 353-355. (1979).

73. Xinwen Jin, Jujuba—*Ziziphus jujuba*, Exotic Fruits, Academic Press, 2018, Pages 263-269, ISBN 9780128031384.

74. X. Kong et al., "Screening and identification of key biomarkers of depression using bioinformatics," Sci Rep, vol. 13, no. 1, p. 4180, Mar. 2023, doi: 10.1038/s41598-023 31413-1.

75. Y. Kurihara, K. Oohubo, H. Tasaki, H. Kodama, Y. Akiyama, A. Yagi and B. Halperm. Studies on taste modifiers. I. Purification and structure in leaves of *Ziziphus jujuba*. Tetrahedron. 44 (1): 61-66 (1988).

76. Yu L, Jiang BP, Luo D, et al. Bioactive components in the fruits of *Ziziphus jujuba Mill*. against the inflammatory irritant action of Euphorbia plants. Phytomedicine. 2012; 19(3–4):239–344.

77. Zare-Zardini H, Tolueinia B, Hashemi A, Ebrahimi L, Fesahat F. Antioxidant and cholinesterase inhibitory activity of a new peptide from *Ziziphus jujuba* fruits. Am J Alzheimers Dis Other Demen. 2013;28(7):702–709.

78. Zhu D, Jiang N, Wang N, Zhao Y, Liu X. A Literature Review of the Pharmacological Effects of Jujube. Foods. 2024 Jan 6;13(2):193.

LIST OF PUBLICATIONS AND THESIS PROOF

Name of Conference: CONFERENCE on Intelligent Computing and Communication Techniques, JNU, New Delhi
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Name of Authors: Anjali Sharma, Deeksha Pandey, Navneeta Bhardvaja*

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Delhi Technological University

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Exploring potential of *Bacopa monnieri's* against B19V induced Erythema Infectiosum: An insilico approach

Anjali Sharma
Dept. of Biotechnology
Delhi Technological University Delhi
anjalisharma$_2k22mscbio59@dtu.ac.in$

Deeksha Pandey
Dept. of Biotechnology
Delhi Technological University Delhi
deeksha$_2k22mscbio17@dtu.ac.in$

Navneeta Bharadvaja
Dept. of Biotechnology
Delhi Technological University Delhi
navneetab@dce.ac.in

***Abstract*—Human pathogenic parvovirus B19 (B19V) causes a variety of inflammatory conditions as well as diseases resulting in bone marrow failure. Human erythroid progenitor cells (EPCs) are highly tropism for B19V infection in the bone marrow and fetal liver. The expression of receptor and co-receptor(s) on the cell surface of human EPCs contributes to the exclusive confinement of B19V replication to erythroid lineage cells. It also depends on intracellular components that are necessary for viral replication. Two important processes that encourage B19V replication are the cell cycle arrest at late S-phase and the DNA damage response (DDR) triggered by the B19V infection. Therefore, *Bacopa Monnieri* (Medhya Rasayana) a medicinal herb whose phytocompounds (Cucurbitacin A, Wogonin, Oroxindin, Quercetin, Luteolin, Ursolic acid, Stigmasterol, Beta sitosterol, Rosavin, Dimethoxane, Caryophyllene oxide, 2,4-quinoline diol, Brahmic acid,2 octanol, Loliolide) possess anti-inflammatory, anxiolytic, and antioxidant properties can inhibit this virus from binding to cells and its receptor in the host. In this paper we have used 16 out of all phytochemical that have the potential in inhibiting the activity of the protein (7y56), to prevent the virus from further replication. In essence, while working on this, we are evaluating the phytochemical-protein interactions and their binding affinities. Ursolic acid is found to have the highest binding affinity of -7.6, indicating its strong binding interactions and high potential in modulating the activity of virus by inhibiting its interaction with host.**

***Index Terms*—B19V, 7Y56 protein, *Bacopa monnieri*, Ursolic acid**

I. Introduction

B19 or human parvo virus is a widespread and prevalent infection causing pathogen first identified in 1974. It belongs to the parvoviridae family, particularly the erythrovirus group [1], [2]. Unlike others in this family, B19 only infects humans. The virus consists of a single-stranded DNA genome and a non-enveloped icosahedral capsid, which is made up of two structural proteins, VP-1 and VP-2. The virus measures about 18 to 26 nm in diameter. The prevalence of parvovirus B19 varies depending on age groups. In developed regions, children under five show the lowest infection rate, between 2 to 10 percent, and adults between 20 and 70 have a higher rate at around 40 to 60 percent.The human parvovirus B19 causes

Studies show 50 out of 100 adults are at risk [1]. People 70 and older have the highest infection rate, with at least 85 percent exposed [3]. Fetuses with undeveloped immune systems can develop life threatening conditions like anemia or hydropus fetalis from the virus [1], [3]. The virus leads to different illnesses, examples include aplastic crisis in people with anemia. Another issue is acute symmetric polyarthropathy, resembling rheumatoid arthritis. This arthritis form occurs more frequently in women. Respiratory droplets spread the B19 virus. Hand-to-mouth contact transmits it too. Organ transplants are another transmission mode. Infected mothers can pass it to unborn babies [4]. During pregnancy, the virus may go into the womb. It might cause infection and the loss of the unborn child. The virus binds to a protein called P blood antigen receptor, or Gb4Cer (globoside), on cell surfaces. This protein is found in the lungs. The virus sticks to this protein. When the virus binds to this protein, it changes the virus and the cell membrane. The cell membrane becomes weak [4], [5]. After the virus goes into the cell, it multiplies inside the nucleus of the cell. The cell tries to fight the virus. But the virus kills the cell. The virus targets erythroid progenitors, which are cells that make red blood cells. The virus stops new red blood cells from being made. This causes a lack of red blood cells during infection [5]. The virus also binds to other proteins, like Ku80 autoantigen and 51 integrin. These proteins help the virus get into the host cell [4]. Apart from these two, NS1 is also an important protein that is directly related to the replication of B19V, playing a crucial role, as it attaches itself and controls the overall expression of both the genes of the host organism as well as itself [1]. Infection testing typically involves looking for serum anti-B19 IgM antibodies [4]. A positive result indicates that the infection occurred two to four months ago. After a week, the IgG antibody test will become positive. IVIG (intravenous immunoglobulins) is the only antiviral treatment approved by the FDA for B19 in cases of chronic infections or, more rarely, severe acute infections in immunocompromised individuals [6], [7]. Though there are various anti-viral drugs available in the market but none has been proved to be highly

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(Formerly Delhi College of Engineering)

Bawana Road, Delhi- 110042

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Resume

Deeksha Pandey

Data Analyst

8077533454 | pandeydeeksha29707@gmail.com | www.linkedin.com/in/deeksha-pandey35
https://www.datascienceportfol.io/Deekshapandey | New DELHI

INTERNSHIP/S & TECHNICAL EXPERIENCE

Internee

Vigyanshala international Kalpana-She for stem

04/2021 - 09/2021 | From Home

Empowering future innovators with accessible science and technology education.

- **Global Networking:** Engaged with renowned STEM role models worldwide, gaining diverse perspectives on innovative career paths.
- **Technical Proficiency:** Completed masterclasses in Python and SQL, enhancing data analysis capabilities.
- **Communication Skills and Professional Development**
- **Analytical and Problem-Solving**

Internee

Bioinformatics CCBI,Association of Indian Biologists (AIB)

06/2021 - 07/2021 | From Home

It excels in integrating computational methods with biological data. Specializing in NCBI databases, microarray analysis, data warehousing, and data mining, drives innovation in bioinformatics, preparing data analysts for advanced biological research and analysis.

- **Data Analysis Techniques:** Learned data warehousing and data mining specific to bioinformatics, enhancing analytical skills.
- **Modeling Skills:** Developed proficiency in bioinformatics modeling, crucial for complex data interpretation and analysis.

EDUCATION

MSc. Biotechnology

Delhi Technological University

07/2022 - 06/2024 | Delhi

BSc. Life Science

Matreyi college, University of Delhi

07/2019 - 06/2022 | Delhi

Class XII(CBSE)

Rrk Senior Secondary School

07/2018 - 05/2019 | Chandausi, Uttar Pradesh

Class X (CBSE)

Rrk Senior Secondary School

07/2016 - 05/2017 | Chandausi, Uttar Pradesh

ACHIEVEMENTS

Selection

Chosen among 180 students nationwide for the prestigious Vigyanshala Internship, recognizing exceptional academic and research skills.

Rank

Achieved 25th rank in DTU MSC Entrance Exam.

SKILLS

Power BI | Tableau | SQL | Python | MS Excel | MS Power Point | Data Management | Data Visualization | Data Analysis | Report Generation

LANGUAGES

Hindi — Native

English — Proficient