Integrated Network Biology and Molecular Docking Studies Identify Sanguinarine as an Effective Phytocompound Against Asbestosis

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1. Abstract

Asbestos, a mineral once widely used, is now known to cause serious health problems like lung cancer and mesothelioma. Early detection of these diseases helps, and advancements like Next-Generation Sequencing (NGS) are helping diagnose them faster. While there's currently no cure for asbestos-related diseases, research in areas like biology holds promise for future treatment breakthroughs. Plants have natural chemicals that may fight diseases like cancer. Our main objective is to find a relevant plant-based supplement for asbestosis with minimum side effects. In the present study, online databases like Gencard, Malacard, and NCBI were explored for the identification of genes responsible for asbestosis. Asbestosis patient samples from GEO (GSE100900) database were retrieved for Differentially Expressed Gene (DEGs) identification. Further, the network biology approach was used to identify the hub genes and the priority gene in asbestosis. STRING and CytoHubba plugin of Cytoscape was used for network construction and identification of hub genes. Cytohubba parameters identified the TNF gene as the key gene regulating the asbestosis network. SwissModel was used to predict the structure of the TNF gene followed by molecular docking studies using SeamDock. This gene codes for multifunctional inflammatory cytokine. Molecular docking studies identified Sanguinarine (-8.26kcal/mol) is the most effective phytocompound against asbestosis. It is a polycyclic quaternary ammonium salt which belongs to the benzylisoquinoline alkaloids family. It is a natural substance found in the roots, seeds, leaves or fruits of many plants, including bloodroot, poppy, eastern horned poppies, opium, poppies, and celandine.

Keywords: TNF, sanguinarine, network pharmacology, asbestosis, phytocompounds

2. Introduction

Asbestos is a kind of fibrous silicate material made up of many microscopic fibrils. It was found that this material was used from the stone age era (Curado A et al, 2024). Asbestos is a naturally occurring mineral that doesn't burn easily and can't be trusted or damaged easily. Because of these properties, it was very popular in the past and used in many things like house insulation, floor tiles, and even cement. There are four main types of asbestos: chrysotile, crocidolite, amosite, and anthophyllite (Wagner JC et al, 1960). These types of asbestos were widely used in industry because of their unique properties. Chrysotile was the most common type, used

in around 90% to 95% of all asbestos use. The other three types, crocidolite, amosite, and anthophyllite, were used for the remaining 5% to 10% of commercial asbestos use. Scientists figured out a connection between asbestos and a type of cancer called mesothelioma way back in 1960. This was when a study done in South Africa by a researcher named Wagner showed the link(Oury TD et al, 2014). Since the 1960s, it's been clear that asbestos exposure can cause two main types of health problems. The first is non-cancerous conditions, like scarring on the lungs (pleural plaques) and asbestosis, a lung disease caused by inhaling a lot of asbestos fibres. The second type is cancer, including lung cancer and mesothelioma, a rare cancer that forms in the lining of the chest, heart, or abdomen (Iliopoulou M et al, 2017).

Breathing in asbestos fibres is bad for your lungs. It can cause several serious illnesses, like mesothelioma, asbestosis and even lung cancer. Because of these dangers, asbestos is seen as a major health and safety risk (Belackova L et al, 2022). It can take a long time, usually around 20 years, for any negative health problems to show up after you've been exposed to something harmful (Pietrofesa RA et al, 2016) (Altmuller J, et al, 2014).

The rapid detection earlier than the latency period is now done by using various advanced technologies. New technology called Next-Generation Sequencing, or NGS for short, is a game-changer in diagnosing diseases caused by pathogens. NGS is like a super-powered magnifying glass that lets scientists quickly and precisely identify the culprit behind an infection (Hughes, L. A. et al, 2019). This makes it much easier to get the right treatment to people faster, which can significantly improve overall public health. Many diseases, maybe even thousands of them, are rooted in changes in our genes. This can happen in a few ways. Sometimes, a single misspelling in our genetic code, like a typo in a book, can cause a health problem. This might be something you inherit from your parents, like sickle cell disease, or it could be a random mistake that happens during development, like lactose intolerance (Qin D, 2019). NGS is a new method for analysing DNA and RNA to find variations in genes.

It combines different techniques to achieve this: special chemicals are used to break down the DNA and RNA, a special platform is used to analyse the pieces, and powerful computers are used to interpret the results (Harold J, 2007). NGS have various advantages like high throughput, cost-effectiveness, speed, accuracy etc.

In everyday terms, this means vitamins and minerals in pill form can be a helpful backup for your regular meals. Even if you eat well, supplements can plug any holes and make sure you're getting all the important nutrients your body needs. This can leave you feeling more energized, improve your appearance, and even help you catch some better shut eye (Advanced Chiropractic and Rehab). Therefore, we are determining which supplements can be useful for this disease, so the harmful impacts are minimized and prevent it from getting it. In everyday terms, this means that popping a daily vitamin could do a lot of good for your body. You might feel more energetic, get sick less often, and have an easier time digesting food and keeping your weight in check. Plus, some vitamins can even lower your chances of getting serious illnesses like cancer, heart disease, and diabetes. On top of that, many supplements have extras like probiotics and antioxidants that can give your health an extra boost (Klebe, S. et al, 2020).

We all try to eat healthily, but it turns out for many of us, it's just not enough to get every single nutrient our bodies need. That's where supplements come in. They can plug any holes in your diet, making sure you get everything you need to stay healthy. They're also great for athletes or people trying to reach their fitness goals, whether that's running a marathon or dropping a few pounds. Finding drugs based solely on specific genes has proven difficult because diseases are intricate and involve many biological processes (RS S, et al, 2005). Systems biology takes a big-picture approach, aiming to understand how these processes work together and predict how diseases develop. While perfectly modelling human cells and tissues remains a challenge, this approach is already making a difference in drug discovery (Kitano H., 2002). Large-scale analyses of genes, proteins, and metabolites (omics) rapidly generate ideas and allow researchers to test them in disease models. Additionally, computer simulations that consider how organs and entire systems respond to drugs help prioritize targets and design better clinical trials. Finally, scientists are automating complex tests using human cells, which better reflect real-world conditions. These advancements in systems biology promise to streamline decision-making throughout the drug development process (Visonà SD et al, 2018).

The study suggests that even low asbestos exposure can cause mesothelioma in some people, possibly due to genetic factors. This research highlights the potential dangers of asbestos, even at low levels (Chamberlin et al, 2019). The identification by researchers of new targets and pathways for existing drugs will enable them to find new uses, which are otherwise time-consuming and resource-intensive when taken through traditional routes of drug discovery (Germain et al, 2017). Traditionally, Doctors diagnose diseases by matching symptoms to known patterns (Tao et al, 2013).

The ultimate promise of systems biology involves both personalized medicine and increased success rates for new drugs (Kim TH et al, 2023). Sustained progress in computational methods and data integration would hence be required for the full exploitation of this potential of network pharmacology for modern medicine (Smith JD et al, 2023) (Gaynor et al, 2020).

Workers having higher dust-level exposure had a heightened incidence of asbestosis; what was surprising, however, is that so many of them were quite young, thus only relatively recent entrants into the industry, indicating a very grave health risk indeed (Germain et al, 2017). Interestingly, it suggests that keeping dust levels below 5 million particles per cubic foot could prevent new cases and the engineering section believes this to be achievable. Traditionally, Doctors diagnose diseases by matching symptoms to known patterns (Dallakyan S et al, 2015). Network pharmacology is the recent computer-aided approach to understanding the interactions of a drug with multiple targets in the body. This enables the understanding of logic behind complex herbal remedies and how existing drugs could be redeployed against new diseases. With its powerful help, it would be possible to design completely new medications (Dennis G. et al, 2003). It provides a paradigm shift in understanding and treatment of diseases by accounting for complex interactions between multiple biological targets and pathways (Bindea G. et al, 2009).

On that ground, effective treatments should hit more than one point within these networks to rebalance them. That brings about the building of interaction maps following the interaction between drugs, targets, and

disease pathways (An J et al, 2021). The identification by researchers of new targets and pathways for existing drugs will enable them to find new uses, which are otherwise time-consuming and resource-intensive when taken through traditional routes of drug discovery (Chamberlin et al, 2019).

3. Materials and Method

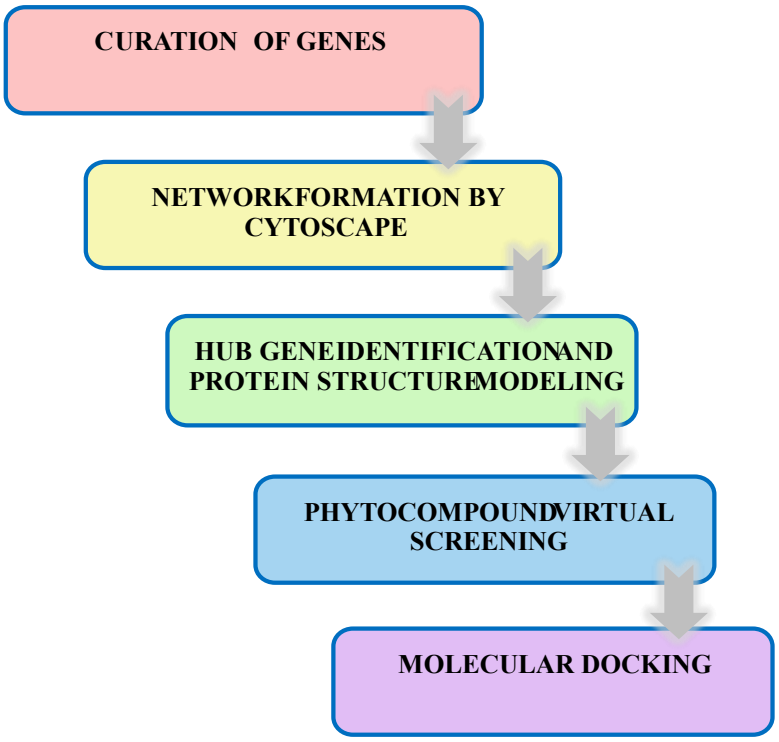

Figure 3.1: This figure shows the complete workflow of the present study

Curation Of Gene List

All the possible genes related to asbestosis were collected from various databases. Databases like GEO2R, Malacard, Omim, Genecard and DisGeNet. A spreadsheet was prepared for collecting all these genes. After collection duplicate genes were removed. Total 423 genes in total were identified.

Protein-Protein Interaction Network Using Cytoscape

Cytoscape was used for network formation of the identified genes. In this STRING and CYTOHUBBA plugins were used. From string we set certain standards like confidence score. Here we identified nodes and edges. From cytohubba we analyse top 20 genes on twelve parameters that are degree, clustering coefficient, closeness, bottleneck, MNC, betweenness, radiality, stress, MCC, EPC, DMNC and EcCentricity.

Hub Gene Identification And Protein Structure Modeling

After getting the node table for different parameters we analyse manually the hub gene. This was done by analysing which gene follows the most parameters. After achieving the hub gene, which is our priority gene used it protein sequence to achieve its protein model from SwissModel. This leads us to have a PDB file with its structure details.

Phytocompound Virtual Screening

From various online webpages and websites, we got the possible phytocompounds which can be utilized as a supplement to prevent or minimize asbestosis disease. Almost 27 phytocompounds were identified. Then we did every phytocompounds virtual screening. This was done in two diff2erent platforms first PubChem where we got its canonical smiles structure and second, we used ADMETlab where these canonical smiles were pasted, and we got to know if it follows Lipinski's rule of 5 or not. If it follows then it was accepted, if not then rejected.

Molecular Docking

The accepted phytocompounds were then used for molecular docking by SeamDock with the modelled pdb structure of the protein. The box coordinates were also set for center it was x: -3 angstrom, y: 7 angstroms, z: -16 angstrom and size were x: 67angstrom, y: 88 angstroms, z: 111 angstrom. Here the compound which has the highest negative binding energy is usually less than -5Kcal/mole.

4. Result

Curation Of Genes

The genes related to asbestosis were collected from various databases. From GEO2R we got 250 genes, from Malacard 26 genes, from Omim 2 genes, from Genecard 194 and from DisGeNet 27 genes. From the spreadsheet prepared for collecting all these genes after collection duplicate genes were removed. Total 423 genes in total were identified.

Network Formation by Cytoscape

From string we set confidence score of 0.99. Here we identified 412 nodes and 236 edges. From cytohubba we analyse top 20 genes on twelve parameters that are degree, clustering coefficient, closeness, bottleneck, betweenness, radiality, stress, MNC, MCC, EPC, DMNC and EcCentricity. Here we got the network graphs of genes and node tables.

Degree	Clustering coefficient	Closeness	Bottleneck	Betweenness	Radiality	Stress	MNC	MCC	EPC	DMNC	EcCentricity
CSF2	HFE	CD4	CD4	IKBKE	CD4	ACTB	CSF2	CSF2	CSF2	CSF2	FN1
ACTB	PPBP	CXCL8	ACTB	ACTB	FGF2	FN1	CXCL8	CCR5	CCR5	CD4	CCN2
CCL5	HLA-A	CCL5	FN1	FN1	CXCL8	IL6	CCL5	CD4	CD4	CCR5	MAPK9
CXCL8	SFTPA1	FN1	IL6	IL6	CCL5	TNF	ACTB	CXCL8	CXCL8	IFNG	TNF
FN1	C1R	IFNG	TNF	TNF	FN1	SPP1	FN1	CCL5	CCL5	IL6	SPP1
IFNG	IGF2	IL6	SPP1	SPP1	IFNG	ALB	IFNG	IFNG	IFNG	IL13	IGFBP3
IL6	TNF	TNF	ALB	ALB	IL6	TP53	IL6	IL6	IL6	ACTN4	ALB
TNF	ACTR3	ALB	TP53	TP53	TNF	NFKB1	TNF	IL13	CCL3	TNF	NFKB1
NFKB1	SFTPA2	NFKB1	IL1B	NFKB1	ALB	IL1B	NFKB1	TNF	TNF	SPP1	ITGA2
TP53	MAP2K1	TP53	TGFB1	IL1B	NFKB1	MYH9	TP53	NFKB1	NFKB1	CXCR3	TGFB1
IL1B	C1S	IL1B	VCL	VCL	TP53	TGFB1	IL1B	CXCR3	TP53	NLRC4	CASP3
CCL2	IL1RN	CCL2	B2M	B2M	IL1B	VCL	CCL2	IL1B	CXCR3	ITGA2	FAS
VCL	BNIP3L	TGFB1	C3	C3	CCL2	PTGS2	IL1A	CCL2	IL1B	MEFV	FBN1
IL1A	FAS	IL1A	CASP3	CASP3	TGFB1	C3	IL4	IL1A	CCL2	IL1A	CASP1
JUN	FLNB	IL4	JUN	JUN	IL1A	CASP3	JUN	IL4	IL1A	IL4	PYCARD
IL4	AIM2	JUN	MMP9	CYCS	IL4	JUN	CCL11	JUN	IL4	IL1R1	ITGB3
CCL11	ACTG2	EGFR	BCL2	MMP9	JUN	MMP9	CASP1	CCL11	JUN	AIM2	ITGAV
EGFR	TRAF3	CASP8	EGFR	BCL2	CASP8	BCL2	EGFR	IL10	CCL11	ITGA3	VTN
CASP8	TNIP1	IL10	CASP8	EGFR	IL10	EGFR	IL10	CCR2	IL10	IL10	ITGA3
IL10	LRIG1	IL18	LTF	CASP8	IL18	CASP8	IL18	IL18	IL18	CCR2	CASP8

Table 1: This table is made by cytohubba plugin analysis, it shows all the 12 parameters gene list with the most repeating gene in all parameters i.e. TNF.

Hub Gene Identification and Protein Structure Modeling

After getting the node table for different parameters we analyse manually the hub gene. This was done by analysing which gene follows the most parameters. TNF gene was the one which follows 12 parameters out of 12. After achieving the hub gene, which is our priority gene used it protein sequence to achieve its protein model from SwissModel. This leads us to have a pdb file with its structure details.

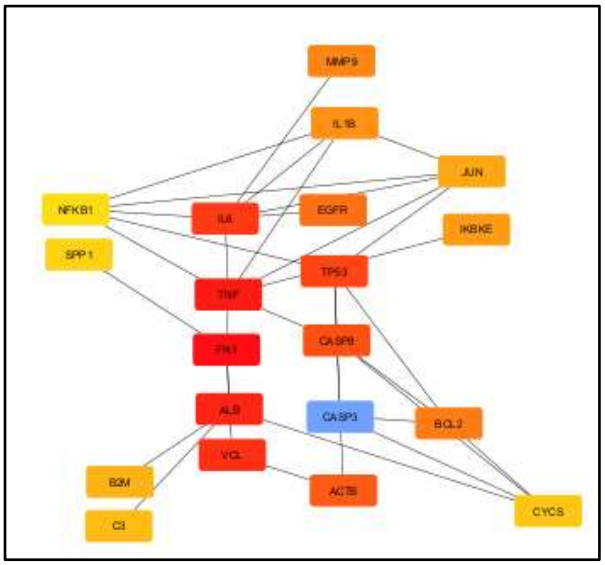

Figure 4.1: Betweenness

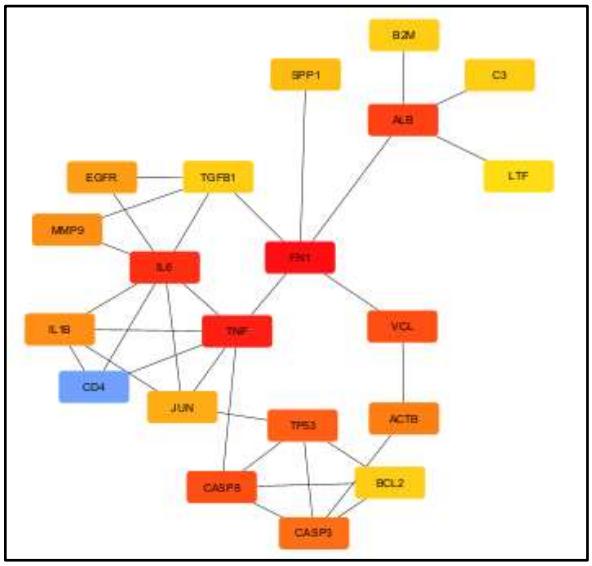

Figure 4.2: Bottleneck

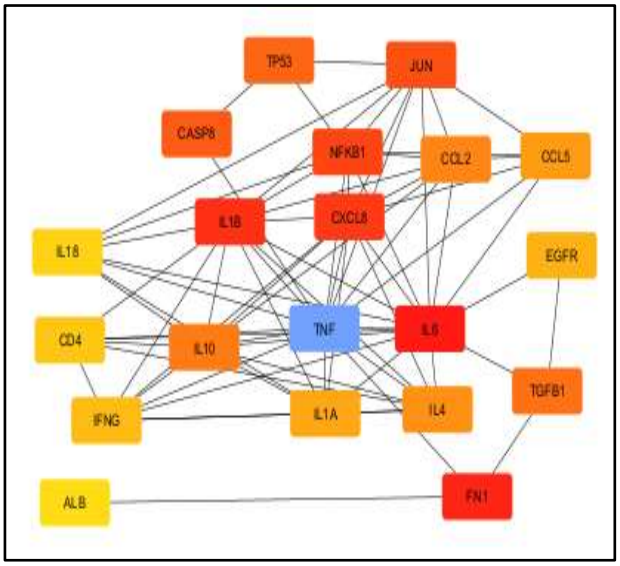

Figure 4.3: Closeness

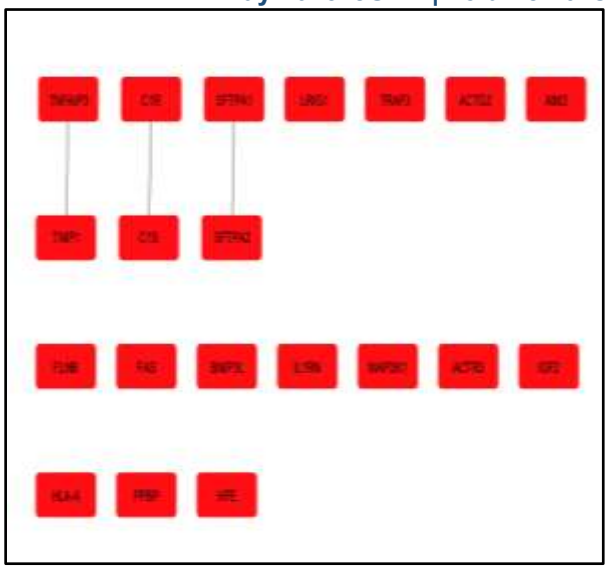

Figure 4.4: Clustering Coefficient

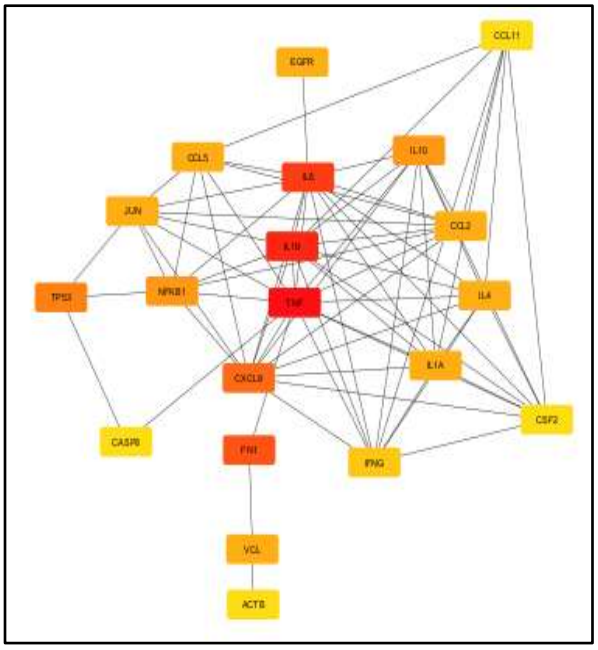

Figure 4.5: Degree

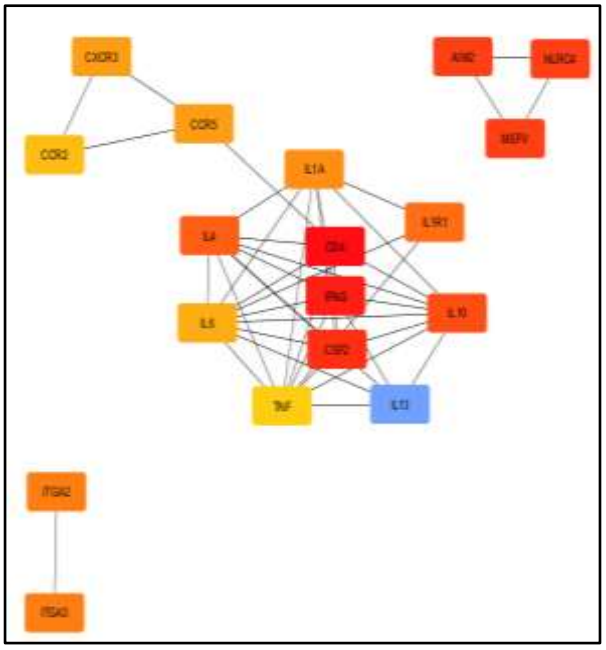

Figure 4.6: DMNC

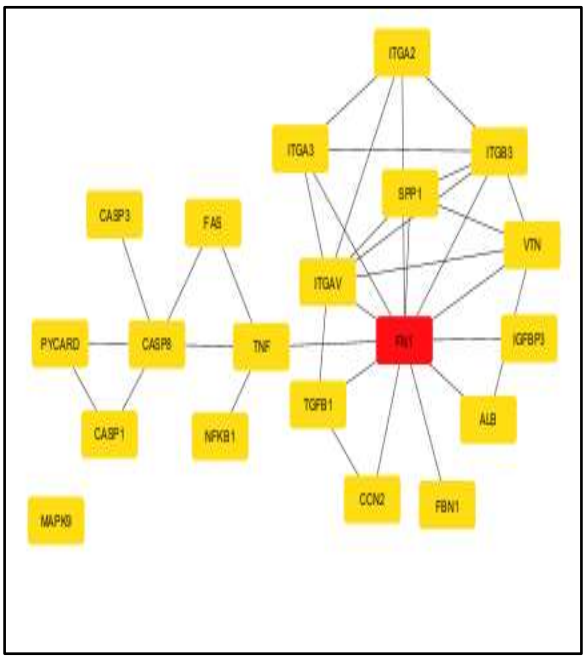

Figure 4.7: EcCentricity

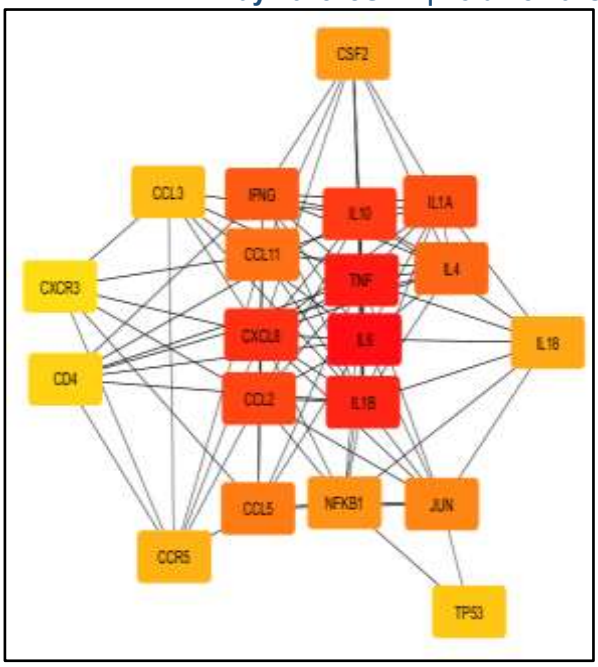

Figure 4.8: EPC

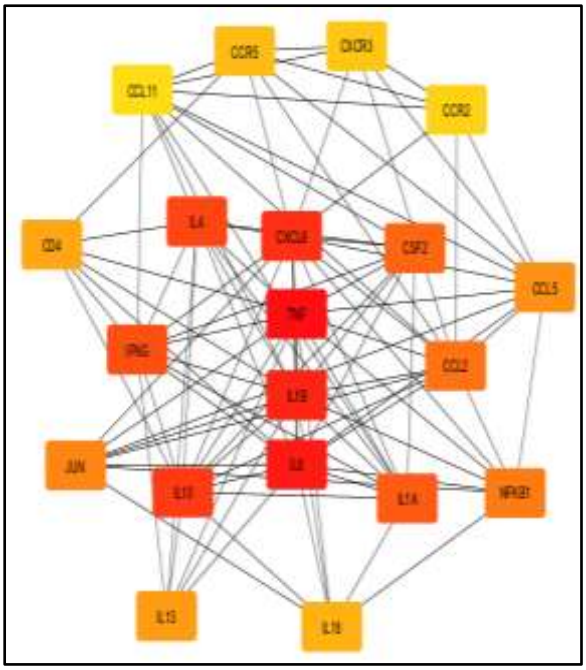

Figure 4.9: MCC

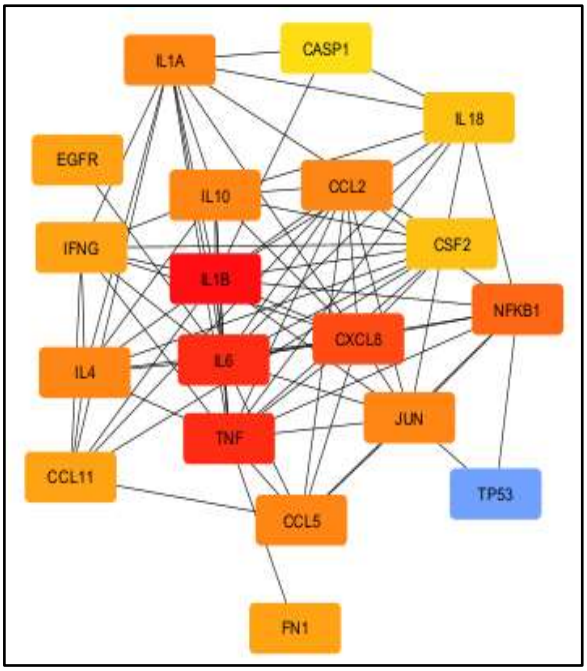

Figure 4.10: MNC

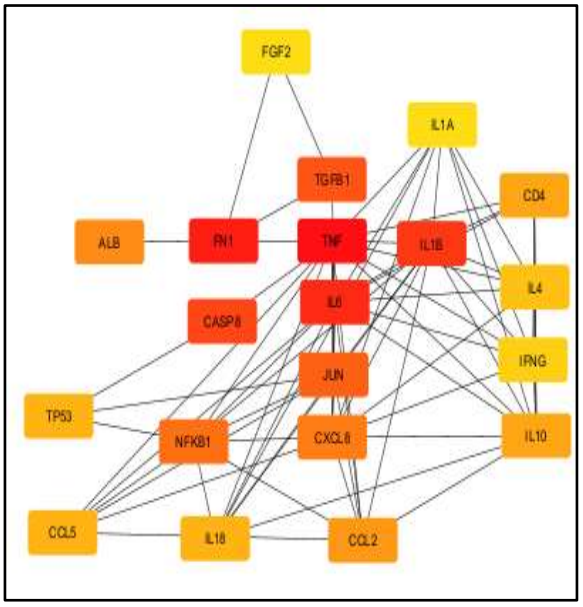

Figure 4.11: Radiality

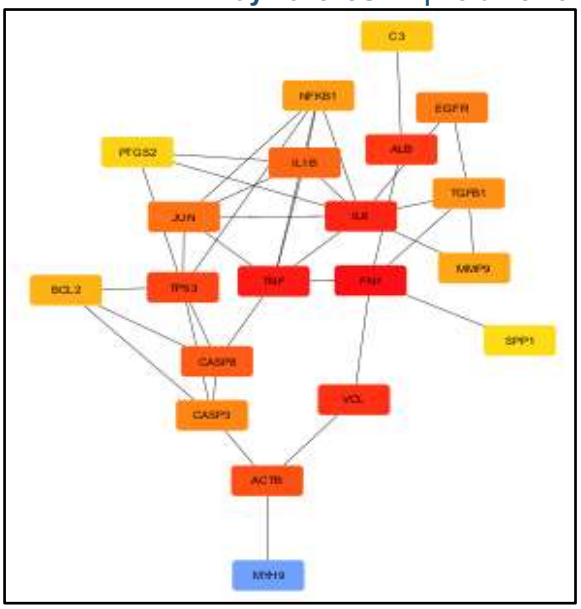

Figure 4.12: Stress

Figure 2 to 13: Shows the network formed by cytoscape on all 12 parameters of cytohubba, red ones are most interactive as compared to orange, yellow, and its color shades in network of many. Darker the color shade more the proximity to be the hub gene and interacting gene among all the given genes. This shows the priority hub genes is linked with many.

Phytocompound Virtual Screening

From various online webpages and websites, we got the possible phytocompounds which can be utilized as a supplement to prevent or minimize asbestosis disease. Almost 27 phytocompounds were identified. Then we did every phytocompounds virtual screening. This was done in two different platforms first PubChem where we got its canonical smiles structure and second, we used ADMETlab 3.0 where these canonical smiles were pasted, and we got to know if it follows Lipinski's rule of 5 or not. If it follows then it was accepted, if not then rejected.

Molecular Docking

The sanguinarine phytocompound was identified to have the highest negative binding energy -8.26Kcal/mole. Other compounds also show the acceptable binding energy to be a phytocompound against asbestosis.

Sr No.	Phytocompounds	Binding Energy (Kcal/Mole)	Amino Acid Residue
1	Sanguinarine	-8.26	V93, R108, A109, D219, S223
2	Withaferin A	-8.21	K141, Q143, Y217, G142, W190
3	Evodiamine	-8.08	R108, A109, F220, V226, G224
4	Kahweol	-7.98	V93, A94, P96, R108, V226, A109, E222, F220
5	Cafestol	-7.53	V93, A94, P96, R108, F220, E222
6	Daidzein	-7.45	A94, R108, A109, V226, D219, S223, G224, S223, F220
7	Piperine	-7.33	V93, P96, R108, N110, S223, V226,

8	Genistein	-7.22	V93, A94, R108, A109, F220, D219, V226, S223, G224
9	Genistein	-7.22	V93, A94, R108, A109, F220, V226, D219, S223, G224,
10	Catechin	-7.1	V93, F220, V226, A94, A221, G224, S223, E222, P96
11	Vitamin A	-6.86	V93, A94, P96, F220, V226
12	Beta Ionone	-6.63	V93, A94, P96, F220, V226
13	Pinoresinol	-6.5	V93, P96, R108, F220, E222, S223, A109, V226, A94
14	Quercetin	-6.43	F220, A109, D219, V226, S223, E222
15	Cyanidin	-6.4	A94, P96, F220, E222, V226, S223, G224
16	Crocetin	-6.35	R28, Q25, R29, F32, L33, F36
17	Honokiol	-6.33	V93, A94, P96, R108, F220, Q225, V226, A109, S223
18	Licochalcone A	-6.29	T181, A185, W190, P176, E186, Q178, C177
19	Luteolin	-6.22	V93, A94, R108, A109, F220, D219, V226
20	Resveratrol (+Clofarabine)	-5.93	V93, A94, P96, R108, A109, F220, V229

Table 2: Molecular docking result of top 20 phytocompounds with their binding energy and amino acid residues.

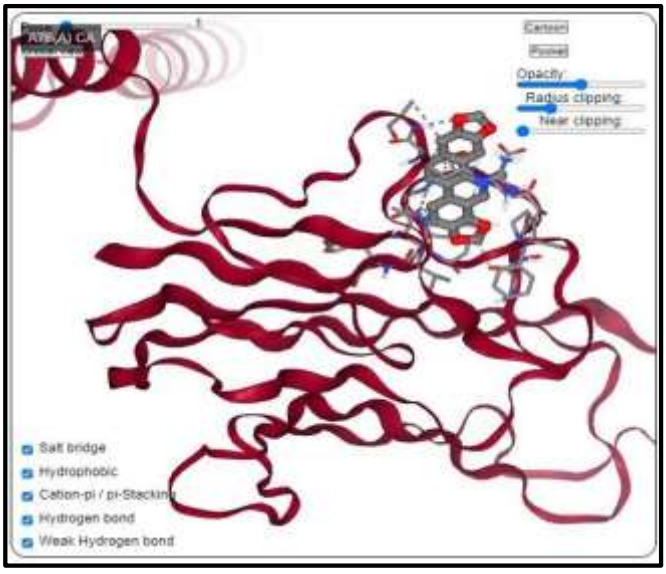

Fig. 4.13: Sanguinarine

Figure 14 shows the molecular docking images of the phytocompound with the hub genes' protein structure. These phytocompounds show acceptable binding energy results, they are of the highest binding phytocompound i.e. of Sanguinarine.

5. Discussion

There is an interesting compound found within the flowering bloodroot plant, called sanguinarine. Some evidence has emerged that this natural chemical might give some benefit to lung health through extinguishing airway inflammation and oxidative stress. These are key drivers of respiratory diseases such as COPD and asthma.

Imagine sanguinarine as just such a tool in the management of these conditions. Research hints it might help by soothing inflamed airways and reducing the production of mucus. There is even a possibility that it may volt against bacterial lung infections due to its antibacterial properties. Research in sanguinarine is at an

infant stage. Most studies have not been conducted on human subjects; thus, the efficacy and safety of its application in lung diseases are not fully established. Consider this: it's a new medicine with promise but that needs more testing.

Another concern is dietary supplements that contain sanguinarine. According to some reports, these supplements interfere with other prescription drugs one may be taking and can be toxic to the liver at higher doses. With limited research and possible risks, sanguinarine does not become a standard approach to lung diseases just yet.

The bottom line is that sanguinarine shows potential for lung health because it reflects anti-inflammatory and antioxidant properties. Further research is needed to deduce whether it would work effectively and safely in humans. In case people are thinking about adding supplements containing sanguinarine into their regime, they should not forget to consult the doctors. They will help weigh potential benefits against possible risks in this case.

6. Conclusion

It is a real danger, asbestos exposure induces scarring and inflammation in lungs, consequently making breathing quite a challenge. There is no cure; therefore, prevention of exposure is the key. Sanguinarine, a natural plant compound, was explored in this study as a prospective preventative measure for use against asbestos exposure.

Asbestos fibers in the lungs cause irritation and scarring of tissue; the result of this is difficulty in breathing and eventually respiratory failure. The current prevention technique includes regulations about asbestos use and protective gear for highly exposed workers. Accidents do happen, and environmental contamination does take place; therefore, looking into other options readily becomes important.

This is quite promising, since sanguinarine is anti-inflammatory, antioxidant, and anti-fibrotic. One of the major problems with asbestos is the inflammation it causes, and sanguinarine might cool things down and prevent tissue damage. Second, asbestos induces the production of harmful molecules that damage the cells of the lungs. Finally, asbestosis involves excessive scar tissue formation that makes the lungs stiff and hard to use. Perhaps it is because of the antifibrotic property that sanguinarine prevents such scarring, enabling the lungs to work well.

The catch is that much of the research conducted regarding sanguinarine and lung diseases is still at its rudimentary stages of study, mostly conducted in labs or on animals. More research is needed to establish if it works in human beings. Also, the optimal dose and route for delivery in the prevention of asbestosis by sanguinarine has not yet been worked out.

The preliminary research in this area indicates that sanguinarine could be another weapon in the prevention of asbestos-related diseases by targeting key processes involved in disease development. Further, more specific research is needed, particularly in-person studies, to determine if it's safe and effective. This

potentially may be another addition of some useful natural compounds to existing preventative measures that might protect people from asbestos exposure if it becomes successful.

7. References

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