Network Pharmacology of colchicine

Gaytri Botre, Pallavi Kavitake, Ritesh Jagtap
Padmini College of Pharmacy Dighanchi

Abstract- **Network pharmacology is an arising interdisciplinary field that integrates systems biology, bioinformatics, and pharmacology to understand the complex relations between medicines, targets, and conditions. This study applies a network pharmacology approach to probe the multi-target mechanisms of colchicine, a natural alkaloid known for its anti-inflammatory parcels. Using tools similar as Swiss Target Prediction, Swiss ADME, and STRING, the molecular relations of colchicine were explored to identify crucial target genes and associated signaling pathways. Results revealed that colchicine interacts with pivotal seditious intercessors, including IL1B, IL10, and TNF, suggesting its nonsupervisory part in vulnerable-affiliated pathways similar as the NOD-suchlike receptor and cytokine- cytokine receptor commerce pathways. These findings punctuate the eventuality of colchicine in modulating multiple natural targets and pathways, supporting its remedial use in complex conditions similar as gout, cardiovascular diseases, and COVID- 19. The study demonstrates the mileage of network pharmacology in uncovering the mechanistic base of traditional medicines within ultramodern biomedical fabrics.**

Key Point- **Network Pharmacology, gene, colchicine, anti-inflammatory**

I. INTRODUCTION OF NETWORK PHARMACOLOGY

Andrew L. Hopkins, a pharmacologist at Dundee University in the United Kingdom, introduced the term "Network Pharmacology."[1]

At the first annual academic meeting of the Chinese Association for Science and Technology in 1999, Shao Li introduced the "Syndrome" of a connection between TCM and biomolecular networks, which is where network pharmacology got its start.[1]

A novel approach to pharmaceutical research is the use of network pharmacology in conjunction with improved detection technology to investigate illness and symptom biomarkers.[1]

Alongside bioinformatics, systems biology, network medicine, artificial intelligence, big data science, and other related fields of study, network pharmacology also evolved and developed.[2]

He proposed the illness gene network a few years later.[1]

Hopkins, a British pharmacist, first proposed network pharmacology as a new field in Nature Biotechnology in 2007. It's innovated on the propositions of pharmacology, bioinformatics, and other fields and is rested on the idea that network databases are developing snappily.[3]

Systematic biomedical technology is integrated with network pharmacology.[3]

Although many academics in the medical profession use network pharmacology technology these days, we should recognize that its growth was not coincidental. The emergence and growth of network pharmacology are widely acknowledged to have been facilitated by bioinformatics and computational biology.[3]

In order to make the network pharmacology system, we must first comprehend the internal connections inside the" medicine – target – gene – complaint" network. Then, we may use these relationships to uncover or forecast the mechanism of action of individual or compound Chinese medicines on the disease.[3]

Network pharmacology filters out the main targets and associated pathways by building a biological network.[3]

Addressing the main issues that the globe has been facing with regard to global health issues has become imperative.[4]

The main goals of network pharmacology research are to find genes linked to compounds and diseases, build a network of protein–protein interactions (PPIs), and then analyze and visualize the network [74–76]. Building molecular networks from massive databases is an easy beginning. Important nodes are then found and important biological pathways are forecasted by network analysis [77]. In order to successfully validate the interaction between highly active components and their potential targets, further network validation is carried out [78,79]. We emphasized each stage of network pharmacology research in this review.[4]

A novel approach to investigating the molecular pathways is network pharmacology.[5]
TCM-NP is built on the concept and basis of AI-based mining of correlations between drugs/formulas and diseases/syndromes from prior knowledge, which has become a contemporary research area of considerable interest as biomedical knowledge has accumulated. From a network perspective, the relationships between the disease/syndrome, biological molecule, and drug/formula levels are the most important.[6]

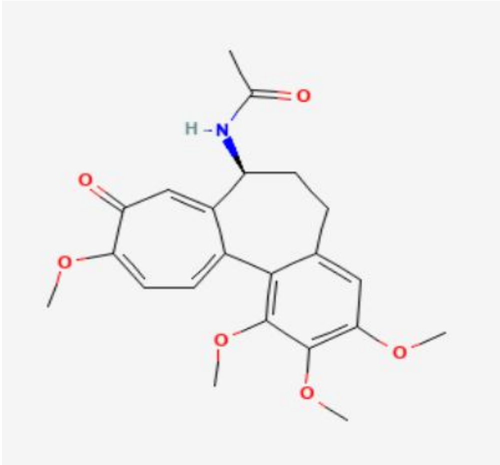
Process in Network Pharmacology Research

- Data Collection and Validation: To maximize the safety and effectiveness of a potential medication and its powerful combinations, network pharmacology considers the previously described concepts. Additionally, these stand for the two crucial phases of any scientific investigation. Choosing original data from experiments to create a biological network is the initial stage in network pharmacology. The second is the projected network model's experimental validation. A variety of integrated techniques, including as proteomics, metabolomics, and genomes, can be used to quantify the validated data.
- Network Analysis and Visualization: Network analysis uses relevant technologies to focus on established networks and extracts valuable data that can be easily used for additional research.
- Using visualization tools, network visualization is used to convert interassociation data into a visual network and extract interaction information.[7]

Advantage

Advantage Network pharmacology has several benefits, similar as controlling the signaling pathway through colorful channels, perfecting remedial efficacity, lowering adverse goods, adding clinical trial success rates, and lowering medicine discovery charges. Numerous genes and functional proteins interact in many complex illnesses.[7]

Molecular Introduction
Molecule name- Colchicine
Trade names Colcrys, Mitigare, others[10]
Bioavailability 45%
Protein binding 35-44%
Metabolism Metabolism, partly by CYP3A4
Elimination half-life 26.6-31.2 hours
Excretion Feces (65%) [10]
IUPAC Name
N-[(7S)-1,2,3,10-tetra O-methoxy-9-oxo-6,7-dihydro-5Hbenzo[a]heptalen-7-yl] acetamide.[9]
Researching and updating the mechanisms of action and therapeutic applications of colchicine in a range of inflammatory disorders is the goal of this article.



[9]

The Moa of Colchicine

- Colchicine's anti-mitotic action and disruption of tubulin
- Colchicine's disruption of tubulin and anti-mitotic action; neutrophils; and inhibition of the NALP3 inflammasome and innate immune responses[8]

Colchicine's medicinal use

Colchicine's use in FMF and gout is more well-established. Beyond these, research on colchicine's potential therapeutic uses in rheumatic osteoarthritis (OA), BD, or nonrheumatic diseases such pericarditis, artherosclerosis, and liver cirrhosis is still ongoing, although as will be discussed below, some of these ailments seem to be promising.[8]

Because of its medicinal qualities, colchicine, a naturally occurring alkaloid obtained from Colchicum autumnale, has been used for centuries. Although its main function in treating gout is well known, considerable emphasis has been paid to the mechanisms behind its wide range of pharmacological actions. With an emphasis on its capacity to disrupt microtubules and its wider implications in cellular processes and disease pathogenesis, this article seeks to present a thorough overview of colchicine's methods of action. First discovered and manufactured in the 19th century, colchicine is a tricyclic alkaloid withantiinflammatory rates that's deduced from the herbaceous Colchicum autumnale factory. Because it was mentioned on an Egyptian papyrus from 1550 BC and was utilized by ancient people, it is one of the very few medications that has survived from antiquity to modern times.[9]

It was used by ancient Greek, Byzantine, and Arabian physicians and was mentioned in an Egyptian papyrus from 1550 BC, making it one of the few medications that has survived from antiquity to modern times. Colchicine has been used to treat gout in the past.

Prospects for the future include: - Continued investigation and new therapeutic applications - Creation of colchicine derivatives and formulations Synergistic effects and combination therapies[9]

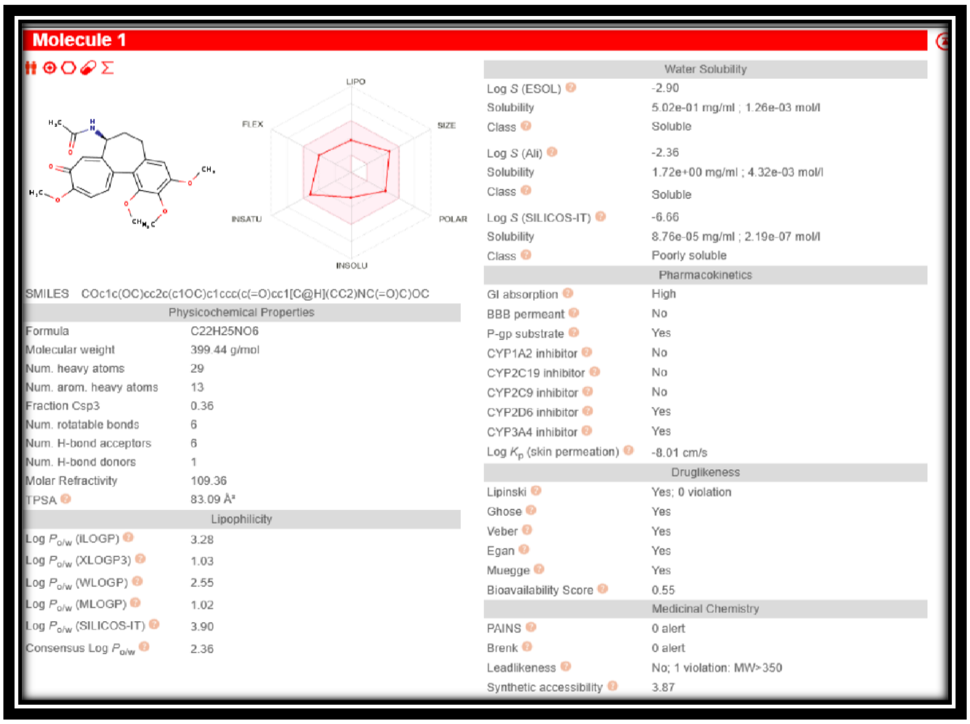
II. MATERIAL AND METHOD

1) Selection of Phytochemical-

SMILIES OF COLCHICINE -PUBCHEM

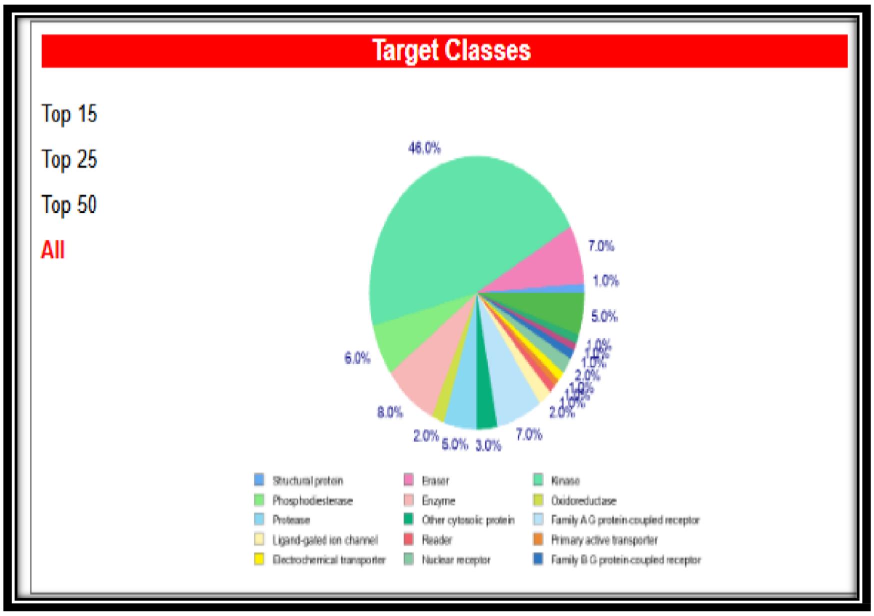
CC(=O)N[C@H]1CCC2=CC(=C(C(=C2C3=CC=C(C(=O)C=C13)OC)OC)OC)OC

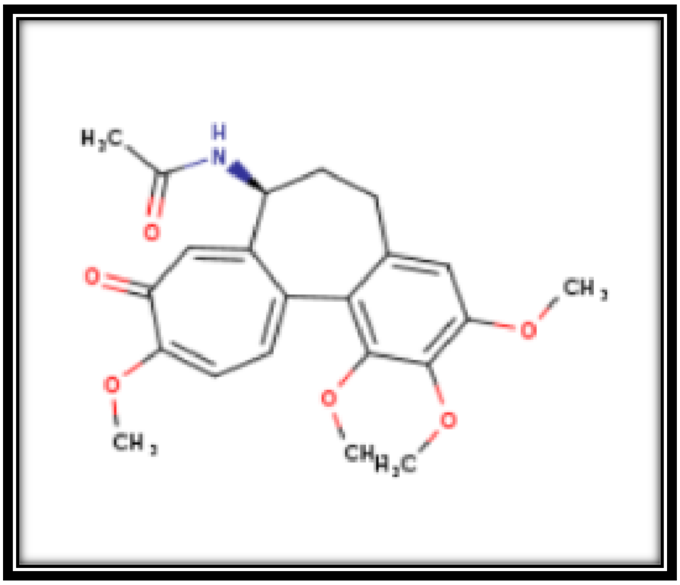
SWISS ADME -



2) Selection of Target Identification -

SWISS TARGET-





3) Disease Gene –

DISGENET		MALACARD		OMIM	
				1.	NLRP3
1.	TNF	1.	PSMB8	2.	TLR8
2.	IL17A	2.	PSMB4	3.	SYK
3.	IL6	3.	PSMB8-AS1	4.	MAD1L1
4.	IL1B	4.	IL6	5.	ILRUN
5.	NFKB1	5.	TNF	6.	IL6
6.	NLRP3	6.	IL1B	7.	NOD2
7.	CRP	7.	CRP	8.	RIPK1
8.	IL12B	8.	IFNG	9.	TLR4
9.	IL1A	9.	IL1RN	10.	NFKB1
10.	NOD2	10.	CXCL8		

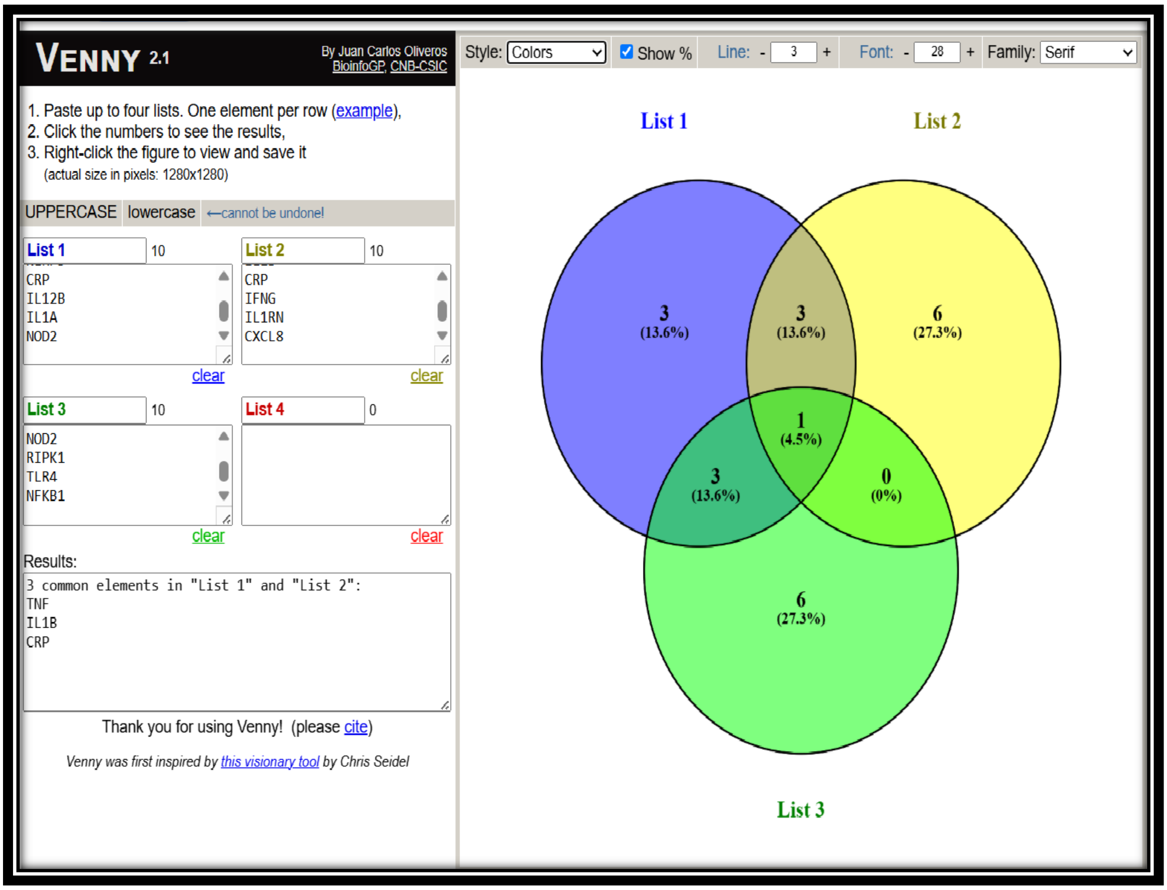
Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PMIDs	N Chemicals	N PMIDs Chemic
TNF	tumor necrosis factor	4015	21	0.45	210	10	11
IL17A	interleukin 17A	1651	15	0.45	103	3	1
IL6	interleukin 6	3805	33	0.45	100	6	7
IL1B	interleukin 1 beta	2641	24	0.35	97	7	7
NFKB1	nuclear factor kappa B subunit 1	1856	110	0.35	85	8	7
NLRP3	NLR family pyrin domain containi...	1044	344	0.35	68	5	5
CRP	C-reactive protein	3137	12	0.35	60	6	5
IL12B	interleukin 12B	1551	108	0.35	43	1	1
IL1A	interleukin 1 alpha	1441	24	0.35	41	1	1
NOD2	nucleotide binding oligomerizati...	590	468	0.35	39	0	0

4) Selection Of Common Gene –

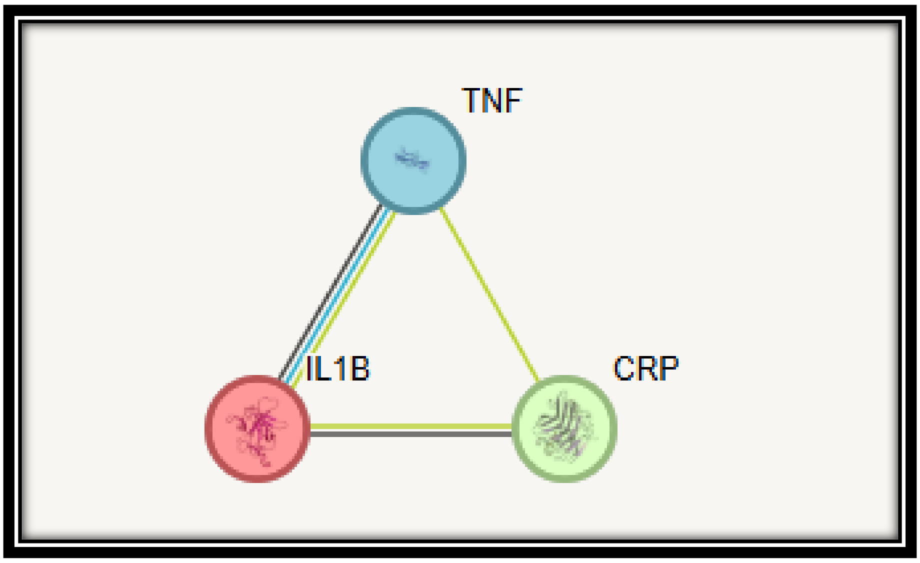
VENNY-

- TNF
- IL1B

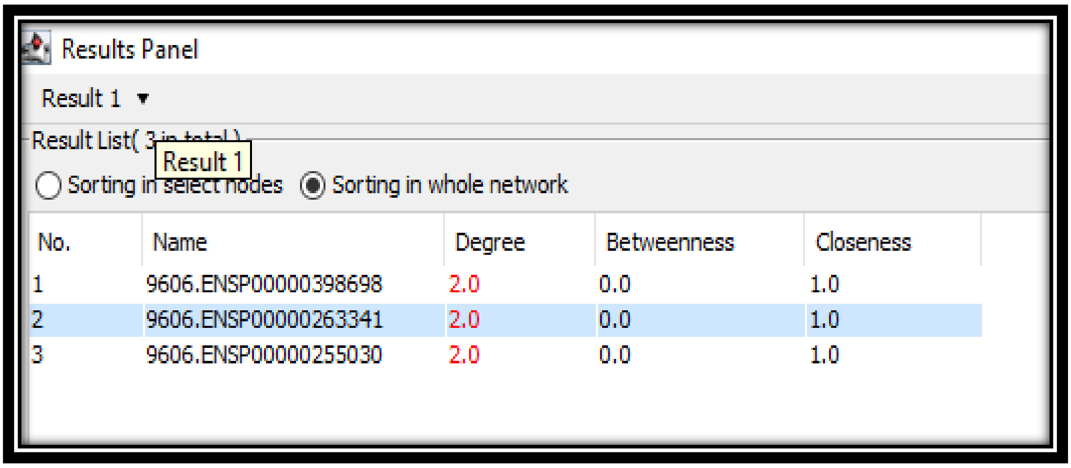
- CRP



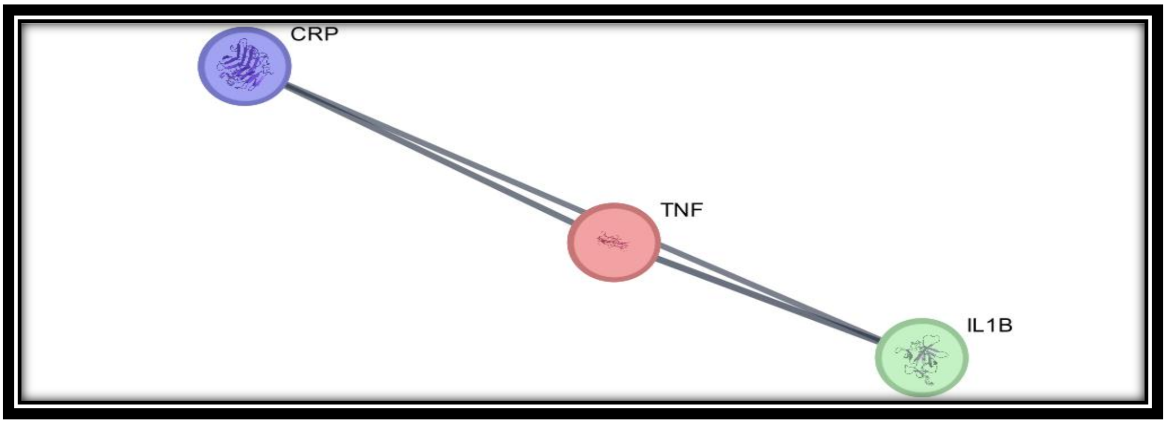
5) PI intraction and ranking-
STRING DATA-



CYTOSCAPE- Centrality measure



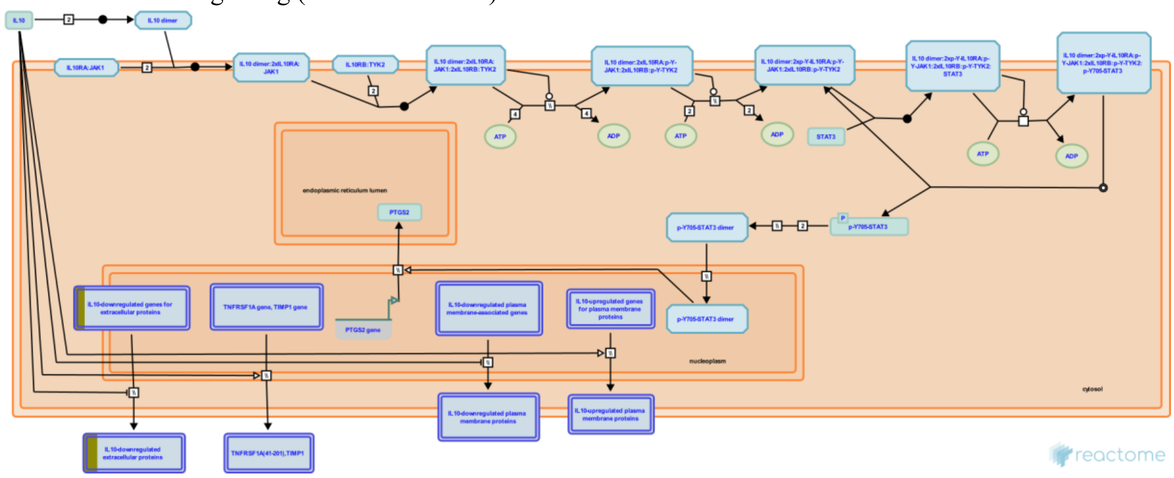
No.	Name	Degree	Betweenness	Closeness
1	9606.ENSP00000398698	2.0	0.0	1.0
2	9606.ENSP00000263341	2.0	0.0	1.0
3	9606.ENSP00000255030	2.0	0.0	1.0



6) Pathway Analysis-
REACTOME-
Pathways details-

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Interleukin-10 signaling (R-HSA-6783783)



Interleukin-10 (IL10) was originally described as a factor named cytokine synthesis inhibitory factor that inhibited T-helper (Th) 1 activation and Th1 cytokine production (Fiorentino et al. 1989). It was found to be expressed by a variety of cell types including macrophages, dendritic cell subsets, B cells, several T-cell subpopulations including Th2 and T-regulatory cells (Tregs) and Natural Killer (NK) cells (Moore et al. 2001). It is now recognized that the biological effects of IL10 are directed at antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), its effects on T-cell development and differentiation are largely indirect via inhibition of macrophage/dendritic cell activation and maturation

(Pestka et al. 2004, Mocellin et al. 2004). T cells are thought to be the main source of IL10 (Hedrich & Bream 2010). IL10 inhibits a broad spectrum of activated macrophage/monocyte functions including monokine synthesis, NO production, and expression of class II MHC and costimulatory molecules such as IL12 and CD80/CD86 (de Waal Malefyt et al. 1991, Gazzinelli et al. 1992). Studies with recombinant cytokine and neutralizing antibodies revealed pleiotropic activities of IL10 on B, T, and mast cells (de Waal Malefyt et al. 1993, Rousset et al. 1992, Thompson-Snipes et al. 1991) and provided evidence for the in vivo significance of IL10 activities (Ishida et al. 1992, 1993). IL10 antagonizes the expression of MHC class II and the co-stimulatory molecules CD80/CD86 as well as the pro-inflammatory cytokines IL1Beta, IL6, IL8, TNFalpha and especially IL12 (Fiorentino et al. 1991, D'Andrea et al. 1993). The biological role of IL10 is not limited to inactivation of APCs, it also enhances B cell, granulocyte, mast cell, and keratinocyte growth/differentiation, as well as NK-cell and CD8+ cytotoxic T-cell activation (Moore et al. 2001, Hedrich & Bream 2010). IL10 also enhances NK-cell proliferation and/or production of IFN-gamma (Cai et al. 1999).

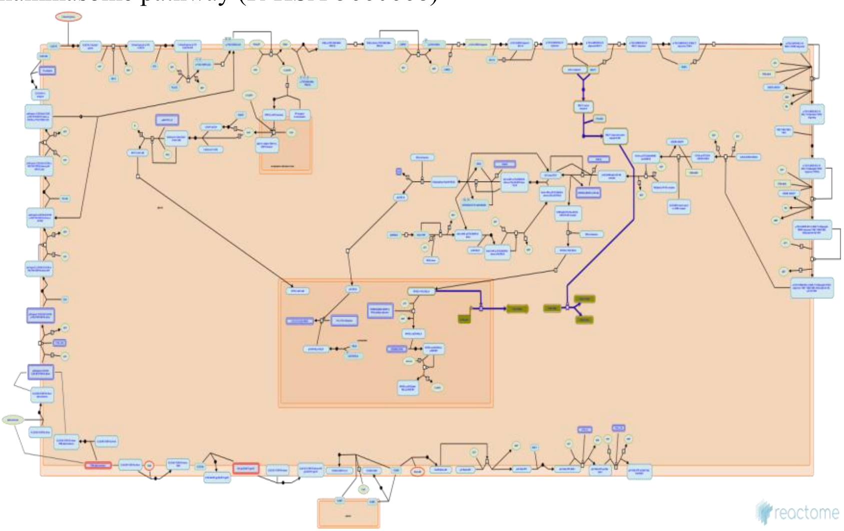
IL10-deficient mice exhibited inflammatory bowel disease (IBD) and other exaggerated inflammatory responses (Kuhn et al. 1993, Berg et al. 1995) indicating a critical role for IL10 in limiting inflammatory responses. Dysregulation of IL10 is linked with susceptibility to numerous infectious and autoimmune diseases in humans and mouse models (Hedrich & Bream 2010).

IL10 signaling is initiated by binding of homodimeric IL10 to the extracellular domains of two adjoining IL10RA molecules. This tetramer then binds two IL10RB chains. IL10RB cannot bind to IL10 unless bound to IL10RA (Ding et al. 2001, Yoon et al. 2006); binding of IL10 to IL10RA without the co-presence of IL10RB fails to initiate signal transduction (Kotenko et al. 1997).

IL10 binding activates the receptor-associated Janus tyrosine kinases, JAK1 and TYK2, which are constitutively bound to IL10R1 and IL10R2 respectively. In the classic model of receptor activation assembly of the receptor complex is believed to enable JAK1/TYK2 to phosphorylate and activate each other. Alternatively the binding of IL10 may cause conformational changes that allow the pseudokinase inhibitory domain of one JAK kinase to move away from the kinase domain of the other JAK within the receptor dimer-JAK complex, allowing the two kinase domains to interact and trans-activate (Waters & Brooks 2015).

The activated JAK kinases phosphorylate the intracellular domains of the IL10R1 chains on specific tyrosine residues. These phosphorylated tyrosine residues and their flanking peptide sequences serve as temporary docking sites for the latent, cytosolic, transcription factor, STAT3. STAT3 transiently docks on the IL10R1 chain via its SH2 domain, and is in turn tyrosine phosphorylated by the receptor-associated JAKs. Once activated, it dissociates from the receptor, dimerizes with other STAT3 molecules, and translocates to the nucleus where it binds with high affinity to STAT-binding elements (SBEs) in the promoters of IL-10-inducible genes (Donnelly et al. 1999).[11]

2. CLEC7A/inflammasome pathway (R-HSA-5660668)



Cellular compartments: plasma membrane, cytosol.
Antifungal immunity through the induction of T-helper 17 cells (TH17) responses requires the production of mature, active interleukin-1beta (IL1B). CLEC7A (dectin-1) through the SYK route induces activation of NF-kB and transcription of the gene encoding pro-IL1B via the CARD9-BCL10MALT1 complex as well as the formation and activation of a MALT1-caspase-8-ASC complex that mediated the processing of pro-IL1B. The inactive precursor pro-IL1B has to be processed into mature bioactive form of IL1B and is usually mediated by inflammatory cysteine protease caspase-1. Gringhuis et al. showed that CLEC7A mediated processing of IL1B occurs through two distinct mechanisms: CLEC7A triggering induced a primary noncanonical caspase-8 inflammasome for pro-IL1B processing that was independent of caspase-1 activity, whereas some fungi triggered a second additional mechanism that required activation of the NLRP3/caspase 1 inflammasome. Unlike the canonical caspase-1 inflammasome, CLEC7A mediated noncanonical caspase-8-dependent inflammasome is independent of pathogen internalization. CLEC7A/inflammasome pathway enables the host immune system to mount a protective TH17 response against fungi and bacterial infection (Gringhuis et al. 2012, Cheng et al. 2011).[12][13]

3. Interleukin-4 and Interleukin-13 signaling (R-HSA-6785807) [14][15][16]

4. Signaling by Interleukins (R-HSA-449147) [17][18]

III. RESULT AND DISSCUSSION

- Genes linked to the lead and receptor molecules were examined in the presence investigation.
- The current study uses the Pubchem program to identify the grins of molecules.
  These smiles were integrated into the sophisticated program known as "swiss target prediction," which obtained uniport ids for both the genes and the receptors.
- The current study then discovered that more genes were obtained from the SEA tool and from the colchicine molecule utilizing a variety of tools, including Swiss target prediction, Malacards, Omim and Disgenet. Additionally, common genes were found using an AI tool.
- Venny 2.1.0 used to obtain common gene.
- Reactome software was then utilized to obtain illness pathways, and a string tool from Cytoscape was employed for centrality metrics in the current Network Pharmacology study.
- As a result, network pharmacology offers fresh perspectives on drug action analysis.

REFERENCE

[1] Li, L., Yang, L., Yang, L., He, C., He, Y., Chen, L., Dong, Q., Zhang, H., Chen, S., & Li, P. (2023). Network pharmacology: a bright guiding light on the way to explore the personalized precise medication of traditional Chinese medicine. *Chinese Medicine*, *18*(1).

[2] Wang, Xin, et al. "TCM Network Pharmacology: A New Trend towards Combining Computational, Experimental and Clinical Approaches." *Chinese Journal of Natural Medicines*, vol. 19, no. 1, 2021, pp. 1–11

[3] Zheng, S., Xue, T., Wang, B., Guo, H., & Liu, Q. (2022). Application of network pharmacology in the study of mechanism of Chinese medicine in the treatment of ulcerative colitis: A review. *Frontiers in Bioinformatics*, *2*.

[4] Noor, F., Qamar, M. T. U., Ashfaq, U. A., Albutti, A., Alwashmi, A. S. S., & Aljasir, M. A. (2022). Network Pharmacology Approach for Medicinal Plants: Review and Assessment. *Pharmaceuticals*, *15*(5), 572.

[5] Xie, Wenrui, et al. "Network Pharmacology Analysis: A Promising Approach for the Research of Traditional Chinese Medicine." *Journal of Exploratory Research in Pharmacology*, vol. 000, no. 000, 2020, pp. 1–2.

[6] Zhang, Peng, et al. "Network Pharmacology: Towards the Artificial Intelligence-Based Precision Traditional Chinese Medicine." *Briefings in Bioinformatics*, vol. 25, no. 1, 2023.

[7] Zhang, G., Li, Q., Chen, Q., & Su, S. (2013). Network Pharmacology: a new approach for Chinese herbal medicine research. *Evidence-based Complementary and Alternative Medicine*, *2013*, 1–9.

[8] Leung, Ying Ying, et al. "Colchicine--Update on Mechanisms of Action and Therapeutic Uses." *Seminars in Arthritis and Rheumatism*, vol. 45, no. 3, 2015, pp. 341–350.

[9] Ref-Jagannath, Bhosale Ganesh, et al. "Mechanism of Colchicine." Ijirt.org, . Accessed 6 May 2025.

[10] ref- *Cdc.gov*, https://www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750016.h. Accessed 6 May 2025
[11] Moore KW, O'Garra A, Coffman RL & de Waal Malefyt R (2001). Interleukin-10 and the interleukin 10 receptor. Annu. Rev. Immunol., 19, 683-765
[12] Cavalieri D, Stoffels M, Netea MG, Preechasuth K, van de Veerdonk FL, Kanneganti TD, ... Lenar don M (2011). The dectin-1/inflammasome pathway is responsible for the induction of protect ive T-helper 17 responses that discriminate between yeasts and hyphae of Candida albicans. J. Leukoc. Biol., 90, 357-66
[13] Geijtenbeek TB, Gringhuis SI, Boekhout T, Theelen B, Wevers BA, van der Vlist M & Kaptein TM (2012). Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1? via a noncanonical caspase-8 inflammasome. Nat. Immunol., 13, 246-54
[14] Ryan JJ, Nelms K, Paul WE, Zamorano J & Keegan AD (1999). The IL-4 receptor: signaling mechan isms and biologic functions. Annu. Rev. Immunol., 17, 701-38.
[15] Hershey GK (2003). IL-13 receptors and signaling pathways: an evolving web. J. Allergy Clin. Im munol., 111, 677-90; quiz 691
[16] Vosshenrich CA & Di Santo JP (2002). Interleukin signaling. Curr Biol, 12, R760-3.
[17] Komlosi Z, Kucuksezer UC, Frei R, Huitema C, Garbani M, Pezer M, ... Eiwegger T (2016). Interleuk ins (from IL-1 to IL-38), interferons, transforming growth factor , and TNF- : Receptors, func tions, and roles in diseases. J. Allergy Clin. Immunol., 138, 984-1010.
[18] Dinarello CA (2009). Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol, 27, 519-5