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Network Pharmacology study on the mechanism of MKA Polyherbal Formulation in combating Respiratory Diseases

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ABSTRACT

The Multi-targeted action of Polyherbal formulation is responsible for enhanced therapeutic efficacy in combating various diseases. But, understanding the mode of action of herbal medicine remains a challenge because of its complex metabolomics. Network pharmacology-based approach enables to explore the mechanism of action of polyherbal formulation in biological system. In present investigation, we have explored the molecular mechanism of action of the Polyherbal formulation MKA comprising of three botanicals *Mimusops elengi* L., *Kedrostis foetidissima* (Jacq.) Cogn. and *Artemisia vulgaris* L. in treating respiratory diseases by network pharmacology-based approach. The protein targets were mined from Binding database for the bioactive present in MKA. The disease associated targets were identified using Open target Platform. Based on ligand-target interactions, it was interpreted that MKA could alleviate the symptoms of respiratory disease by multiple mechanisms like EGFR inhibition by Quercetin and Quercetin-3-O-rhamnoside, KDR inhibition by Quercetin, STAT-3 inhibition by β-sitosterol- β-D-glucoside, TRPV1 inhibition by phytol acetate, etc. The Protein-protein interaction (PPI) network was constructed using STRING database. KEGG pathway based functional enrichment was also predicted for the PPI network. It was found that multiple ligand-target interactions and protein-protein interactions is responsible for pharmacological activity of MKA in respiratory diseases.

Keywords: Polyherbal formulation, Respiratory, Ligand, Protein-protein interactions (PPIs), Inhibition.

INTRODUCTION

Respiratory diseases are the most common cause of illness and death all over the world. Among the respiratory diseases, asthma, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS) are related to high mortality rate [1,2,3]. The main causative agents of these infectious diseases are virus and bacteria. SARS-CoV infection, mainly targets the respiratory tract leading to chronic inflammation and arrests the lung function [4,5]. In most of the cases, a single compound extracted and purified from polyherbal formulation or traditional medicine may have lower activity compared to the formulation, and in certain cases, the single compound extracted may be more toxic. This confirms that, there is a difference in activity of the compound individually and as such in the formulation. So, synergistic action of compounds in polyherbal formulation has to be considered for its therapeutic value [6,7].

Network pharmacology is a newly emerging area which deals with relationship between ligands, protein targets and its associated diseases in biological network of herbal formulations. It clearly demonstrates the synergistic action of multiple ligands on multiple targets in herbal formulations [8]. The MKA Polyherbal formulation comprising of three selected plants *Mimusops elengi, Kedrostis foetidissima* (Jacq.) Cogn. and *Artemisia vulgaris* L. were reported to possess anti-inflammatory potential in LPS induced RAW 264.7 macrophages. The MKA treatment decreased the release of Reactive Oxygen Species (ROS) and nitrite level in inflammatory macrophages [9]. Also, the MKA was explored to possess therapeutic effect on LPS treated macrophages by reducing the rate of lipid peroxidation and restoring the mitochondrial membrane potential and cell membrane integrity [10].

In present investigation, network pharmacological method was employed to understand the molecular mechanisms underlying the action of three botanicals *Mimusos elengi, Kedrostis foetidissima* (Jacq.) Cogn. and *Artemisia vulgaris* L. in MKA herbal formulation in combating respiratory diseases. The potential protein targets of the bioactives present in polyherbal formulation MKA were identified from binding database. The respiratory disease associated protein targets were identified from Open target platform. The protein-protein interactions (PPIs) were interpreted by constructing the protein network map using STRING database.

MATERIALS AND METHODS

Mining of phytochemicals and Protein targets

The bioactive compounds present in each plant constituent of Polyherbal formulation MKA were mined from scientific literatures, journals and biological databases. In total, five research reports were used as references to study the phytocompounds in *Mimusops elengi* L., *Kedrostis foetidissima* (Jacq.) Cogn. and *Artemisia vulgaris* L. [11-15].

The PUBCHEM Compound ID and canonical SMILES for all the chemical compounds were retrieved from PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov/) [16]. The chemical compounds without PUBCHEM Compound ID were excluded. The Potential protein targets were identified from binding database (https://www.bindingdb.org/bind/index.jsp) using CANONICAL SMILES as query input. The targets having at least 70% ligand template similarity were selected for further studies [17]. The ligand target interaction was also predicted from Binding database based on the assay description.

Respiratory disease associated target identification

The target proteins associated with respiratory diseases were predicted from open targets (https://www.targetvalidation.org/), which is a platform for therapeutic target identification and validation [18]. The lists of proteins identified from binding database were given as input using "Batch search" option. The Open Target output, gives the details of the relevant disease associated proteins. The respiratory disease associated protein targets were screened from the Open Target output. The affinity of the ligand present in MKA with respiratory disease associated protein targets was analyzed.

Construction of PPI network

The metabolic interactions of the protein targets associated with respiratory diseases were studied using STRING database. The list of proteins identified from Open target Platform associated with respiratory disease, was given as input in STRING database. Multiple protein search was conducted to predict the protein-protein interactions (PPIs) network [19].

RESULTS AND DISCUSSION

Phtoconstituents present in MKA Polyherbal formulation

The phytoconstituents present in individual plants *Mimusops elengi* L., *Kedrostis foetidissima* (Jacq.) Cogn. and *Artemisia vulgaris* L. of MKA were identified by mining of literatures and databases. The chemical compounds with their PUBCHEM CID and CANONICAL SMILES were illustrated in Table 1. It is inferred that, MKA is a rich source of phytocompounds which is responsible for its therapeutic effect. For present investigation, 13 bioactives from *Mimusops elengi* L., 14 bioactives from *Kedrostis foetidissima* (Jacq.) Cogn. and 13 phytocomponents from Artemisia vulgaris L. were used for prediction of multi-target pharmacological mechanism of action of MKA Polyherbal formulation in treating respiratory diseases.

Table 1: Bioactives present in MKA Polyherbal formulation

BOTANICALS	LIGANDS	PUBCHEM ID	CANONICAL SMILES
Mimusops elengi L.	Quercetin	5280343	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
	Quercitol	441437	C1C(C(C(C(C1O)O)O)O)O
	β-sitosterol- β-D-glucoside	71628	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)OC5C(C(C(C(O5)CO)O)O)O)C)C)C(C)C
	Ursolic acid	64945	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1C)C)C(=O)O
	Stearic acid 3-(octadecyloxy) propyl ester	551406	CCCCCCCCCCCCCCCCCCCCOCCCOC(=O)CCCCCCCCCCCCCCCCCC
	Hexadecanoic acid, methyl ester	8181	CCCCCCCCCCCCCCCC(=O)OC
	10-Octadecenoic acid, methyl ester	25642	CCCCCCCC=CCCCCCCCCC(=O)OC
	Spinasterol	5281331	CCC(C=CC(C)C1CCC2C1(CCC3C2=CCC4C3(CCC(C4)O)C)C)C(C)C
	Hentriacontane	12410	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	β-carotene	5280489	CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CCCC2(C)C)C)C)C
	Stearic acid 3-(octadecyloxy) propyl ester	551406	CCCCCCCCCCCCCCCCCCCCOCCCOC(=O)CCCCCCCCCCCCCCCCCC
	Squalene	638072	CC(=CCCC(=CCCC(=CCCC=C(C)CCC=C(C)CCC=C(C)C)C)C)C
	β-sitosterol	222284	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Kedrostis foetidissima (Jacq.) Cogn.	Quercetin-3-O-rhamnoside	5280459	CC1C(C(C(C(O1)OC2=C(OC3=CC(=CC(=C3C2=O)O)O)C4=CC(=C(C=C4)O)O)O)O)O
	7,10-Hexadecadienoicacid, methylester (CAS)	548878	CCCCCC=CCC=CCCCCCC(=O)OC
	Eicosanoic acid, methyl ester(CAS)	14259	CCCCCCCCCCCCCCCCCCCC(=O)OC
	Phytol Acetate	6428538	CC(C)CCCC(C)CCCC(C)CCCC(=CCOC(=O)C)C
	Curcurbitacin	181183	CC(=O)OC(C)(C)CCC(=O)C(C)(C1C(CC2(C1(CC(=O)C3(C2CC=C4C3CC(C(C4(C)C)O)O)C)C)C)O)O

	1H-Indole, 1-methyl- (CAS)	11781	CN1C=CC2=CC=CC=C21
	Rutin	5280805	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O
	Docosanoic acid	8215	CCCCCCCCCCCCCCCCCCCCCCC(=O)O
	9-Octadecenoic acid, methyl ester	5280590	CCCCCCCCC=CCCCCCCCC(=O)OC
	2-Hexadecen-1-ol, 3,7,11,15-tetramethyl- ,[R-[R*,R*-(E)]]-(CAS)	5366244	CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C
	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	6782	CC(C)COC(=O)C1=CC=CC=C1C(=O)OCC(C)C
	1H-1,2,4-Triazole-3,5-dicarbaldehyde	638657	C(=O)C1=NC(=NN1)C=O
	m-carboxyphenyl alanine	57370423	CC(C(=O)O)N(C1=CC=C(C=C1)C(=O)O)C(=O)OC(C)(C)C
	Citrulline	833	C(CC(C(=O)O)N)CNC(=O)N
Artemisia vulgaris L.	chavicol	68148	C=CCC1=CC=C(C=C1)O
	borneol	64685	CC1(C2CCC1(C(C2)O)C)C
	Osopulegol	24585	CC1CCC(C(C1)O)C(=C)C
	myrtenol	10582	CC1(C2CC=C(C1C2)CO)C
	Camphor	2537	CC1(C2CCC1(C(=O)C2)C)C
	p-Cymene	7463	CC1=CC=C(C=C1)C(C)C
	1,8-Cineole	2758	CC1(C2CCC(O1)(CC2)C)C
	α-Pinene	440968	CC1=CCC2CC1C2(C)C
	β-Caryophyllene	5281515	CC1=CCCC(=C)C2CC(C2CC1)(C)C
	(Z)-β-Farnesene	5317319	CC(=CCC/C(=C\CCC(=C)C=C)/C)C
	Trans-2-Hexenal	5281168	CCCC=CC=O
	β-Pinene	440967	CC1(C2CCC(=C)C1C2)C
	D-Limonene	440917	CC1=CCC(CC1)C(=C)C

Table 2: Potential protein targets of Phytoconstituents present in MKA

PHF	Botanicals	Protein targets
MKA	*Mimusops elengi* L.	SCD, FABP1, CACNA1S, FABP3, FABP2, SLC22A20P, FLT3, GLO1, PRKCH, F7, HSD11B2, OSBP, CYP17A1, CYP19A1, CYP51A1, AAAS, ESR2, NR1H2, RORC, PTPN1, SREBF2, SHBG, PTPN2, HSD11B1, HMGCR, AR, ALOX15B, CD81, CDC25B, PTPRC, ELANE, PPARA, PTGES2, HINT1, CCT7, SLCO1B1, SLCO1B3, SRC, CA2, CA4, CA6, CA1, NR6A1, RXRG, RARA, ADORA1, RXRA, ADORA2A, ADORA3, ADORA2B, VDR, STAT3, POLL, DUSP3, PTPN7, GLS, MRPL57, IL2, BCL2L1, UBE2N, ABCC4, AKR1B10, TOP2A, TOPBP1, CRHBP, CYP3A5, ALOX15, MAOA, ALOX5, AHR, ABCG2, AURKB, CA12, CA7, CISD1, CDK1, CDK5, CDK6, PTGS1, CYP1A1, CYP1B1, ELAVL3, EGFR, HSD17B2, MET, IGF1R, MMP12, NOX4, PI4KA, PIK3CG, PIM1, TTR, TYR, LCK, AXL, KDR, XDH, PRKCA, FNTA, FABP4, FABP5, SLC22A11, TLR2, DNM1, GPR84, FFAR1, FAAH, FFAR4, NR1I2, MAOB
	Kedrostis foetidissima (Jacq.) Cogn.	ITGAL, ARHGAP35, PRKD1, F10, SCD, F7, ATG4B, MAOB, FABP1, FABP3, FABP2, CA4, CA6, CA1, CA2, KIF23, NQO2, CDK4, DDC, CDK2, AAAS, ADK, HTR2A, HTR2C, HTR6, HSP90AA1, PTPN1, TRPV1 (VR1), FABP4, FABP5, AKR1B10, SLC22A11, TLR2, DUSP3, PTPN7, DNM1, GPR84, FFAR1, FNTA, ALOX5, GSK3B, CDC25A, OXER1, PTGS1, TECRL, CYP19A1, PLA2G15, FAAH, LTB4R, TOPBP1, SOAT1, FFAR4, PPARA, NR1I2, SLC6A4, CTSB, CTSK, DDAH1, NOS3, NOS1, NOS2, CYP3A5, ADORA3, ADRA2A, CA12, CA7, PDE6C, CHRM5, EGFR, IL2, ALPI, NOX4, AMY2A, RPS6KA3, TNF, HSD11B1, AKR1C1, CTRC, CYP17A1, ESR2, NR3C1, NR3C2, PLA2G2A, PGR, PTGES2, PRKCA, PRKCD, CDC42BPA, CDC42BPB, SHBG, PRSS1
	Artemisia vulgaris L.	NR1H3, NR1H2, PRKCB, PRKCA, G6PD, F12, SOAT1, MAOA, MAOB, TRPA1, CNR2, CNR1, FAAH, PTGS1, PPARA, SLCO1B1, ESRRG, TYR, TAAR1, AAAS, CYP19A1, HSD11B1, SQLE, GLI2, GLI1, CYP3A5, CYP2D6, CES2, CA2, CA1, CA4, CA6, GPBAR1, FASN, MBOAT4, TOP2A, PTPN1, PRKCE, ESR2, AR, RORA, NR5A1, SHBG, ALDH5A1, ABAT, MET, AKR1B10, TOPBP1, CDC25A, DUSP3

Table 3: Respiratory disease associated Protein targets

Botanicals	Ligand	Protein targets
Mimusops elengi L. (72)	Quercetin	→EGFR, →KDR, →MET, →CDK6, →LCK, →IGF1R, →CDK1, →AURKB, →TTR, →TYR, →CDK5, →PI4KA, →ABCG2, →CA4, →CYP1A1, →PIK3CG, →AXL, →ALOX5, →NOX4, →MAOA, →ALOX15, →ADORA3, →AKR1B10, → CYP19A1
	Quercitol	→SRC, →CA4
	β-sitosterol- β-D-glucoside	→STAT3, →BCL2L1, →UBE2N, →F7, →TOPBP1, →AKR1B10, →POLL, →TOP2A, →IL2, →ABCC4
	Ursolic acid	→AKR1B10, →PTPRC, →ELANE, →ALOX15, →HSD11B2, →HSD11B1, →CDC25B, →PRKCH, →PPARA, →F7
	Stearic acid 3-(octadecyloxy) propyl ester	→PRKCA
	Hexadecanoic acid, methyl ester	→TLR2, →FFAR1, →DNM1, →FABP4
	10-Octadecenoic acid, methyl ester	→TOPBP1, →CACNA1S, →SCD, →FFAR4, →FFAR1, →FABP4
	Spinasterol	→CYP17A1, →CYP19A1, →PTPN2, →SREBF2, →AAAS, →RORC
	β-carotene	→ADORA2B, →ADORA2A, →ADORA1, →ADORA3
	β-sitosterol	→CYP17A1, →CYP19A1, →PTPN2, →SREBF2, →RORC
Kedrostis foetidissima (Jacq.) Cogn. (78)	Quercetin-3-O-rhamnoside	→EGFR, →F10, →CHRM5, →TNF, →NOX4, →ADORA3, →RPS6KA3, →ADRA2A, →AKR1B10, →ALOX5, →CA4, →IL2
	7,10-Hexadecadienoicacid, methylester	→TOPBP1, →F7, →ATG4B, →FABP4, →SOAT1, →OXER1, →CYP19A1
	Eicosanoic acid, methyl ester(CAS)	→TLR2, →DNM1, →FFAR1, →AKR1B10, →FABP4
	Phytol acetate	→TRPV1 (VR1)
	Curcurbitacin	→PRKCA, →NR3C1, →CYP17A1, →HSD11B1, →CYP19A1, →PRKCD, →AKR1C1, →ITGAL →ARHGAP35, →F10, →PLA2G2A, →PRSS1
	1H-Indole, 1-methyl-(CAS)	→HSP90AA1, →AAAS, →HTR2C, →HTR2A, →HTR6, →DDC, →KIF23, →CA4
	Rutin	→IL2, →ADRA2A, →CA4, →ALOX5, →ADORA3, →AKR1B10, →CHRM5, →NOX4, →RPS6KA3, →F10, →TNF
	Docosanoic acid	→CDC25A, →FABP4, →AKR1B10, →TLR2, →DNM1, →FFAR1, →ALOX5
	9-Octadecenoic acid, methyl ester	→PPARA, →SCD, →FABP4, →FFAR4, →TOPBP1, →CYP19A1, →F7, →SOAT1, →ATG4B, →FFAR1
	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	→CTSK, →CTSB
	Citrulline	→NOS3, →NOS1, →NOS2
Artemisa vulgaris L. (35)	Chavicol	→TAAR1
	Borneol	→RORA, →HSD11B1, →AKR1B10
	Osopulegol	→PRKCB, →PRKCA, →PRKCE, →TOP2A
	Myrtenol	→TOPBP1, →CDC25A, →AKR1B10, →TOP2A
	Camphor	→F12, →G6PD, →CYP19A1, →SOAT1, →TRPA1, →CA4, →FASN
	p-Cymene	→TAAR1, →AAAS
	1,8-Cineole	→HSD11B1, →CYP19A1
	α-Pinene	→PPARA, →CNR1, →CNR2
	β-Caryophyllene	→CNR1, →CNR2, →PPARA
	(Z)-β-Farnesene	→MAOA
	Trans-2-hexenal	→TRPA1
	D-Limonene	→TRPA1, →PPARA, →CNR1, →CNR2

[Red arrow (→) indicates the ligands inhibitory action. Green arrow (→) indicates the activator action of the ligand and Black arrow (→) indicates the unknown modulation]

Search for Potential protein targets

Protein targets for each phytoconstituent present in the herbal formulation MKA was identified from Binding database and presented in Table 2. In MKA, 110 protein targets were found for *Mimusops elengi* L., 91 targets for *Kedrostis foetidissima* (Jacq.) Cogn. and 50 protein targets for *Artemisia vulgaris* L. The combinatorial action of these multiple ligands is the key factor enhancing the activity of Polyherbal formulation MKA.

Disease associated target identification in Open target platform

Respiratory disease associated protein targets of MKA were identified from Open target Platform and illustrated in Table 3. In MKA, 72/110

protein targets of *Mimusops elengi* L., 78/91 targets of *Kedrostis foetidissima* (Jacq.) Cogn. and 35/50 protein targets of *Artemisia vulgaris* L. were found to be the respiratory disease associated therapeutic targets. In Table 3, Red colored arrow (→) indicates the ligands inhibitory action, Green arrow (→) indicates the activator action of the ligand and Black arrow (→) indicates the unknown modulation].

Ligand-target interactions in respiratory disease

In MKA, β-sitosterol- β-D-glucoside has inhibitory action on Signal tranducer and activator of transcription 3 (STAT3). STAT-3 inhibitors were found to reduce the production of cytokines responsible for lung inflammation [20]. EGFR signalling pathway inhibitors reduces the pathogenesis of Chronic lung disease [21]. Quercetin and Quercetin-3-O-rhamnoside acts as inhibitor of Epidermal Growth factor receptor (EGFR), which confirms its therapeutic potential in treating respiratory disease. There is dramatic increase in level of TRPV1 (VR1) and TRPA1 in airway cell in respiratory virus infection [22]. Phytol acetate has inhibitory action on TRPV1, which validates its therapeutic activity in treating respiratory virus infection. Camphor, Trans-2-hexenal and D-Limonene acts as inhibitor of TRPA1 validating its potential in acting against respiratory viral infection.

Carbonic anhydrase inhibitors functions as respiratory stimulant in patients with Chronic Obstructive Pulmonary disease (COPD) [23]. Quercetin, Quercitol, Quercetin-3-O-rhamnoside, 1H- Indole, 1-methyl- (CAS), rutin and camphor has inhibitory action on carbonic anhydrase. PPARA agonists has anti-inflammatory property and inhibits the formation of lung fibrosis [24]. Ursolic acid, 9-Octadecenoic acid, methyl ester, α-Pinene, β-Caryophyllene and D-Limonene functions as activator of PPARA, which further proves the efficacy of MKA in alleviating the respiratory disease. Inhibition of KDR reduces the pathogenesis of lung cancer [25]. Quercetin has inhibitory action on KDR. The β-sitosterol-β-D-glucoside acts as inhibitor of STAT-3. Inhibition of SteroylCoA desaturase 1 (SCD1) induces apoptosis of lung cancer cells and reduce the pathogenesis of the disease [26]. 9-Octadecenoic acid, methyl ester and 10-Octadecenoic acid, methyl ester in MKA has inhibitory action on SCD1. The multi-targeted action of MKA is responsible for enhanced therapeutic property in fighting respiratory disease.

Construction of Protein-protein network

Multi-target interactions of MKA were illustrated in terms of PPI network in Figure 1.

The MKA network has 98 different protein targets interacting differently to produce therapeutic benefit in treating respiratory disease. In MKA network, 98 protein targets interact in different manner to produce the combined pharmacological effect. There are 460 metabolic interactions in MKA network. The KEGG pathway based functional enrichment analysis of MKA network was studied. The top 20 pathways involved in molecular mechanism of MKA is given in the Table 4.

This research proves the combinatorial action of multiple bioactive compounds present in herbal formulation MKA against respiratory disease. The molecular mechanism underlying the action of MKA herbal formulation was studied in terms of ligand-protein interaction and multi-target interactions.

Table 4: KEGG Pathway Functional Enrichment analysis

S. No	Pathway	Description	Count in Network	Strength	P-value
1	hsa00220	Arginine biosynthesis	3 of 20	1.48	0.00096
2	hsa00360	Phenylalanine metabolism	2 of 17	1.37	0.0095
3	hsa04750	Inflammatory mediator regulation of TRP channels	10 of 92	1.34	1.00E-08
4	hsa05223	Non-small cell lung cancer	6 of 66	1.26	1.74E-05
5	hsa04370	VEGF signaling pathway	5 of 59	1.23	0.00012
6	hsa00330	Arginine and proline metabolism	4 of 48	1.22	0.00071
7	hsa04540	Gap junction	7 of 87	1.21	7.88E-06
8	hsa00380	Tryptophan metabolism	3 of 40	1.18	0.004
9	hsa04066	HIF-1 signaling pathway	7 of 98	1.15	1.28E-05
10	hsa04659	Th17 cell differentiation	7 of 102	1.14	1.44E-05
11	hsa00591	Linoleic acid metabolism	2 of 29	1.14	0.0205
12	hsa04020	Calcium signaling pathway	12 of 179	1.13	1.51E-08
13	hsa04270	Vascular smooth muscle contraction	8 of 119	1.13	4.95E-06
14	hsa04710	Circadian rhythm	2 of 30	1.12	0.0215
15	hsa05222	Small cell lung cancer	5 of 92	1.04	0.00069
16	hsa00590	Arachidonic acid metabolism	3 of 61	0.99	0.0095
17	hsa04926	Relaxin signaling pathway	6 of 130	0.96	0.00038
18	hsa04064	NF-kappa B signaling pathway	4 of 93	0.93	0.0043
19	hsa03320	PPAR signaling pathway	3 of 72	0.92	0.0132
20	hsa04620	Toll-like receptor signaling pathway	3 of 102	0.77	0.0272

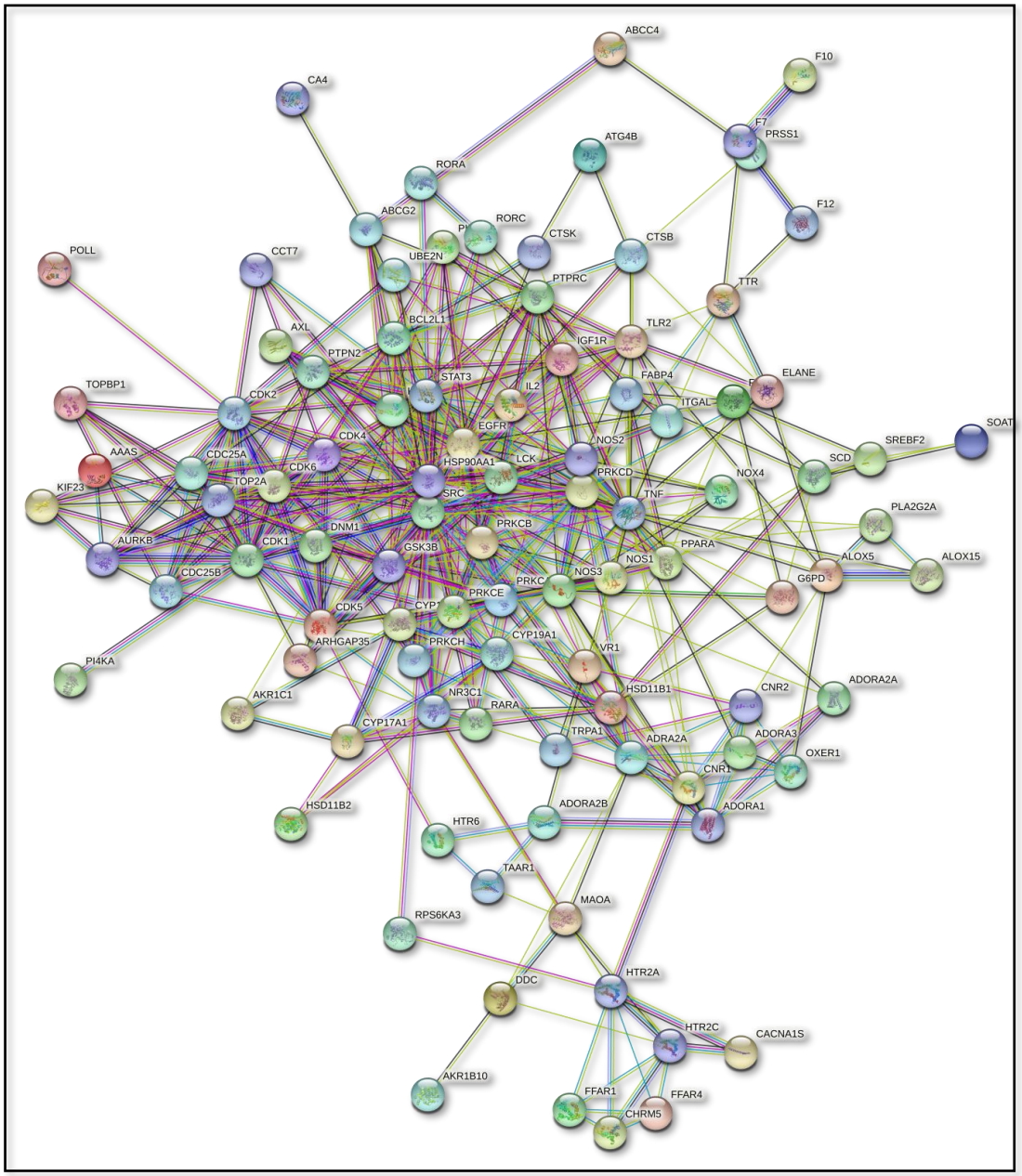

Figure 1: Protein-Protein Interaction network of MKA in respiratory diseases: The MKA network has average node degree of 9.39 and average local clustering coefficient of 0.579. There are 98 nodes and 460 edges. PPI enrichment p-value is less than 1.0e-16

CONCLUSION

To conclude, bioactives in herbal formulation MKA, exert their therapeutic effects against respiratory disease by multiple mechanisms like STAT-3 inhibition by β-sitosterol-β-D-glucoside, EGFR inhibition by Quercetin and Quercetin-3-O-rhamnoside, TRPA1 inhibition by D-Limonene, etc. The therapeutic benefit of MKA in treating respiratory disease is validated by its multi-targeted actions like inhibition of carbonic anhydrase by Quercetin, Quercitol, Quercetin-3-O-rhamnoside, 1H- Indole, 1- methyl- (CAS), rutin and camphor. It was evident that 98 protein targets interact differently in Protein-protein interaction network of MKA polyherbal formulation. The key target proteins were found to be EGFR, KDR, CA4, STAT-3, TRPA1, TRPV1 (VR1), PPARA and SCD1.

Thus, the network pharmacological approach was used to interpret the biological action of Polyherbal formulation MKA against respiratory diseases.

Conflict of interest

Authors declare no conflict of interests.

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None.

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