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APPENDIX I (SUPPLEMENTARY INFORMATION)

Table S1 Changes in body weight in control and test animals on day 14 (Acute toxicity study)

Groups	Weight gain (in gm)	% Weight gain
Control	4.76 ± 2.60	3.32 ± 2.09
Test	6.22 ± 1.74	4.30 ± 1.36

Table S2 Relative organ weight after day 14 (Acute toxicity study)

ROW (%)	Liver	Heart	Kidney	Spleen	Stomach	Pancreas	Lung	Ovary
Control	3.37 ± 0.11	0.36 ± 0.01	0.81 ± 0.04	0.20 ± 0.01	0.89 ± 0.04	0.16 ± 0.01	0.57 ± 0.01	0.29 ± 0.01
Test	3.37 ± 0.16	0.37 ± 0.06	0.83 ± 0.06	0.22 ± 0.02	0.90 ± 0.05	0.17 ± 0.01	0.59 ± 0.04	0.30 ± 0.02

Table S3 Effect of single dose extract (5000 mg/kg) on biochemical parameters (Acute toxicity study)

Biochemical Parameters	Control	Test
Total protein (g/L)	55 ± 1.58	61.2 ± 2.28
Albumin (g/L)	37.2 ± 1.79	40.6 ± 2.70
Globulin (g/L)	14.8 ± 1.34	20 ± 1.887
Alkaline phosphatase (ALP) (U/L)	162.8 ± 4.83	173.4 ± 23.5
Aspartate aminotransferase (AST) (U/L)	127 ± 1.58	136 ± 5.66
Alanine aminotransferase (ALT) (U/L)	76.6 ± 2.3	79.8 ± 4.76
Total cholesterol (mg/dL)	65.3 ± 0.55	64.7 ± 0.75
Triglycerides (mg/dL)	36.6 ± 1.11	37.6 ± 0.79
Creatinine (mg/dL)	0.57 ± 0.08	0.57 ± 0.05
Uric acid (mg/dL)	2.87 ± 0.35	2.99 ± 0.75
Urea (mg/dL)	35.51 ± 2.50	33.35 ± 4.66

Table S4 Relative organ weight (%) of female rats on 28th day (except for satellite group on 42nd day) of repeated 28 day oral toxicity study

Group	Liver	Heart	Kidney	Spleen	Stomach	Pancreas	Lung	Ovary
Control	3.47 ± 0.10	0.39 ± 0.01	0.87 ± 0.05	0.22 ± 0.01	0.92 ± 0.06	0.17 ± 0.01	0.58 ± 0.01	0.31 ± 0.01
NH500	3.52 ± 0.06	0.38 ± 0.01	0.86 ± 0.05	0.20 ± 0.03	0.92 ± 0.05	0.17 ± 0.01	0.60 ± 0.01	0.31 ± 0.01
NH1000	3.50 ± 0.08	0.39 ± 0.01	0.85 ± 0.04	0.21 ± 0.01	0.93 ± 0.03	0.17 ± 0.01	0.59 ± 0.01	0.31 ± 0.01
NH2000	3.44 ± 0.14	0.37 ± 0.01	0.80 ± 0.04	0.22 ± 0.01	0.92 ± 0.05	0.16 ± 0.01	0.60 ± 0.02	0.30 ± 0.01
Satellite	3.33 ± 0.10	0.38 ± 0.03	0.85 ± 0.01	0.22 ± 0.01	0.89 ± 0.02	0.16 ± 0.01	0.56 ± 0.04	0.30 ± 0.01

Table S5 Relative organ weight (%) of male rats on 28th day (except for satellite group on 42nd day) of repeated 28 day oral toxicity study

Group	Liver	Heart	Kidney	Spleen	Stomach	Pancreas	Lung	Testis
Control	3.52 ± 0.12	0.39 ± 0.01	0.85 ± 0.02	0.22 ± 0.01	0.95 ± 0.03	0.17 ± 0.01	0.59 ± 0.01	1.32 ± 0.07
NH500	3.53 ±0.09	0.38 ± 0.01	0.85 ± 0.03	0.21 ± 0.01	0.96 ± 0.09	0.17 ± 0.01	0.58 ± 0.01	1.31 ± 0.09
NH1000	3.53 ± 0.09	0.38 ± 0.01	0.84 ± 0.03	0.21 ± 0.01	0.93 ± 0.05	0.17 ± 0.01	0.58 ± 0.02	1.23 ± 0.25
NH2000	3.51 ± 0.01	0.39 ± 0.02	0.83 ± 0.07	0.22 ± 0.01	0.92 ± 0.03	0.16 ± 0.01	0.57 ± 0.05	1.30 ± 0.14
Satellite	3.50 ± 0.28	0.38 ± 0.02	0.82 ± 0.05	0.21 ± 0.02	0.93 ± 0.08	0.16 ± 0.02	0.56 ± 0.11	1.28 ± 0.01

Table S6 Changes in biochemical parameters in female rats on day 28 (except for satellite group on day 42). All values are Mean ± SD (n = 5). *P <0.05, **P <0.01, ***P <0.001 compared to Control [One-way ANOVA; Dunnet's multiple comparison test]

Biochemical parameters	Control	NH500	NH1000	NH2000	Satellite
Total protein (g/L)	55.6 ± 2.40	56 ± 1.58	57.2 ± 1.49	61 ± 1.00**	56 ± 1.41
Albumin (g/L)	35.6 ± 2.40	36.2 ± 1.64	38.6 ± 1.95	38.9 ± 3.00	37 ± 1.41
Globulin (g/L)	15.8 ± 1.10	16 ± 1.58	19.4 ± 1.14**	22.3 ± 2.52***	18 ± 1.00
Alkaline phosphatase (ALP) (U/L)	130.4 ± 3.94	128.4 ± 7.54	130 ± 3.39	142.7 ± 2.31*	128.5 ± 2.12
Aspartate aminotransferase (AST) (U/L)	120.4 ± 5.03	125 ± 4.90	126.6 ± 3.78*	143.7 ± 3.21***	126 ± 1.41
Alanine aminotransferase (ALT) (U/L)	57.4 ± 5.03	58.2 ± 2.59	60.8 ± 2.77	68.7 ± 2.08**	59 ± 1.41
Total cholesterol (mg/dL)	62.3 ± 4.51	65.4 ± 2.70	63.3 ± 3.40	62.0 ± 5.55	63.4 ± 3.23
Triglycerides (mg/dL)	39.4 ± 2.71	37.7 ± 4.72	36.3 ± 4.57	40.4 ± 2.34	39.9 ± 2.81
Creatinine (mg/dL)	0.55 ± 0.07	0.57 ± 0.99	0.50 ± 0.85	0.56 ± 0.59	0.53 ± 0.38
Uric acid (mg/dL)	2.70 ± 0.30	2.80 ± 0.77	2.65 ± 0.39	2.73 ± 0.80	2.65 ± 0.38
Urea (mg/dL)	34.50 ± 4.91	33.77 ± 2.44	34.88 ± 3.56	30.50 ± 6.91	39.54 ± 2.50

Table S7 Changes in biochemical parameters in male rats on day 28 (except for satellite group on day 42). All values are Mean ± SD (n = 5). *P <0.05, **P <0.01, ***P <0.001 compared to Control [One-way ANOVA; Dunnet's multiple comparison test]

Biochemical parameters	**Control**	**NH500**	**NH1000**	**NH2000**	**Satellite**
Total protein (g/L)	53 ± 2.12	55 ± 1.58	55.8 ± 2.05	59 ± 2.65**	53.5 ± 0.71
Albumin (g/L)	36.6 ± 1.14	36.4 ±2.19	35.6 ±3.05	38.3 ± 1.53	33.5 ± 0.71
Globulin (g/L)	18 ± 2.12	17 ± 1.58	16.6 ± 2.07	21.7 ± 2.31	14 ± 1.41
Alkaline phosphatase (ALP) (U/L)	150.6 ± 8.59	150.6 ± 4.62	148.6 ± 1.82	171.3 ± 2.31***	148 ± 2.83
Aspartate aminotransferase (AST) (U/L)	120.8 ± 7.29	120.6 ± 3.05	123.2 ± 2.49	131.3 ± 1.53*	125 ± 2.83
Alanine aminotransferase (ALT) (U/L)	71.8 ± 6.30	71.6 ± 2.88	72 ± 5.00	85.3 ± 2.52**	65.5 ± 3.54
Total cholesterol (mg/dL)	65.5 ± 5.53	67.4 ± 1.75	63.3 ± 5.45	69.2 ± 5.25	66.4 ± 3.01
Triglycerides (mg/dL)	42.4 ± 3.33	39.0 ± 6.55	42.3 ± 3.58	39.9 ± 4.35	38.2 ± 5.85
Creatinine (mg/dL)	0.59 ± 0.03	0.57 ± 0.45	0.55 ± 0.35	0.56 ± 0.31	0.60 ± 0.18
Uric acid (mg/dL)	2.98 ± 0.20	2.85± 0.74	2.75 ± 0.69	2.88 ± 0.50	2.69 ± 0.39
Urea (mg/dL)	35.56 ± 2.91	34.12 ± 2.55	36.78 ± 3.50	33.50 ± 2.91	36.54 ± 2.66

Table S8 List of compounds obtained from LC-MS analysis of the aqueous extract of *Natsiatum herpeticum*

Compound Abbreviation	Compound Name
HPA	2-hydroxynonanoic acid
HME	(E)-N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methylnon-6-enamide
MLC	(3E)-5-[(4-hydroxyphenyl)methyl]-3-[(2E,4E,6E,8R,10R)-1-hydroxy-6,8,10-trimethyldodeca-2,4,6-trienylidene]pyrrolidine-2,4-dione
MOA	3-methyl-octanoic acid
COG	5-hydroxy-2-(4-hydroxyphenyl)-7-[(2S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-6-[(2S,4S,5R)-3,4,5-trihydroxyoxan-2-yl]chromen-4-one
AZA	nonanedioic acid
HTN	1-O-[(2S,3S,6R)-4-methoxy-16,18-dioxa-10-azapentacyclo[11.7.0.02,6.06,10.015,19]icosa-1(20),4,13,15(19)-tetraen-3-yl] 4-O-methyl (2R)-2-hydroxy-2-(3-hydroxy-3-methylbutyl)butanedioate
MAA	(2S)-N-[(4S,4aS,6R,8S,8aR)-6-[(2S)-2,3-dihydroxypropyl]-8-methoxy-7,7-dimethyl-4a,6,8,8a-tetrahydro-4H-pyrano[3,2-d][1,3]dioxin-4-yl]-2-hydroxy-2-[(2R,5R,6R)-2-methoxy-5,6-dimethyl-4-methylideneoxan-2-yl]acetamide
LMS	[(1S,4aR,5R,7S,7aS)-4a,5-dihydroxy-4,7-dimethyl-1-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-1,5,6,7a-tetrahydrocyclopenta[c]pyran-7-yl] acetate
NMC	(3R,5R,6S,7S,9R,11E,13R,14R)-6-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11-ene-2,4,10-trione
MMA	(2E,4E,6R)-N-[(1S,5S,6R)-5-hydroxy-5-[(1E,3E,5E)-7-[(2-hydroxy-5-oxocyclopenten-1-yl)amino]-7-oxohepta-1,3,5-trienyl]-2-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]-2,4,6-trimethyldeca-2,4-dienamide
SPA	[(3S,4S,5R,6S)-5-acetyloxy-6-[[(8R,9R,10S,13R,14S,16R,17R)-17-[(E,2R)-2,6-dihydroxy-6-methyl-3-oxohept-4-en-2-yl]-2-hydroxy-4,4,9,13,14-pentamethyl-3-oxo-7,8,10,11,12,15,16,17-octahydrocyclopenta[a]phenanthren-16-yl]oxy]-4-hydroxyoxan-3-yl] acetate
PPD	(2S,3R,5R,9R,10R,13R,14S,17R)-2,3,14-trihydroxy-17-[(3R,5S)-3-hydroxy-5,6-dimethylhept-1-en-2-yl]-10,13-dimethyl-2,3,4,5,9,11,12,15,16,17-decahydro-1H-cyclopenta[a]phenanthren-6-one
HHA	16-hydroxyhexadecanoic acid

KKD	[(1S,4aS,6S,7R,7aS)-6-hydroxy-7-(hydroxymethyl)-4-[[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]oxan-2-yl]oxymethyl]-1,4a,5,6,7,7a-hexahydrocyclopenta[c]pyran-1-yl] 3-methylbutanoat
FLC	(E)-1-(5-hydroxy-2,2,8,8-tetramethylpyrano[2,3-f]chromen-6-yl)-3-phenylprop-2-en-1-one
APP	methyl (1R,15S,17R,18R,19S,20S)-6,18-dimethoxy-17-(3,4,5-trimethoxybenzoyl)oxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate
KLD	(6S)-6-hydroxy-3-[(1E,3E,5E,7E,9E,11E,13E,15E,17E)-18-[(1S,4S)-4-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-2,4,4-trimethylcyclohex-2-en-1-one
STG	[2,4-diphenyl-3-[5-[(2R)-piperidin-2-yl]-3,4-dihydro-2H-pyridine-1-carbonyl]cyclobutyl]-[5-[(2R)-piperidin-2-yl]-3,4-dihydro-2H-pyridin-1-yl]methanone
AXT	(1R)-4-[(3E,5E,7E,9E,11E,13E,15E)-18-[(4R)-4-hydroxy-2,6,6-trimethylcyclohexen-1-yl]-3,7,12,16-tetramethyloctadeca-3,5,7,9,11,13,15-heptaen-1,17-diynyl]-3,5,5-trimethylcyclohex-3-en-1-ol
DPA	[(E,6R)-6-[(3S,8S,9R,10R,13R,14S,16R,17R)-3,16-dihydroxy-9-(hydroxymethyl)-4,4,13,14-tetramethyl-11-oxo-1,2,3,7,8,10,12,15,16,17-decahydrocyclopenta[a]phenanthren-17-yl]-6-hydroxy-2-methyl-5-oxohept-3-en-2-yl] acetate

Table S9 Predicted targets for representative compounds (probability score = 0.1-1.0)

HPA	HME	MOA	AZA	HTN	NMC	PPD	HHA	FLC	DPA
FABP3	PTGS1	FABP4	FABP4	ADCY1	FLT3	HSD11B1	FFAR1	ODC1	ITGAL
PPARD	CYP1A2	FABP3	FABP3	KCNJ1	CDK2 CCNA1 CCNA2	FNTA FNTB	PPARA	MAPK APK2	STAT3
FABP2	TRPV1	HSD11B1	FABP5	PDE9A	JAK3	NPC1L1	PPARD	PRKCD	
AR	CNR1	PPARD	PPARD	PDE1C	JAK1	NR3C1	HSD11B1	MAPK APK5	
VDR	CNR2	FABP5	FFAR1	REN	JAK2	CYP19A1	FABP4	NOS2	
NR1H4	BCHE	SLC22A6	FABP2	MMP1	TYK2	AR	CDC25A		
G6PD	ACHE	PPARA	PPARA	MTOR	BACE1	TNF	FABP3		
GPBAR1	SIGMAR1	AKR1B10	HSD11B1	PIK3CA	EGFR	BACE1	FABP5		
AKR1B10	FAAH	VDR	AR	BACE1	CCR2	CDC25A	FABP2		
FFAR1	PTPN1	NR1H4	VDR	HTR1B	BRD4	MAPK3	NR1H4		
HSD11B2	DRD2	POLB	NR1H4	HTR1D	ATAD2	PRKCH	SLC22A6		
HAO1	RAF1	CDC25A	POLB	SLC6A4	GHSR	NOS2	GPBAR1		
KDM2A	BRAF	GPBAR1	CDC25A	BACE2	LAP3	PTPN1	VDR		
PHF8	SCD	FFAR1	GPBAR1	CSF1R	KCNH2	NR3C2	AR		
UGT2B7	CDK5R1 CDK5	FABP2	SLC22A6	FLT3	SYK	ADORA3	UGT2B7		
SERPINA6	DYRK1A		UGT2B7	JAK3	REN	SIGMAR1	AKR1B10		

SHBG	CHRM4		CYP19A1	JAK1	XIAP	CES2	PTGER2		
HSD17B3	HDAC6		SERPINA6	JAK2	SLC6A4	SLC6A3	SERPINA6		
HSD11B1	HDAC1		SHBG	CDK2	BIRC2	HSD11B2	SHBG		
PPARA	SLC6A11		HSD17B3	CDK9	BACE2	SHBG	HSD17B3		
PTGFR	SLC6A13		G6PD	TYK2	GNRHR	PTGES	G6PD		
FABP4	SREBF2		GABBR1	TRPV3	MCHR1	SRD5A2	GABBR1		
FABP5	NOX4		KDM2A	PLK4	FYN	PGR	POLB		
NPC1L1	NOX1		KDM5C	CTSD	MC5R	SLC6A4	CYP19A1		
GABRA2 GABRB2 GABRG2	MMP16			MCHR1	MC3R	NR1H3	NPC1L1		
BACE1	LIPG			ACHE	IMPDH2	SERPINA6	GABRA2 GABRB2 GABRG2		
CHRNA7	ERBB2			PDE4B	ADRB3	BCHE	PTGFR		
CDC25A	FGFR1			XIAP	OPRD1	ESR1	KDM2A		
CA2	TLR9			BIRC2	INSR	ESR2	HAO1		
CA1	FLT3			CCR1	MAPKAPK 2	AKR1B10	KDM5C		
SLC22A6	MPEG1			MDM2	PRCP	PTPN11	PHF8		
HSPA1A	CHEK1			PIK3CD	TACR1	PTGS2	FNTA FNTB		
FBP1	RELA			PIK3CB	CDK2	ITGAL	HSD11B2		

PLG	PTGDR			PIK3CG	ALK	HTR1A	GSTK1		
POLB	GRIN1 GRIN2B			EGFR	PDE8B	CCR1	CDC45		
AKR1C2	CDC25A			PIM3	P2RX7	MAPK14	CA2		
AKR1C1	VCP			EHMT2	CRHR1	SHH	PTPN1		
CPA1	HSP90AA1			HRH3	ADRB2	IDO1	CA1		
TTR	BMP1			PRKCA	ADRB1	MET	LTA4H		
AKR1C3	STK17B			PRKCQ	MLX	PIK3CA	PTGER4		
COMT	STAT3			CHEK1	KIF11	PTPN2	CACNA2D1		
CSNK2A1	MAPK1			ADRA2C	MAPK14	MAP2	PLA2G4A		
HCAR2	CHRM2			GABRA5	CTSK	SMO	SELL		
CTNNB1	HIF1A			IRAK4	CCR3	PDGFRB	SELE		
SLC22A12	MDH2			PDE8B	HSP90AB1	KIT	SELP		
CDC45	PLAA			DRD2	CFD	KDR	CHRNA7		
CYP19A1	MELK			HTR2A	PDE4B	CDK2 CCNA1 CCNA2	PLG		
FDFT1	HDAC3			CNR2	DPP4	MTOR	PTGER3		
	HDAC8			ABL1	DPP8	RORA	RARG		
	ALK			KIT	RET	MME	RARB		
	CDC7			YES1	PIM1	SORD	PTGDR		

	MIF			LCK	PRKDC	ALK	TBXA2R		
	WEE1			CSK	PIK3CG	MDM2	SAE1 UBA2		
	AKR1B10			SRC	F2R	ALOX5	GRM5		
	CDK4			SSTR5	PIM2	PPARG	RARA		
	CHRM1			HTR2B	PIM3	CHRM1	THRA		
	CHRM3			HRH1	ABL1	SLC10A2	THRB		
	ROCK2			P2RX3	FLT1	PDE10A			
	DRD3			PLAT	CTSD	CDK1			
	ADORA1			F2	FGFR1	SLC22A6			
	ITK			F10	MKNK2	ABL1			
	GRK6			NOX4	MKNK1	CFD			
	SQLE			PRKDC		PYGL			
	HDAC7			ESR1		GYS1			
	ODC1			ESR2		POLB			
	ADORA2A			AKT2		FGFR1			
	AR			GSK3B		CHEK1			
	MAPKAPK 2			MAP3K12		CYP17A1			
	GSK3A			OPRM1		S1PR2			
	CDK2			OPRD1		ITK			

	EGLN1			ERBB2		DRD2			
	ROCK2 ROCK1			RET		CETP			
	PIK3CG			ATAD2		CTSL			
	CYP11B1			SYK		CTSB			
	ADORA2B			MST1R		IGF1R			
	CYP11B2			ERBB4		CDK2			
	MTOR			AURKB		AURKA			
	PIK3CA			KDR		CASP3			
	PRF1			CCR3		KCNH2			
	NEK1			CCKBR		SYK			
	EPHX2			AKT3		CASP7			
	MYLK			ADRB2		HCRTR2			
	PIM2			ADRB1		HCRTR1			
	MARK1			ADRB3		ALPL			
	ALPL			PARP1		CCNB3 CDK1 CCNB1 CCNB2			
	RET			HTR2C		MAPK8			
	ESR1			ABCC1		MAPK10			
	ESR2			PRKCB		S1PR3			

	SLC6A4			MKNK2		MAPK9			
	ABL1			MKNK1		S1PR1			
	PTK6			CHRM2		GABRA5			
	PFKFB3			CHRM3		JAK3			
	HRH4			LAP3		CHEK2			
	ADAMTS5			XPNPEP2		JAK1			
	DRD4			DOT1L		P2RX3			
	PDGFRB			HTR4		AGTR1			
	FASN			ADRA1D		BRD4			
	ALOX5AP			ADRA1A		BRD2			
	ABCG2			ADRA1B		BRD3			
	STAT6			HTR3A		EGFR			

Table S10 List of overlapping genes retrieved from GeneCard and DisGeNET database

Sl. No.	Gene	UniProt	Gene Full Name
1.	TBCE	Q15813	Tubulin folding co-factor E
2.	SDC4	P31431	Syndecan 4
3.	NOD1	Q9Y239	Nucleotide binding oligomerization domain containing 1
4.	TLR4	O00206	Toll like receptor 4
5.	TLR2	O60603	Toll like receptor 2
6.	NOD2	Q9HC29	Nucleotide binding oligomerization domain containing 2
7.	IRAK4	Q9NWZ3	Interleukin 1 receptor associated kinase 4
8.	MYD88	Q99836	MYD88 innate immune signal transduction adaptor
9.	MBL2	P11226	Mannose binding lectin 2
10.	IL6	P05231	Interleukin 6
11.	IL1B	P01584	Interleukin 1 beta
12.	IFNG	P01579	Interferon gamma
13.	CRP	P02741	C-reactive protein
14.	CFTR	P13569	CF transmembrane conductance regulator
15.	TNF	P01375	Tumor necrosis factor

Table S11 Node centrality measure of the disease-target network calculated using cytoHubba

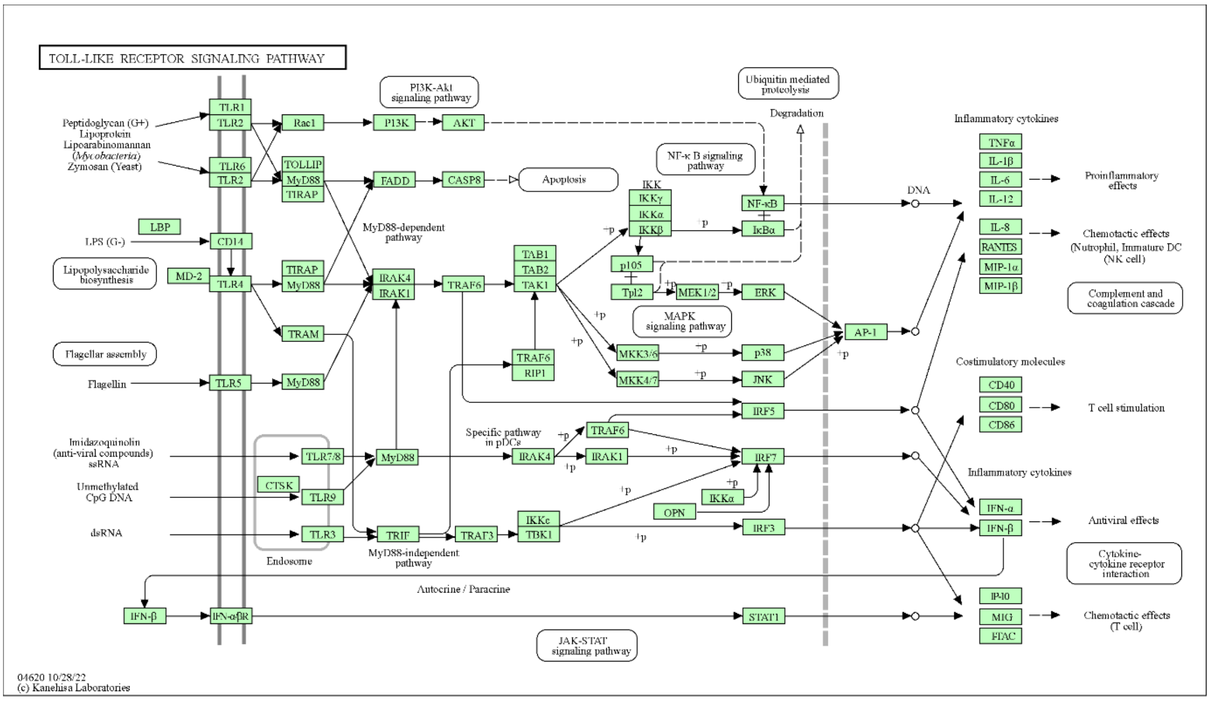
Node	Degree	Closeness	Radiality	Betweenness	Clustering Coefficient
NOD1	9	11	1.92308	0.25000	0.97222
TLR2	11	12	2.07692	2.02381	0.87273
MYD88	10	11.5	2.00000	0.78571	0.93333
IRAK4	8	10.5	1.84615	0.00000	1.00000
NOD2	11	12	2.07692	2.02381	0.87273
IFNG	9	11	1.92308	0.25000	0.97222
CRP	9	11	1.92308	0.57143	0.94444
TNF	12	12.5	2.15385	5.22381	0.78788
TLR4	12	12.5	2.15385	5.22381	0.78788
MBL2	8	10.5	1.84615	1.20000	0.89286
IL1B	13	13	2.23077	29.22381	0.66667
SDC4	1	7	1.30769	0.00000	0.00000
IL6	12	12.5	2.15385	5.22381	0.78788
CFTR	5	9	1.61538	0.00000	1.00000

Table S12 Rank of nodes in the PPI network based on various node centrality metrics

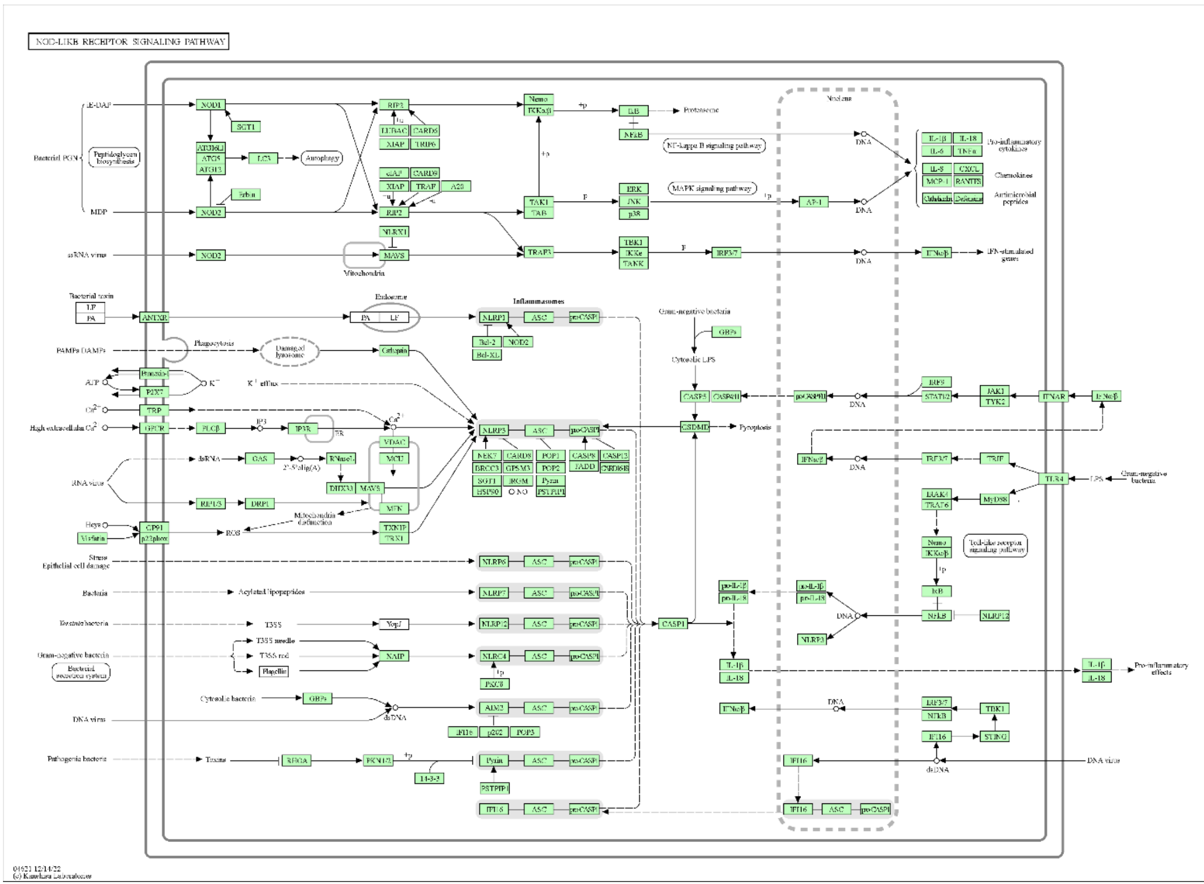
Rank	Node Centrality										
	Betweenness	**Bottleneck**	**Closeness**	**Clustering Coefficient**	**Degree**	**DMNC**	**Eccentricity**	**EPC**	**MCC**	**Radiality**	**Stress**
1	IL1B	IL1B	IL1B	IRAK4	IL1B	MYD88	IL1B	TNF	IL1B	IL1B	IL1B
2	TLR4	TNF	TLR4	CFTR	TLR4	NOD1	SDC4	TLR4	TLR4	TLR4	TLR4
3	IL6	SDC4	IL6	NOD1	IL6	IFNG	NOD1	IL1B	IL6	IL6	IL6
4	TNF	NOD1	TNF	IFNG	TNF	IRAK4	NOD2	TLR2	TNF	TNF	TNF
5	NOD2	NOD2	NOD2	CRP	NOD2	NOD2	MYD88	IL6	NOD2	NOD2	NOD2
6	TLR2	MYD88	TLR2	MYD88	TLR2	TLR2	TLR2	NOD2	TLR2	TLR2	TLR2
7	MBL2	TLR2	MYD88	MBL2	MYD88	CRP	MBL2	MYD88	MYD88	MYD88	MYD88
8	MYD88	MBL2	NOD1	NOD2	NOD1	IL1B	IRAK4	CRP	NOD1	NOD1	MBL2
9	CRP	IRAK4	CRP	TLR2	CRP	TLR4	TLR4	IFNG	IFNG	CRP	CRP
10	NOD1	TLR4	IFNG	TLR4	IFNG	IL6	CFTR	NOD1	CRP	IFNG	NOD1
11	IFNG	CFTR	MBL2	IL6	MBL2	TNF	IL6	MBL2	IRAK4	MBL2	IFNG
12	SDC4	IL6	IRAK4	TNF	IRAK4	MBL2	TNF	IRAK4	MBL2	IRAK4	SDC4
13	IRAK4	CRP	CFTR	IL1B	CFTR	CFTR	CRP	CFTR	CFTR	CFTR	IRAK4
14	CFTR	IFNG	SDC4	SDC4	SDC4	SDC4	IFNG	SDC4	SDC4	SDC4	CFTR

Table S13 STRING identified KEGG pathways for TNF and IRAK4

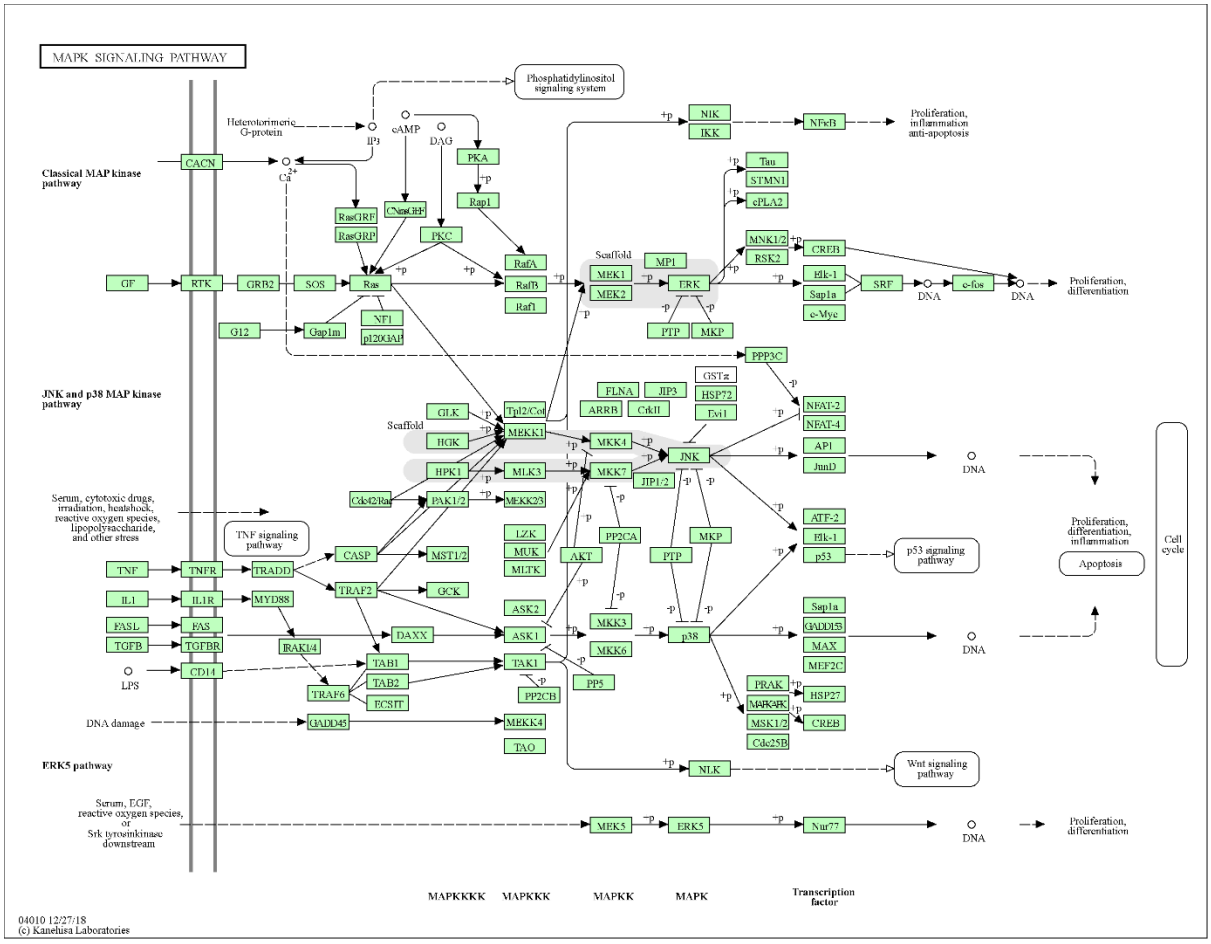
Term ID	Term description
hsa05140	Leishmaniasis
hsa05133	Pertussis
hsa05142	Chagas disease
hsa04064	NF-kappa B signaling pathway
hsa04620	Toll-like receptor signaling pathway
hsa05145	Toxoplasmosis
hsa05135	Yersinia infection
hsa05161	Hepatitis B
hsa05152	Tuberculosis
hsa05164	Influenza A
hsa04621	NOD-like receptor signaling pathway
hsa05130	Pathogenic Escherichia coli infection
hsa05169	Epstein-Barr virus infection
hsa05170	Human immunodeficiency virus 1 infection
hsa05132	Salmonella infection
hsa04010	MAPK signaling pathway
hsa05168	Herpes simplex virus 1 infection


TOLL-LIKE RECEPTOR SIGNALING PATHWAY
Peptidoglycan (G+)
Lipoprotein
Lipoarabinomannan
(Mycobacteria)
Zymosan (Yeast)
TLR1
TLR2
TLR6
TLR2
Rac1
PI3K
AKT
PI3K-Akt signaling pathway
TOLLIP
MyD88
TIRAP
FADD
CASP8
Apoptosis
Ubiquitin mediated proteolysis
Degradation
NF-κ B signaling pathway
IKK
IKKγ
IKKα
IKKβ
NF-κB
IκBα
DNA
LBP
LPS (G-)
CD14
Lipopolysaccharide biosynthesis
MD-2
TLR4
TIRAP
MyD88
MyD88-dependent pathway
IRAK4
IRAK1
TRAF6
TAB1
TAB2
TAK1
p105
Tpl2
MEK1/2
ERK
MAPK signaling pathway
AP-1
TRAM
Flagellar assembly
Flagellin
TLR5
MyD88
TRAF6
RIP1
MKK3/6
p38
MKK4/7
JNK
IRF5
Imidazoquinolin
(anti-viral compounds)
ssRNA
Unmethylated CpG DNA
dsRNA
TLR7/8
CTSK
TLR9
TLR3
Endosome
MyD88
Specific pathway in pDCs
IRAK4
TRAF6
IRAK1
IRF7
IKKα
OPN
TRIF
TRAF3
IKKε
TBK1
MyD88-independent pathway
IRF3
Inflammatory cytokines
TNFα
IL-1β
IL-6
IL-12
Proinflammatory effects
IL-8
RANTES
MIP-1α
MIP-1β
Chemotactic effects
(Nutrophil, Immature DC (NK cell)
Complement and coagulation cascade
Costimulatory molecules
CD40
CD80
CD86
T cell stimulation
Inflammatory cytokines
IFN-α
IFN-β
Antiviral effects
Cytokine-cytokine receptor interaction
Autocrine / Paracrine
IFN-β
IFN-αβR
STAT1
JAK-STAT signaling pathway
IP-10
MIG
I-TAC
Chemotactic effects (T cell)
04620 10/28/22
(c) Kanehisa Laboratories

(1)


NOD-LIKE RECEPTOR SIGNALING PATHWAY
NOD1
NOD2
RIP2
TAK1
TAB
ERK
JNK
p38
AP-1
IκB
NFκB
MAPK signaling pathway
NF-kappa B signaling pathway
TRAF3
TBK1
IKKε
TANK
IRF3/7
IFNα/β
Inflammasomes
NLRP1
NLRP3
ASC
pro-CASP1
CASP1
CASP5
GSDMD
Pyroptosis
Nucleus
TLR4
LPS
IFNAR
JAK1
TYK2
STAT1/2
IRF9
NLRP6
NLRP7
NLRP12
NLRC4
NAIP
AIM2
Pyrin
IFI16
STING
DNA virus
IL-1β
IL-18
Pro-inflammatory effects
Pro-inflammatory cytokines
Chemokines
Antimicrobial peptides
Toll-like receptor signaling pathway

(2)



(3)

Fig. S1 KEGG Pathway- (1) Toll-like receptor signaling pathway (2) NOD-like receptor signaling pathway and (3) MAPK signaling pathway

Table S14 Overlapping inflammation-associated genes retrieved from DisGeNET and GeneCard database

MMP2	CRHR2	CCL5	AGT	SDC1	TLR2
EDN1	EGR1	PLAUR	CHRNB2	CAMK2A	SULT2B1
BDKRB1	IFNL3	ACSL4	AHR	ABCB4	CD3E
TF	ABCB1	SPINK1	TBX21	TLR4	ANXA1
CYP1A1	IL17A	NLRP3	IRF7	TLR9	NGF
HP	PLA2G4A	BDNF	AGER	AKT1	ALOX5
ATP7B	STAT3	TLR6	VEGFA	MIR217	NPPB
MUC2	S100A8	TSC2	ASIC3	LCN2	WDR1
JAK2	NPY5R	PPARG	MIR21	SERPINC1	FGG
CASP1	PDPN	CXCL8	TNFAIP3	F3	BDKRB2
TAC1	NPFF	KYNU	TRPV1	APOA1	CALCA
GAL	PTPN1	TFRC	SLC22A5	TREX1	MTOR
DUSP10	IFNG	PARP1	CCL11	PCSK1	ASIC1
NTRK2	FGF2	MYD88	IDO1	ACSL3	IL15
IL10	CXCL1	ASIC2	MIR34A	CCL4	CCK
ALOX5AP	ACSL6	COL2A1	CXCL2	SELENOS	CCL2
EGFR	KLK1	ICAM1	SOD1	TGFB1	ANGPT1
MASP2	OXT	NR1H4	PDE5A	TIMP1	LTB4R
MVK	PTGES	OPRM1	TACR3	IL13	KCNK2
MIR22	CRP	CCR5	UCN3	PTGER4	PPARA
TSLP	ZFP36	MIF	CX3CR1	HMOX1	ADORA1
APOA4	TNF	CCL3	PROCR	GATA3	CHRNA4
GALNS	IL1A	ADIPOQ	HMGB1	TFAM	LTF
SERPINA3	TRPA1	NOS2	TP73	F2R	SH2B3
EPO	PTGS2	LEP	MPO	EIF4EBP1	TGFA
UCN	PCSK2	EFNB1	AIF1	IL17RA	CDK5
TNFRSF11B	SCGB1A1	A2M	PLAA	STS	F11R
TNFSF15	CXCR3	F2RL1	IL6	RORC	CSF2
CXCR2	IL1RN	TACR1	PIK3CG	IL1B	MMP9

Table S15 List of inflammation-associated genes overlapping with compound-target genes.

MTOR	TLR9	ALOX5	PTGS2	ADORA1	PPARG	NR1H4
IDO1	PTPN1	JAK2	PIK3CG	F2R	PLAA	PARP1
NOS2	PLA2G4A	STAT3	MIF	TACR1	PTGER4	OPRM1
TNF	PPARA	ALOX5AP	EGFR	PTGES	TRPV1	

Table S16 Topological properties of the STRING network.

Node	Betweenness Centrality	Closeness Centrality	Clustering Coefficient	Degree	Eccentricity	Neighborhood Connectivity	Number of Undirected Edges	Radiality	Stress	Topological Coefficient
TNF	0.363029341	0.961538462	0.289855072	24	2	7.75	24	0.998333	432	0.31
PTGS2	0.076899711	0.757575758	0.463235294	17	2	9.882352941	17	0.986667	166	0.395294118
EGFR	0.072125782	0.714285714	0.428571429	15	2	9.266666667	15	0.983333	132	0.370666667
STAT3	0.048514671	0.694444444	0.494505495	14	2	10.07142857	14	0.981667	100	0.402857143
PPARG	0.029346801	0.675675676	0.564102564	13	2	11.30769231	13	0.98	84	0.452307692
PTGER4	0.011642857	0.625	0.688888889	10	2	12.3	10	0.975	34	0.492
PPARA	0.017513468	0.625	0.533333333	10	2	12	10	0.975	58	0.48
NOS2	0.050162097	0.625	0.511111111	10	2	10.8	10	0.975	112	0.445833333
TRPV1	0.051679173	0.609756098	0.444444444	9	2	10.66666667	9	0.973333	104	0.439814815
JAK2	0.009673401	0.609756098	0.722222222	9	2	12.55555556	9	0.973333	26	0.502222222
MTOR	0.008865079	0.595238095	0.694444444	9	3	12.33333333	9	0.971667	22	0.513888889

ALOX5	0.002865079	0.581395349	0.821428571	8	3	12.125	8	0.97	10	0.505208333
PTGES	0.004531746	0.595238095	0.821428571	8	2	12.125	8	0.971667	16	0.485
PLA2G4A	0.002865079	0.581395349	0.821428571	8	3	12.125	8	0.97	10	0.505208333
ALOX5AP	0.003888889	0.568181818	0.80952381	7	3	11.57142857	7	0.968333	8	0.482142857
IDO1	0.003253968	0.568181818	0.8	6	2	12.83333333	6	0.968333	8	0.513333333
PTPN1	8.10E-04	0.555555556	0.866666667	6	3	14.16666667	6	0.966667	4	0.590277778
PIK3CG	0.005	0.543478261	0.7	5	3	11.8	5	0.965	6	0.491666667
TLR9	0	0.555555556	1	5	2	14.2	5	0.966667	0	0.568
PARP1	0	0.531914894	1	4	3	15.5	4	0.963333	0	0.645833333
ADORA1	0	0.531914894	1	3	2	16	3	0.963333	0	0.64
MIF	0	0.520833333	1	3	3	18.66666667	3	0.961667	0	0.777777778
NR1H4	0	0.520833333	1	3	3	17.66666667	3	0.961667	0	0.736111111
F2R	0	0.510204082	1	2	3	14.5	2	0.96	0	0.604166667
OPRM1	6.67E-04	0.431034483	0	2	3	9.5	2	0.945	2	0.653846154
TACR1	0	0.520833333	1	2	2	16.5	2	0.961667	0	0.66

Table S17 Topological analysis of sub-network of top 10 nodes.

Node	Betweeness	Bottleneck	Closeness	Clustering Coefficient	Degree	DMNC	Eccentricity	EPC	MCC	MNC	Radiality	Stress
TNF	217.8176	21	24.5	0.28986	24	0.36036	0.5	10.64	3076	24	3.12	432
PTGS2	46.13983	2	21	0.46324	17	0.51001	0.5	9.825	2868	17	2.84	166
EGFR	43.27547	1	20	0.42857	15	0.45067	0.5	9.316	1314	15	2.76	132
STAT3	29.1088	1	19.5	0.49451	14	0.50675	0.5	9.345	1398	14	2.72	100
PPARG	17.60808	1	19	0.5641	13	0.56202	0.5	9.135	1944	13	2.68	84
PTGER4	30.09726	1	17.5	0.51111	10	0.54893	0.5	7.675	289	9	2.56	112
PPARA	10.50808	1	17.5	0.53333	10	0.47886	0.5	8.34	216	10	2.56	58
NOS2	6.98571	1	17.5	0.68889	10	0.61853	0.5	8.248	1680	10	2.56	34
TRPV1	5.31905	1	16.83333	0.69444	9	0.59666	0.33333	7.77	888	9	2.48	22
JAK2	5.80404	1	17	0.72222	9	0.62053	0.5	8.003	984	9	2.52	26

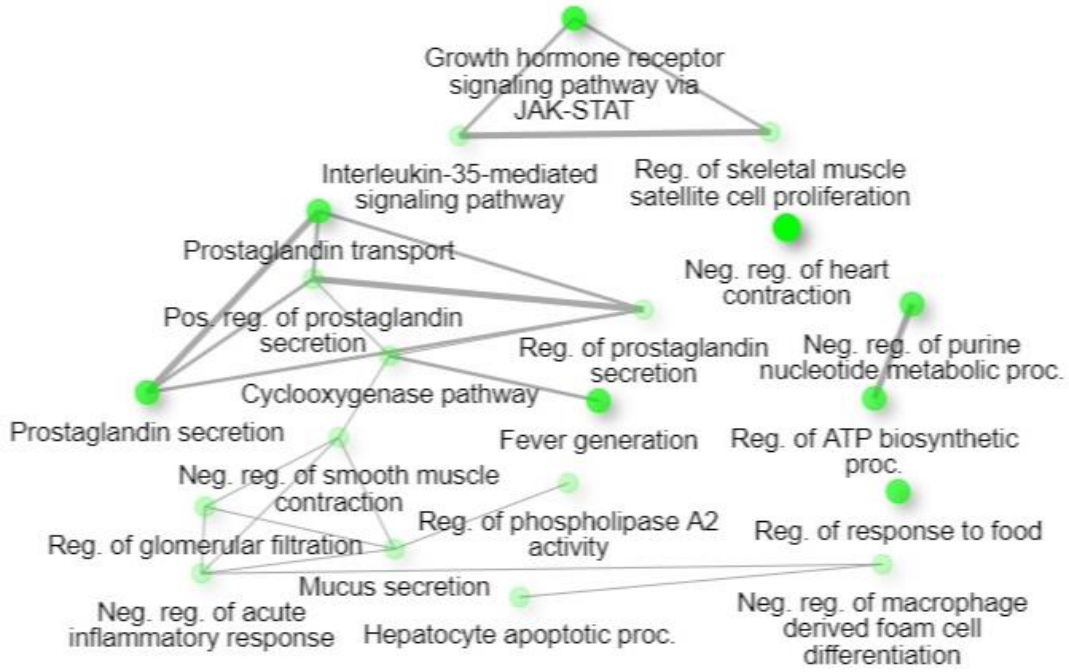


Fig. S2 Network showing interaction of enriched GO-Biological processes. Green coloured dots indicate node (Biological process). Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

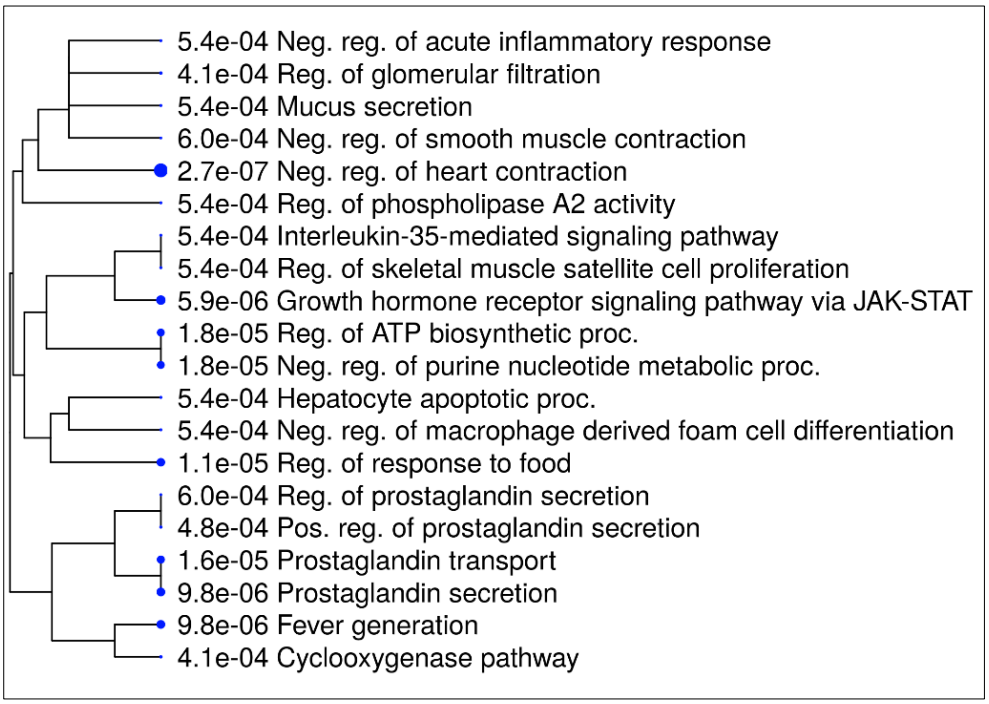


Fig. S3 Hierarchical clustering tree of GO-Biological process enrichment analysis

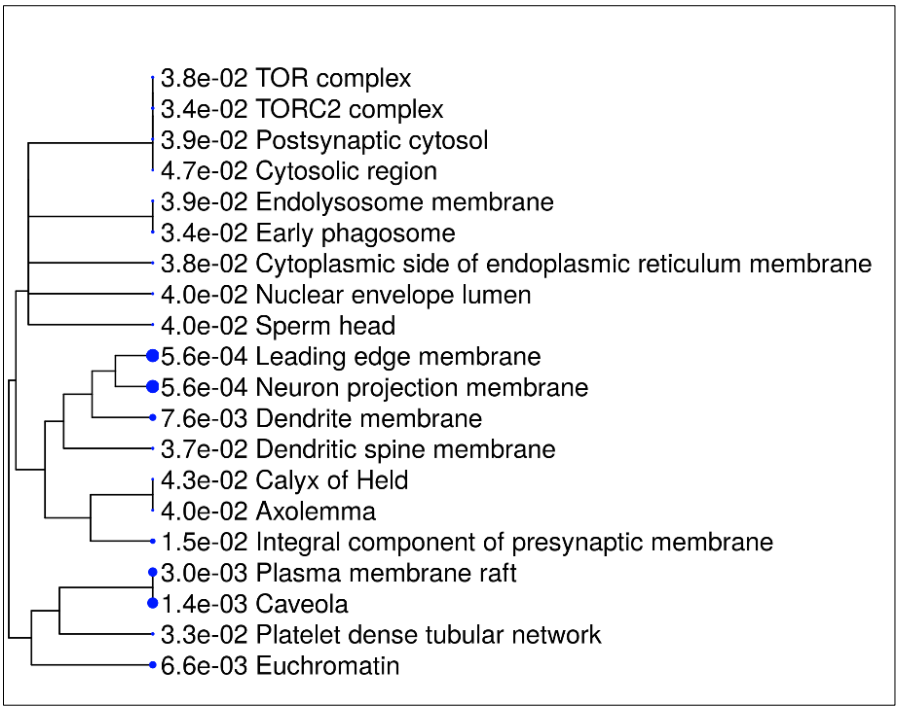


Fig. S4 Hierarchical clustering tree of GO-Cellular component enrichment analysis.

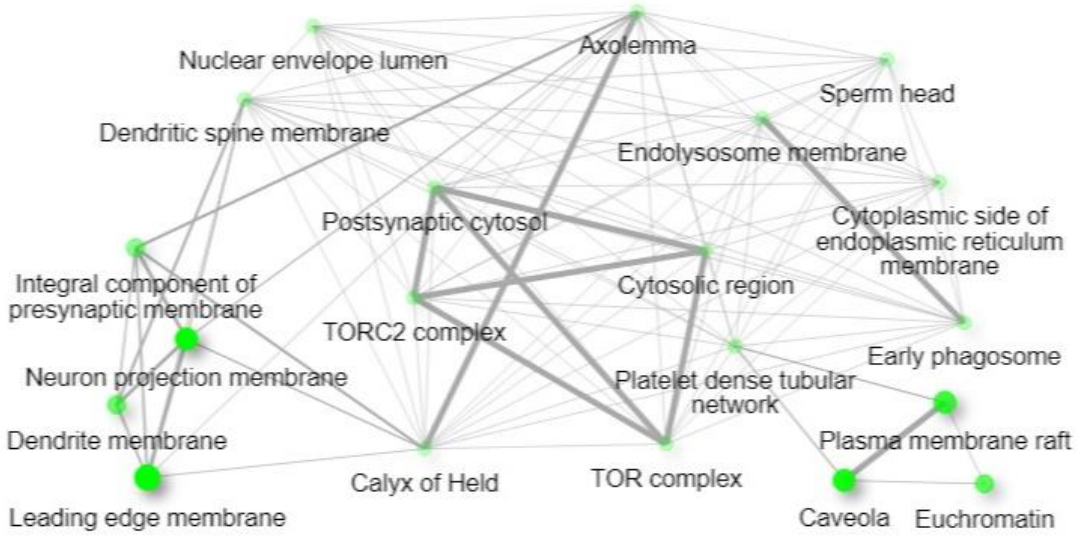


Fig. S5 Network showing interaction of enriched GO-Cellular components. Green coloured dots indicate node (Biological process). Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

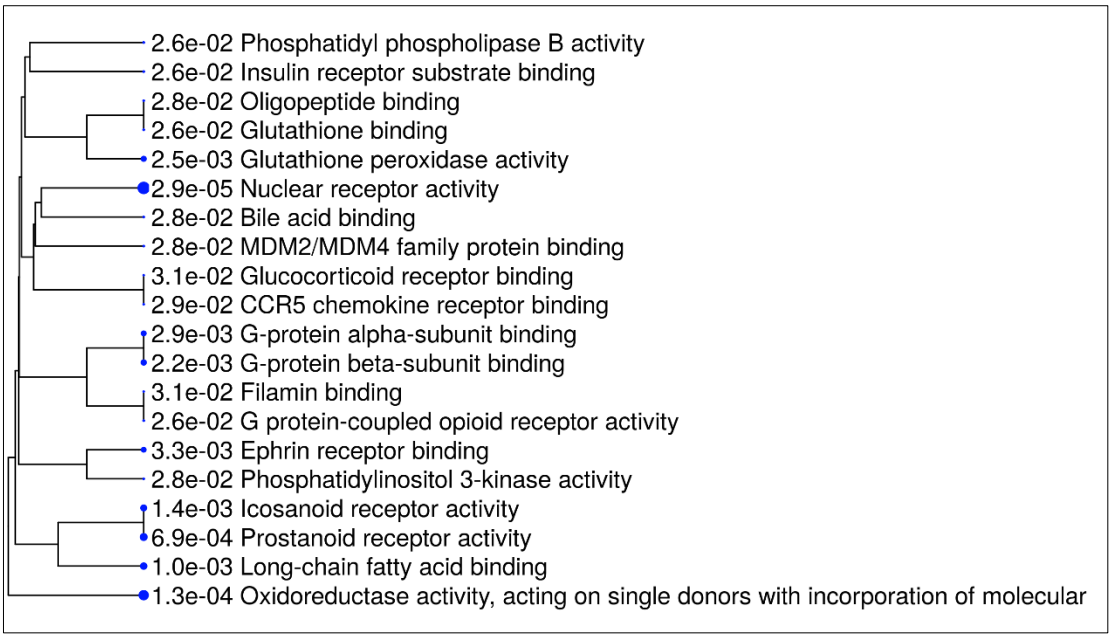


Fig. S6 Hierarchical clustering tree of GO- Molecular function enrichment analysis.

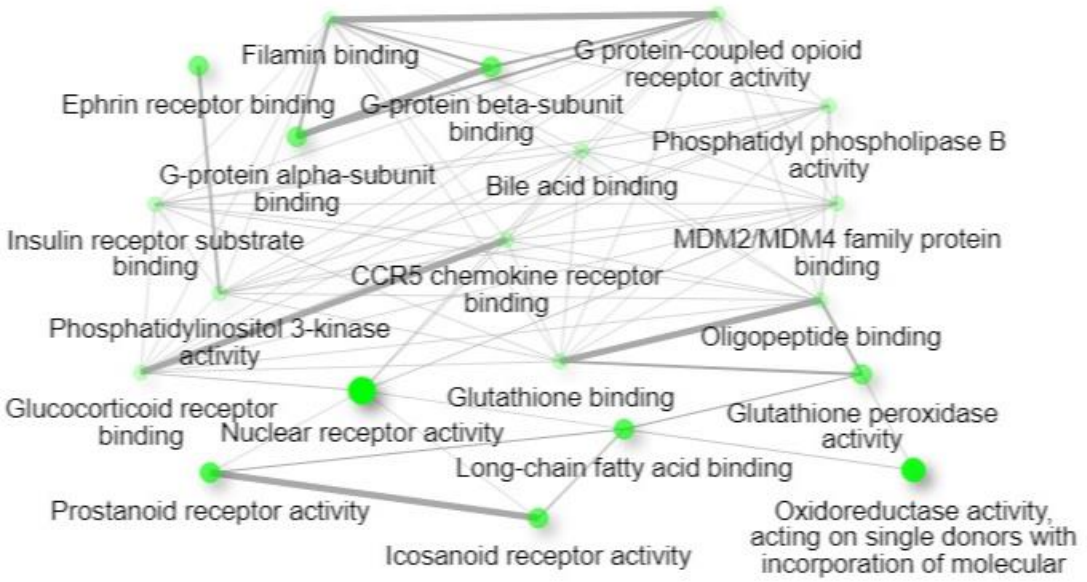


Fig. S7 Network showing interaction of enriched GO-Molecular functions. Green coloured dots indicate node (Biological process). Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

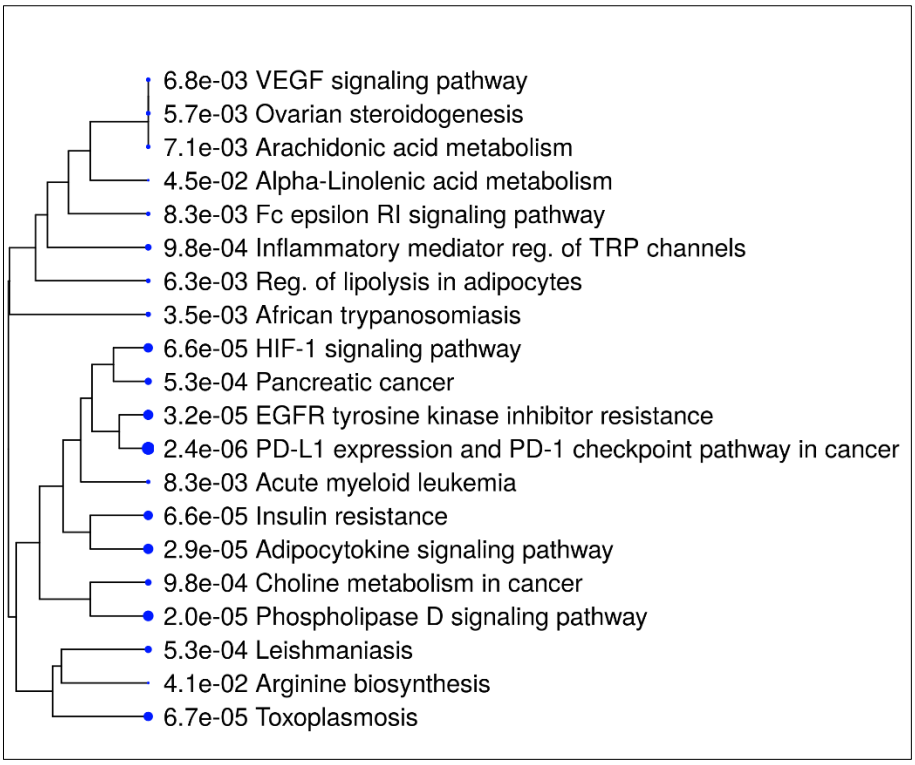


Fig. S8 Hierarchical clustering tree of KEGG pathways

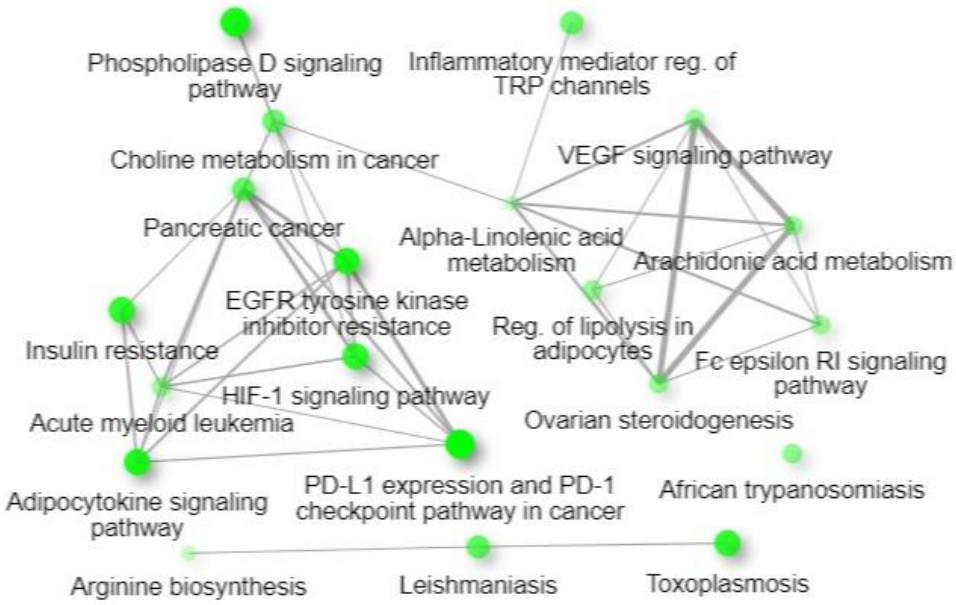
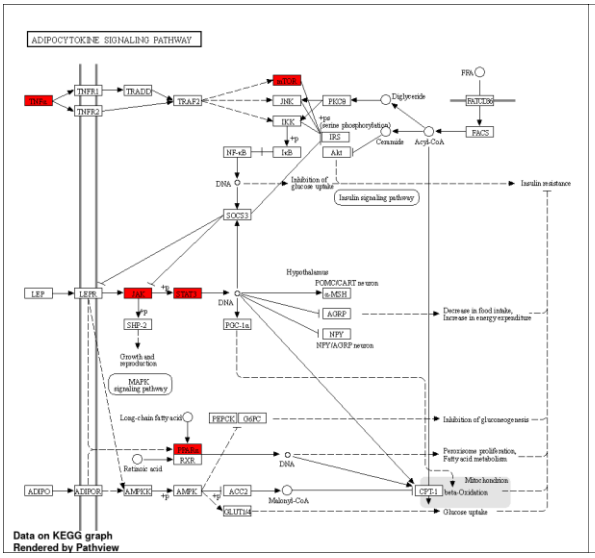
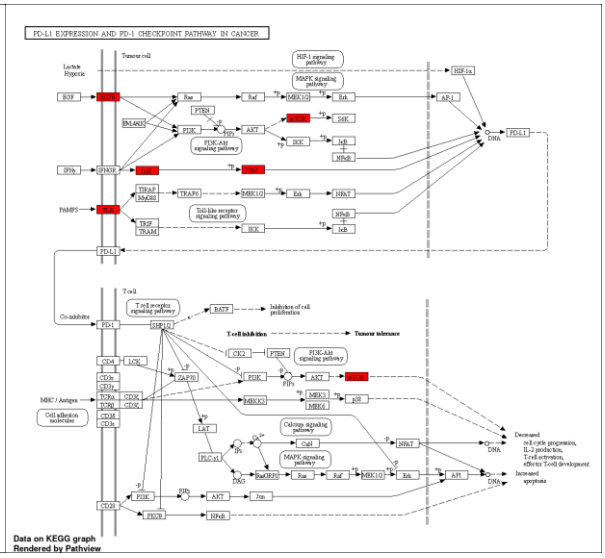


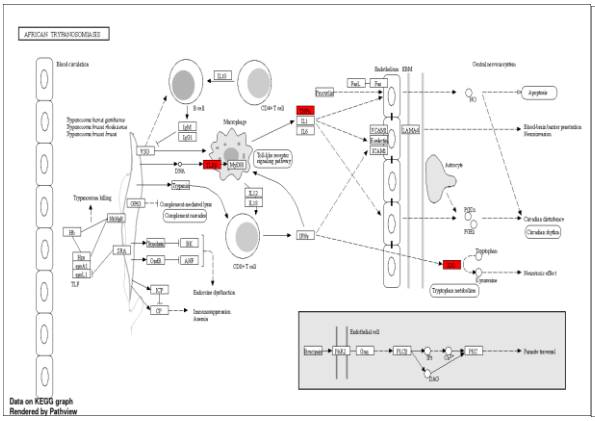
Fig. S9 Network showing interaction of enriched KEGG pathways. Green coloured dots indicate node (KEGG pathway). Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.


ADIPOCYTOKINE SIGNALING PATHWAY
Data on KEGG graph
Rendered by Pathview

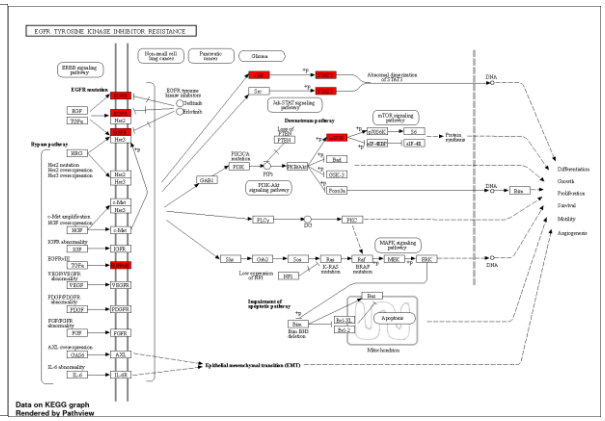
(1)


PD-L1 EXPRESSION AND PD-1 CHECKPOINT PATHWAY IN CANCER
Data on KEGG graph
Rendered by Pathview

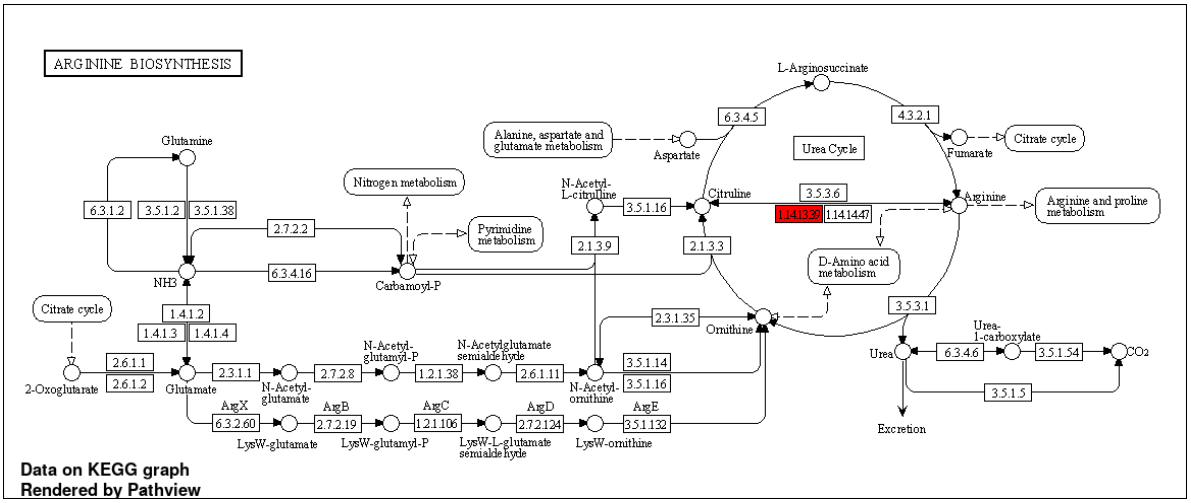
(2)


AFRICAN TRYPANOSOMIASIS
Data on KEGG graph
Rendered by Pathview

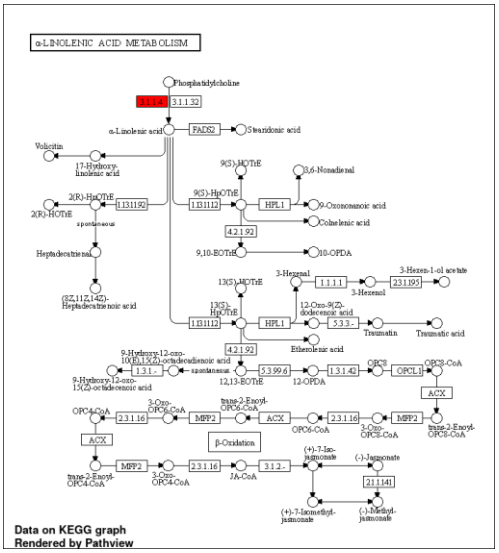
(3)


EGFR TYROSINE KINASE INHIBITOR RESISTANCE
Data on KEGG graph
Rendered by Pathview

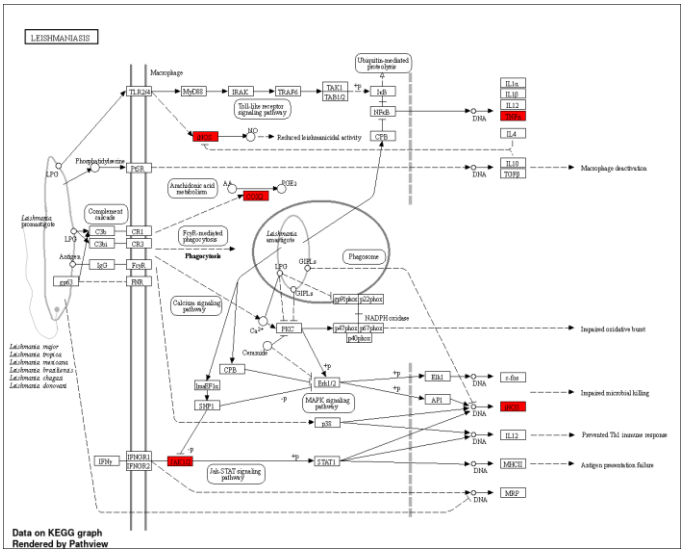
(4)


ARGININE BIOSYNTHESIS
L-Arginosuccinate
Glutamine
Alanine, aspartate and glutamate metabolism
Aspartate
Urea Cycle
Fumarate
Citrate cycle
Nitrogen metabolism
N-Acetyl-L-citrulline
Citrulline
Arginine
Arginine and proline metabolism
Pyrimidine metabolism
NH3
Carbamoyl-P
D-Amino acid metabolism
Ornithine
Urea
Urea-1-carboxylate
CO2
Excretion
2-Oxoglutarate
Glutamate
N-Acetyl-glutamate
N-Acetyl-glutamyl-P
N-Acetylglutamate semialdehyde
N-Acetyl-ornithine
AgrX
AgrB
AgrC
AgrD
AgrE
LysW-glutamate
LysW-glutamyl-P
LysW-L-glutamate semialdehyde
LysW-ornithine
Data on KEGG graph
Rendered by Pathview

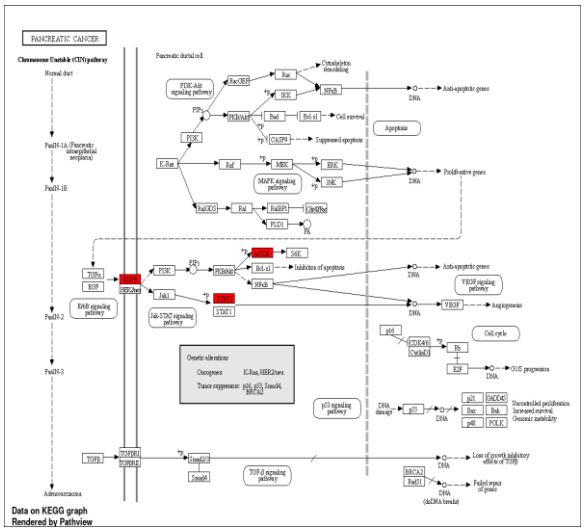
(5)


α-LINOLENIC ACID METABOLISM
Data on KEGG graph
Rendered by Pathview

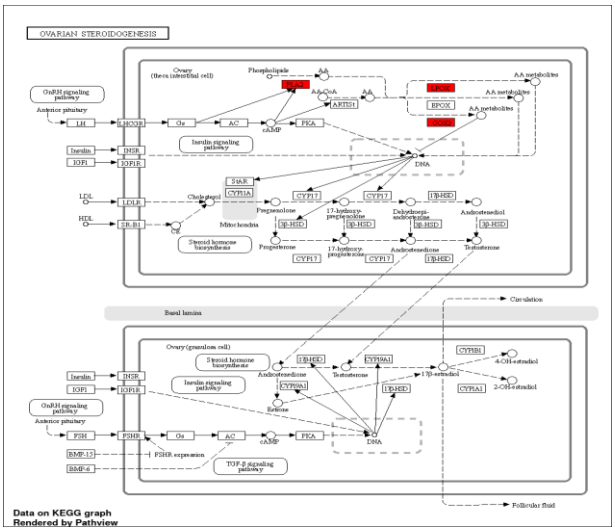
(6)


LEISHMANIASIS
Data on KEGG graph
Rendered by Pathview

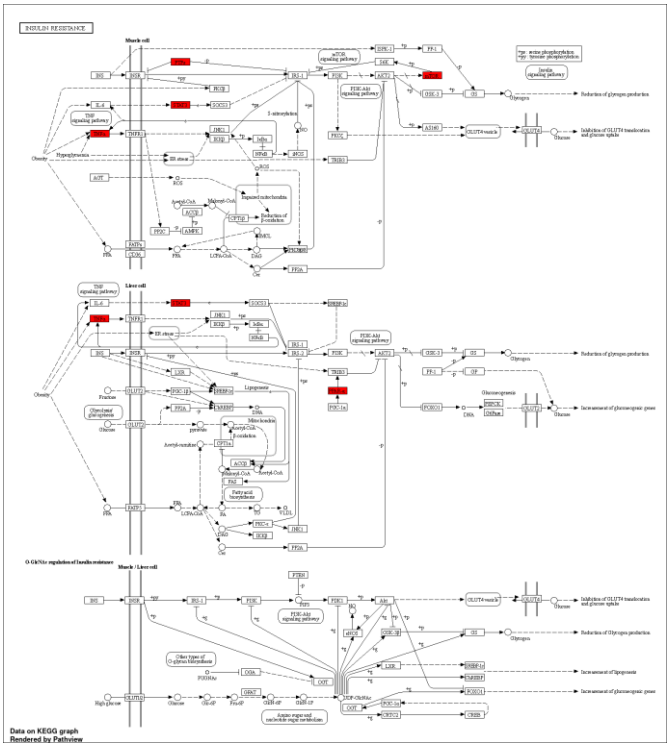
(7)


PANCREATIC CANCER
Data on KEGG graph
Rendered by Pathview

(8)


OVARIAN STEROIDOGENESIS
Data on KEGG graph
Rendered by Pathview

(9)



(10)

Fig. S10 KEGG pathways- (1) Adipocyte signalling pathway (2) PD-L1 expression and PD-1 checkpoint in cancer (3) African trypanosomiasis (4) EGFR tyrosine kinase inhibitor resistance (5) Arginine biosynthesis (6) Alpha-linolenic acid metabolism (7) Leishmaniasis (8) Pancreatic cancer (9) Ovarian steroidogenesis and (10) Insulin resistance. Red colored box indicate target genes.

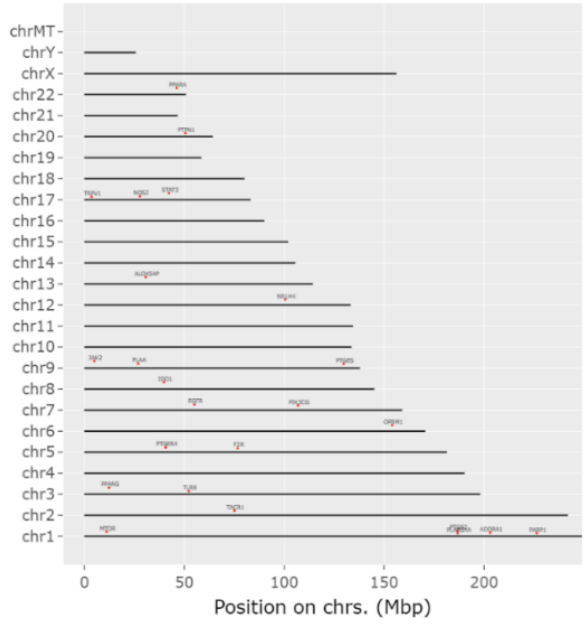


Fig. S11 Plot showing the position of genes on the chromosome

LIST OF PUBLICATIONS

1. **Sangeeta Hazarika** and Siva Hemalatha. Quality control assessment, toxicity profiling, and experimental validation of network pharmacology-predicted anti-inflammatory potential of *Natsiatum herpeticum* Buch.-Ham. ex Arn.. *Journal of Ethnopharmacology*. 2024; 318, Part A, 116902, https://doi.org/10.1016/j.jep.2023.116902 (Impact factor: 5.4)
2. **Sangeeta Hazarika**, Siva Hemalatha, and Katharigatta N. Venugopala. Phytochemical screening and pharmacological evaluation of *Natsiatum herpeticum* Buch.-Ham. ex Arn.. *Indian Journal of Pharmaceutical Education and Research*. 2023; 57(4): 1098-1103, doi:10.5530/ijper.57.4.132 (Impact factor: 0.8)
3. **Sangeeta Hazarika**, Shikha Thakur, Hemant R. Jadhav, Pankaj Chetia, Damiki Laloo, and Siva Hemalatha. Investigation of antibacterial potential of *Natsiatum herpeticum* Buch.-Ham. ex Arn using in silico-in vitro approach. *South African Journal of Botany*. 2024; 164: 167-179, https://doi.org/10.1016/j.sajb.2023.11.041 (Impact factor: 3.1)