

## Supplementary file 1

# Multi-target mechanism of polyherbal extract to treat diabetic foot ulcer based on network pharmacology and molecular docking

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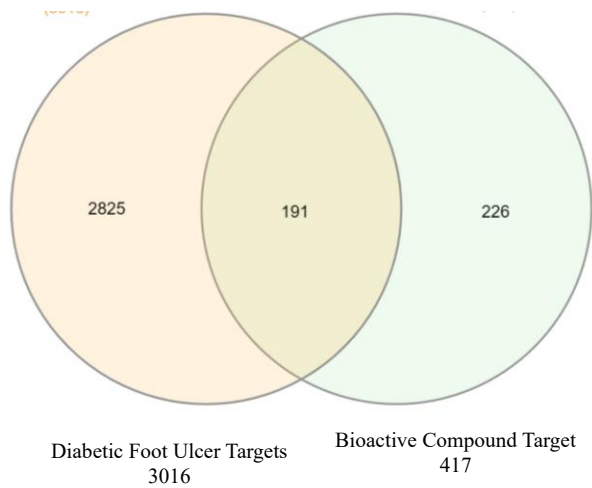
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**Table S1.** The proteins contained in TIP-Heal and their effect on DFU with human subjects.

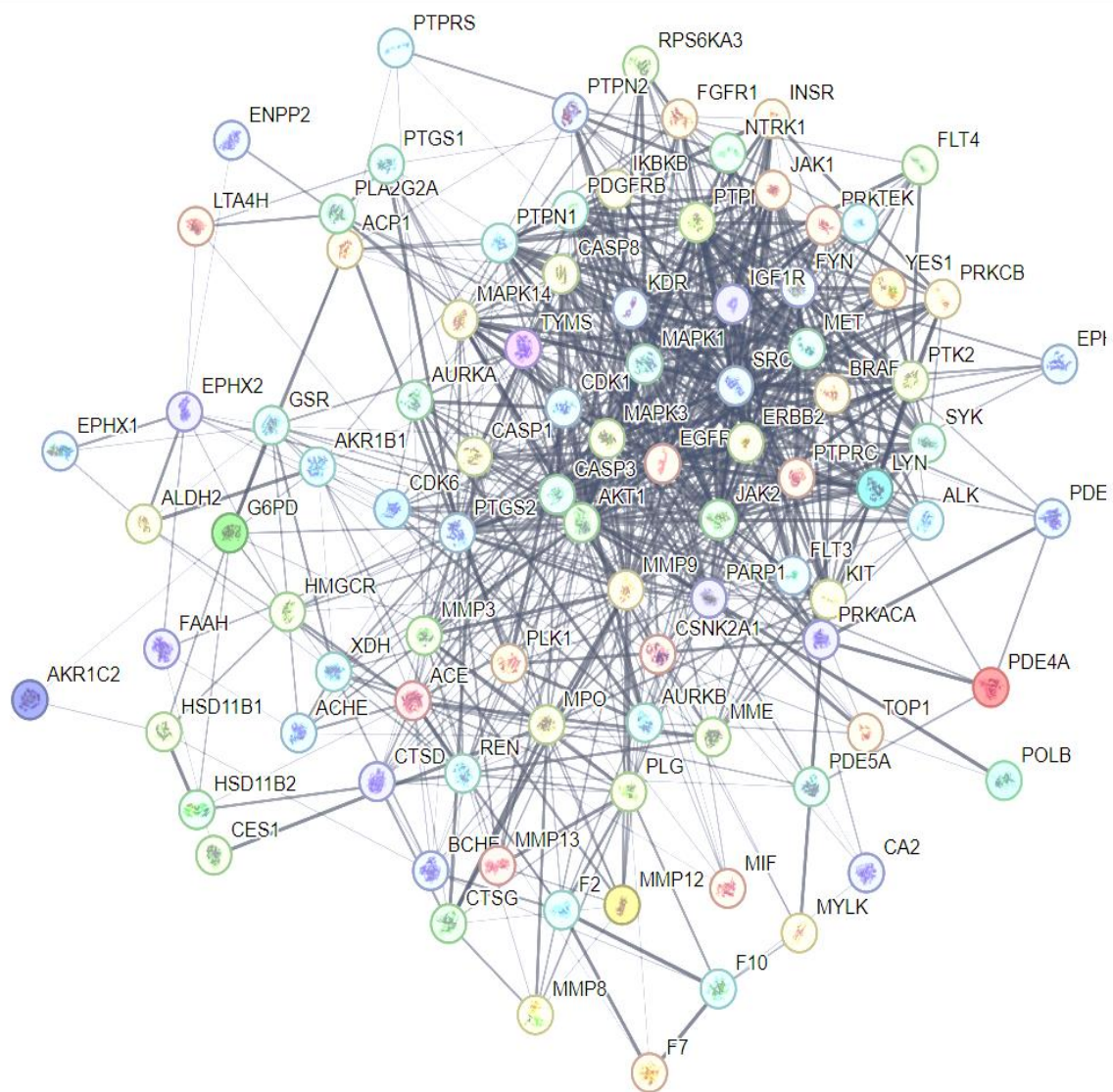
Gene symbol	Protein names	Uniprot ID	Degree	Betweenness	Closeness
AKT1	AKT Serine/Threonine Kinase 1	P31749	60	0.137095819	0.741935484
CASP3	Caspase-3	P42574	54	0.06409366	0.696969697
EGFR	Epidermal growth factor receptor	P00533	53	0.055438798	0.681481481
MMP9	Matrix metalloproteinase-9	P14780	49	0.062723504	0.666666667
SRC	Proto-oncogene tyrosine-protein kinase Src	P12931	49	0.065317643	0.657142857
PTGS2	Prostaglandin G/H synthase 2	P35354	43	0.070756868	0.647887324
MAPK3	Mitogen-activated protein kinase 3	P27361	41	0.037379152	0.638888889
ERBB2	Erb-B2 Receptor Tyrosine Kinase 2	P04626	39	0.020514442	0.613333333
JAK2	Tyrosine-protein kinase JAK2	O60674	38	0.018390231	0.605263158
MAPK1	Mitogen-activated protein kinase 1	P28482	34	0.021400045	0.60130719
PTPRC	Protein Tyrosine Phosphatase Receptor Type C	P08575	34	0.008857518	0.578616352
PARP1	Poly [ADP-ribose] polymerase 1	P09874	33	0.032142572	0.582278481
PTPN11	Protein Tyrosine Phosphatase Non-Receptor Type 11	Q06124	33	0.008249939	0.557575758
KDR	Kinase Insert Domain Receptor	P35968	32	0.007795511	0.585987261
FYN	FYN Proto-Oncogene, Src Family Tyrosine Kinase	P06241	30	0.011712861	0.547619048
MAPK14	Mitogen-activated protein kinase 14	Q16539	29	0.006643624	0.571428571
ACE	Angiotensin-converting enzyme	P12821	28	0.045708823	0.571428571

MET	MET Proto-Oncogene, Receptor Tyrosine Kinase	P08581	27	0.004574652	0.56097561
IGF1R	Insulin-like growth factor 1 receptor	P08069	27	0.004805704	0.557575758
PTPN1	Tyrosine-protein phosphatase non-receptor type 1	P18031	27	0.009613218	0.547619048
LYN	Tyrosine-protein kinase Lyn	P07948	27	0.009446721	0.538011696
CASP8	Caspase-8	Q14790	26	0.003274269	0.550898204
PTK2	Focal adhesion kinase 1	Q05397	26	0.005348567	0.544378698
MPO	Myeloperoxidase	P05164	25	0.034642203	0.564417178
PDGFRB	Platelet-derived growth factor receptor beta	P09619	25	0.004323956	0.554216867
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase	P15056	25	0.00516275	0.550898204
JAK1	Janus Kinase 1	P23458	25	0.002468161	0.534883721
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase	P10721	23	0.003386971	0.544378698
SYK	Spleen Associated Tyrosine Kinase	P43405	23	0.00194326	0.538011696
CDK1	Cyclin-dependent kinase 1	P06493	23	0.00730412	0.531791908
PLG	Plasminogen	P00747	22	0.026031806	0.547619048
CASP1	Caspase-1	P29466	21	0.005101627	0.541176471
FLT3	Fms Related Receptor Tyrosine Kinase 3	P36888	21	0.00338945	0.531791908
FGFR1	Fibroblast growth factor receptor 1 (FGFR-1)	P11362	21	0.002850245	0.528735632
REN	Renin (Angiotensinogenase)	P00797	19	0.014388461	0.544378698
IKBKB	Inhibitor of nuclear factor kappa-B kinase subunit beta	O14920	19	0.001836719	0.525714286
PRKCD	Protein kinase C delta type	Q05655	19	0.002574398	0.511111111
PRKACA	cAMP-dependent protein kinase catalytic subunit alpha (PKA C-alpha)	P17612	18	0.011226893	0.525714286
MMP3	Matrix Metalloproteinase 3	P08254	17	0.008192762	0.528735632
NTRK1	Neurotrophic Receptor Tyrosine Kinase 1	P04629	17	0.003057759	0.511111111
INSR	Insulin receptor (IR)	P06213	16	0.001037742	0.508287293
TYMS	Thymidylate synthase	P04818	16	0.005138592	0.505494505
YES1	YES Proto-Oncogene 1, Src Family Tyrosine Kinase	P07947	16	8.56E-04	0.50273224
ALK	ALK tyrosine kinase receptor	Q9UM73	16	0.001071176	0.494623656
XDH	Xanthine dehydrogenase/oxidase	P47989	15	0.007602906	0.531791908
MME	Membrane Metalloendopeptidase	P08473	15	0.003834303	0.508287293
GSR	Glutathione-Disulfide Reductase	P00390	14	0.022898835	0.519774011
CDK6	Cyclin-dependent kinase 6	Q00534	14	0.001731663	0.508287293
AURKA	Aurora kinase A	O14965	14	0.001989958	0.486772487
PRKCB	Protein kinase C beta	P05771	13	8.03E-04	0.486772487
CSNK2A1	Casein kinase II subunit alpha	P68400	12	0.006493032	0.508287293
CTSD	Cathepsin D	P07339	12	0.001680264	0.50273224
PTGS1	Prostaglandin-Endoperoxide Synthase 1	P23219	12	0.004110202	0.497297297
TEK	Tunica interna endothelial cell kinase	Q02763	12	3.69E-04	0.494623656
PTPN2	Tyrosine-protein phosphatase non-receptor type 2	P17706	12	7.18E-04	0.489361702
HMGR	3-Hydroxy-3-Methylglutaryl-CoA Reductase	P04035	11	0.012975696	0.516853933
BCHE	Butyrylcholinesterase	P06276	11	0.015211678	0.50273224
AKR1B1	Aldo-keto reductase family one member B1	P15121	11	0.00516785	0.497297297

AURKB	Aurora kinase B	Q96GD4	11	8.99E-04	0.474226804
EPHX2	Epoxide Hydrolase 2	P34913	10	0.020281601	0.479166667
G6PD	Glucose-6-phosphate 1-dehydrogenase (G6PD)	P11413	10	0.026851414	0.474226804
FLT4	Fms Related Receptor Tyrosine Kinase 4	P35916	10	1.07E-04	0.46
ACHE	Acetylcholinesterase	P22303	9	0.002971495	0.494623656
MMP12 HME	Matrix metalloproteinase-12	P39900	9	9.93E-04	0.476683938
PLK1	Polo Like Kinase 1	P53350	9	0.003443713	0.462311558
RPS6KA 3	Ribosomal protein S6 kinase alpha-3	P51812	9	1.43E-04	0.457711443
CTSG	Cathepsin G (CG)	P08311	9	8.81E-04	0.442307692
MMP13	Matrix metalloproteinase-13	P45452	8	2.56E-04	0.494623656
PLA2G2 A	Phospholipase A2 Group IIA	P14555	8	0.014056149	0.474226804
TOP1	DNA topoisomerase 1	P11387	8	0.003093371	0.46
ACP1	Acid Phosphatase 1	P24666	8	0.004948398	0.46
F2	Coagulation Factor II, Thrombin	P00734	8	0.002537419	0.450980392
MIF	Macrophage migration inhibitory factor (MIF)	P14174	6	0	0.484210526
PDE5A	Phosphodiesterase 5A	O76074	6	6.62E-04	0.469387755
PDE4D	Phosphodiesterase 4D	Q08499	6	5.16E-04	0.431924883
MMP8	Neutrophil collagenase (Matrix metalloproteinase-8)	P22894	6	7.17E-05	0.425925926
ALDH2	Aldehyde Dehydrogenase 2 Family Member	P05091	6	0.002418559	0.4
F10	Coagulation factor X	P00742	6	0.002480333	0.384937238
EPHB4	Ephrin type-B receptor 4	P54760	5	2.18E-05	0.45320197
PDE4A	cAMP-specific 3',5'-cyclic phosphodiesterase 4A	P27815	5	5.07E-04	0.446601942
HSD11B 1	Hydroxysteroid 11-Beta Dehydrogenase 1	P28845	5	0.003349961	0.37398374
MYLK	Myosin light chain kinase	Q15746	4	0.002277153	0.45320197
CA2	Carbonic anhydrase 2	P00918	4	0.002220067	0.45320197
PTPRS	Receptor-type tyrosine-protein phosphatase S	Q13332	4	4.44E-04	0.425925926
FAAH	Fatty-acid amide hydrolase 1	O00519	4	0.001952871	0.410714286
LTA4H	Leukotriene A-4 hydrolase	P09960	4	2.73E-04	0.410714286
F7	Coagulation factor VII	P08709	4	3.04E-04	0.389830508
HSD11B 2	Hydroxysteroid 11-Beta Dehydrogenase 2	P80365	4	0.001046956	0.386554622
EPHX1	Epoxide hydrolase 1	P07099	3	0	0.355212355
POLB	DNA polymerase beta	P06746	2	0	0.372469636
CES1	Carboxylesterase 1	P23141	2	2.28E-04	0.369477912
ENPP2	Ectonucleotide pyrophosphatase/phosphodiesterase family member 2	Q13822	2	1.47E-04	0.344569288
AKR1C2	Aldo-Keto Reductase Family 1 Member C2	P52895	2	0	0.327402135



**Figure S1.** The intersection between TIP-Heal and diabetic foot ulcers of the target protein is shown in the Venn diagram.



**Figure S2.** The protein-protein interaction (PPI) network between the TIP-Heal and diabetic foot ulcers systems.

Each node in the form of a bubble symbolizes a protein, and the inclusion of a 3D structure within these nodes indicates that the spatial arrangement of the protein is either known or predicted. The connections among internal nodes depict the interrelation between distinct proteins, while the thickness of these connections is determined by the level of empirical evidence supporting the association.