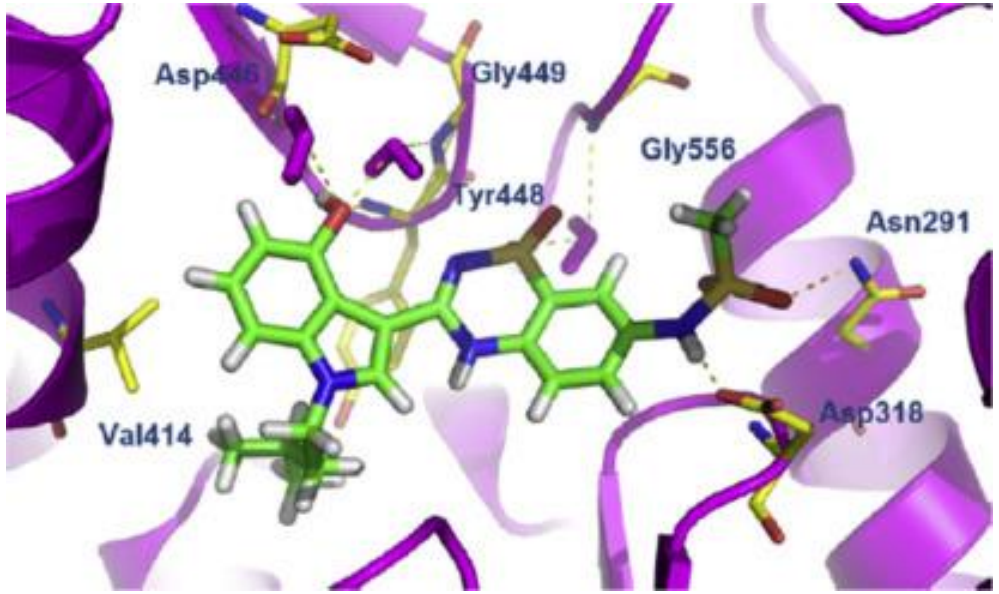
Iran University of Medical Sciences

"GOD is GOOD"

Evaluation of plant extract using bioinformatics tools



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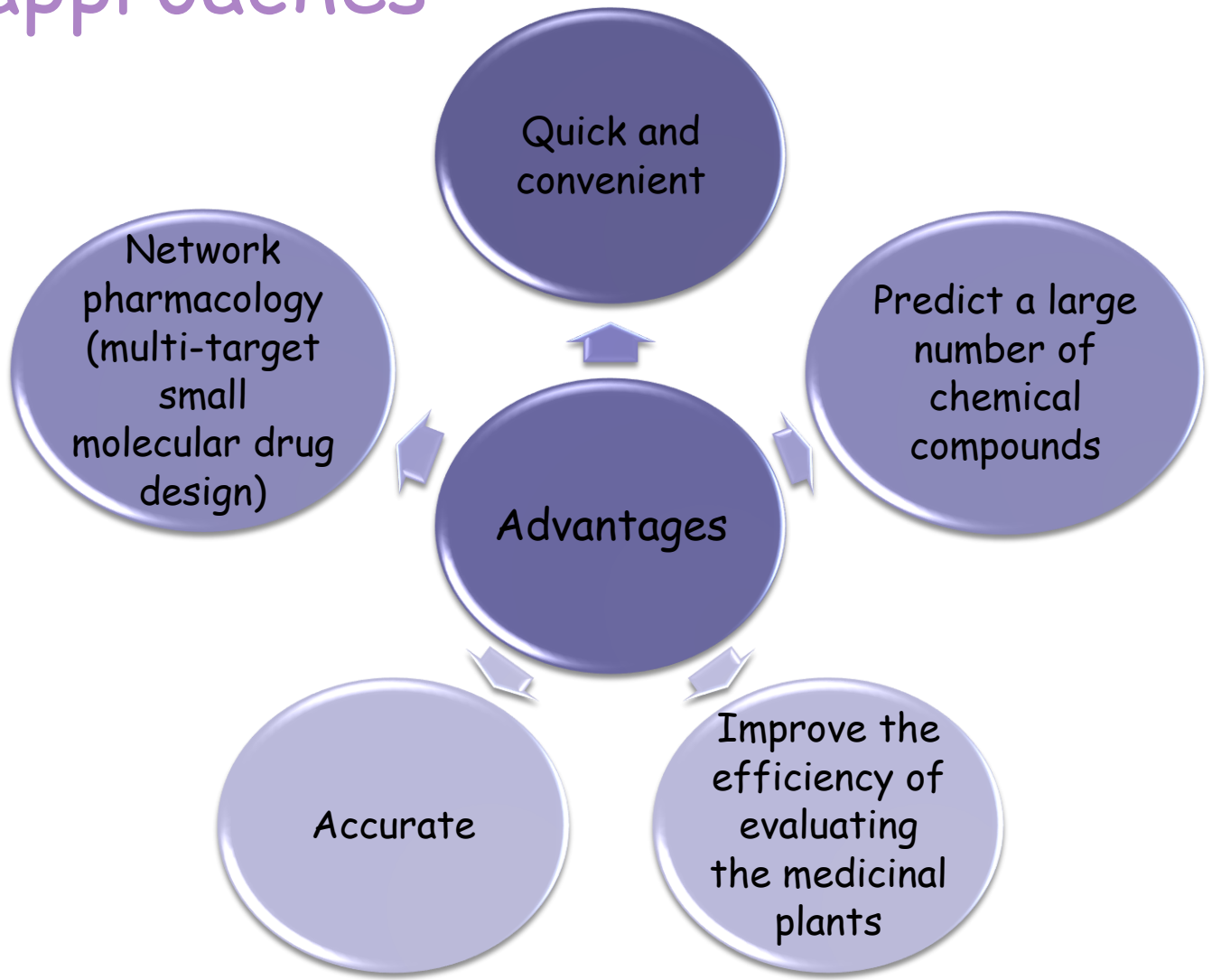
Medicinal plants

- WHO report: over 30% of all plant species been used for medicinal purposes
- Important but Complex task:
  - Varied and complex chemical constituents of medicinal plants
  - Time consuming
  - Expensive
- So…

Need for new technologies and methods:
in silico approaches

In silico approaches



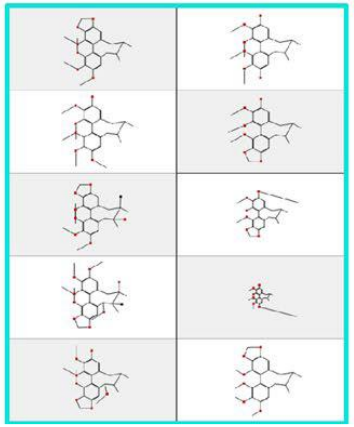
Methodology

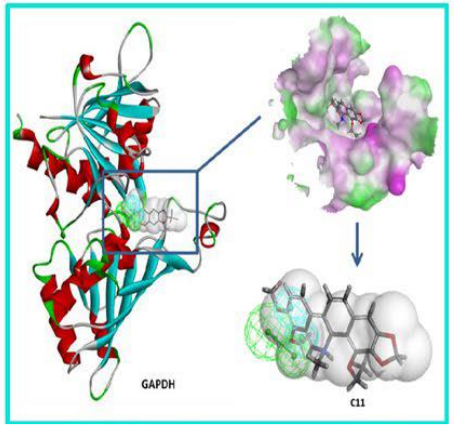
1 MEDI-PLANTS
- *Wide Usages*
- *Unclear Mechanisms*
- *New Utilization*

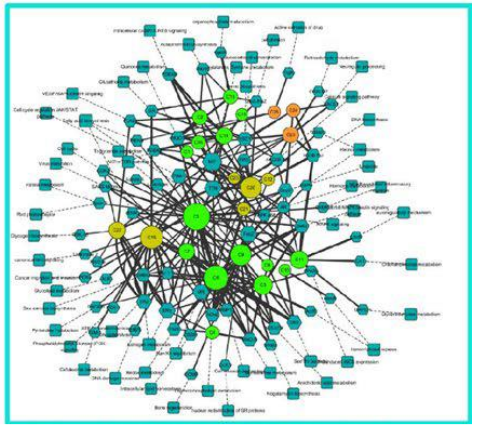
2 PRE-TREATMENT
- *Druggable Prediction*
- *ADME/T Selection*
- *False-positive Exclusion*

3 VIRTUAL SCREEING
- *Pharmacophore Searching*
- *Shape Similarity Validation*
- *Docking Accurate verification*

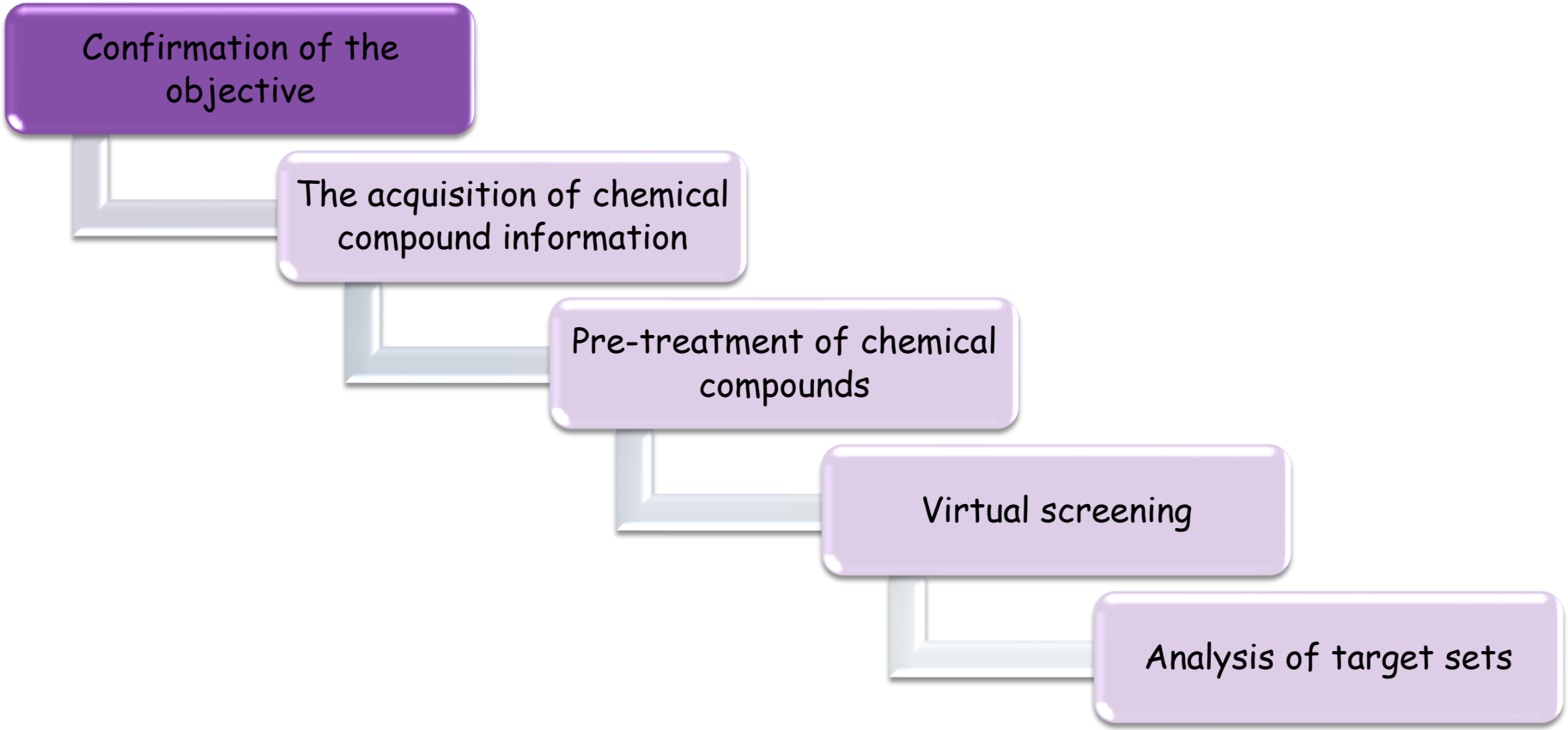
4 TARGETS ANALYSIS
- *Targets Annotation*
- *Pathways/Diseases Analysis*
- *Network Construction*







Methodology steps



Confirmation of the objective

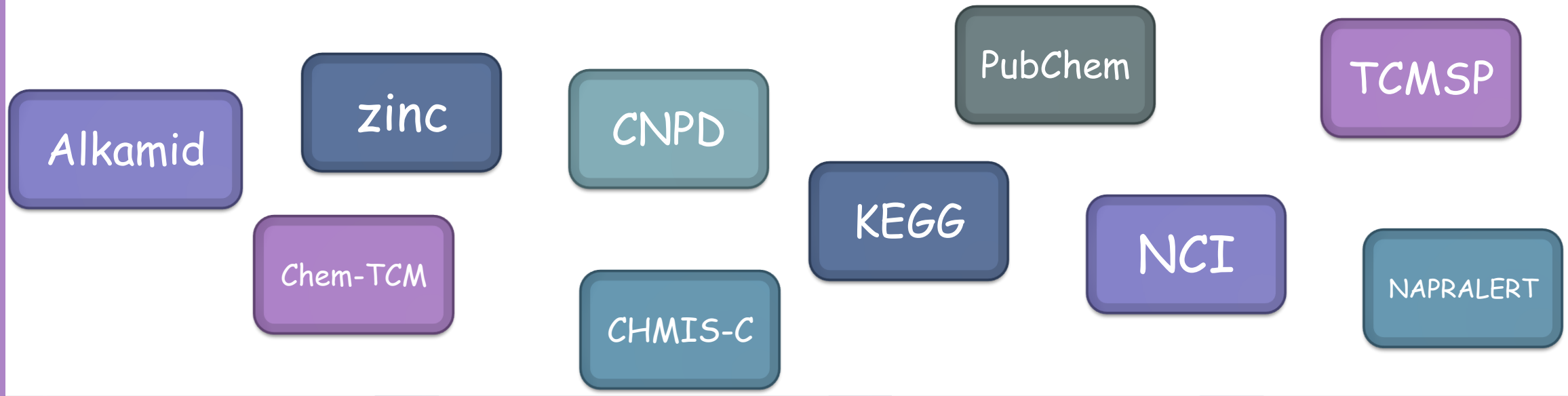
I. Common herbs with a more complex mechanism that of other herbs.

II. Herbs with a long history of traditional usage but fewer studies on their phytochemistry and pharmacology.

III. Herbs with a history of traditional usage but now with a new utilization.

The acquisition of chemical compound information

I. Collection of chemical compound information
   i. separation and purification of the compounds in a local laboratory
   ii. literature reports
   iii. small molecule compound databases



Pre-treatment of chemical compounds

I. Prediction of drug-like properties
   i. Structural characteristics: hydrogen bonding, polar surface area, lipophilicity, shape, molecular weight, and acid dissociation constant (pKa).
   ii. Physicochemical properties: solubility, pH value, permeability and chemical stability.
   iii. Biochemical properties: metabolism protein binding affinity and transport ability.
   iv. Pharmacokinetics and toxicity: half-life, bioavailability,drug interactions and half lethal dose, LD50.

II. ADME/T selection
   i. absorption, distribution,metabolism, excretion and toxicity

III. Exclusion of false-positive compounds

Virtual screening

Molecular docking

- relies on the characteristics of the receptor

Pharmacophore theory

- is an abstract set of molecular features that are necessary for the molecular recognition of a ligand by a biological macromolecule

Small molecular shape similarity

- defined as a database search technique based on the quantitative structure-activity relationships of compounds with the same mechanisms

Common virtual screening softwares

Molecular Docking	Pharmacophore model	Small molecule shape similarity
• Affinity • AutoDock • Dock • Glide • FlexX • Dockit • ZDock	• Apex-3D • DISCOtech • Discovery Studio • GASP • SEAware	• CerberuS • FlexS • BRUTUS • WEGA

Analysis of target sets

Analysis and annotation of target information

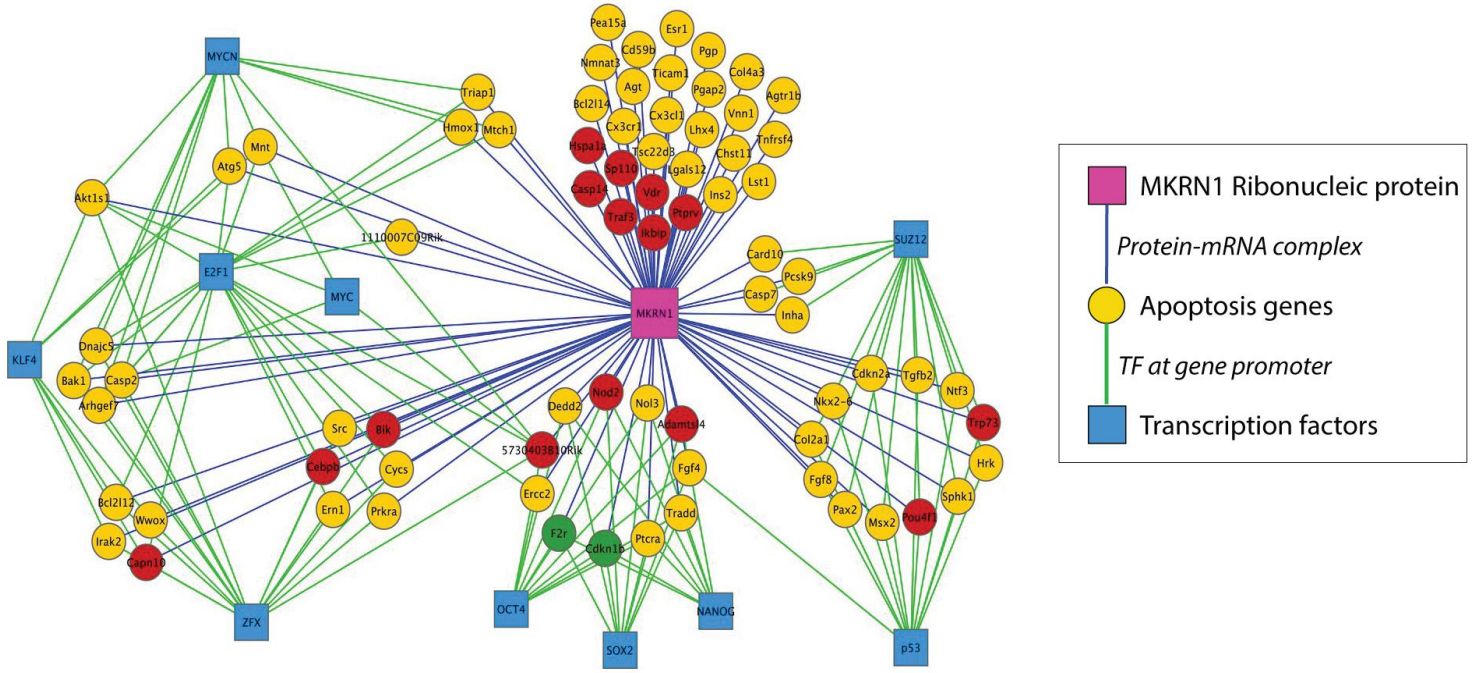
- Uniprot
- RCSB
- BindingDB
- BioGRID
- DRUGBANK
- KEGG
- STRING

Construction of network pharmacology

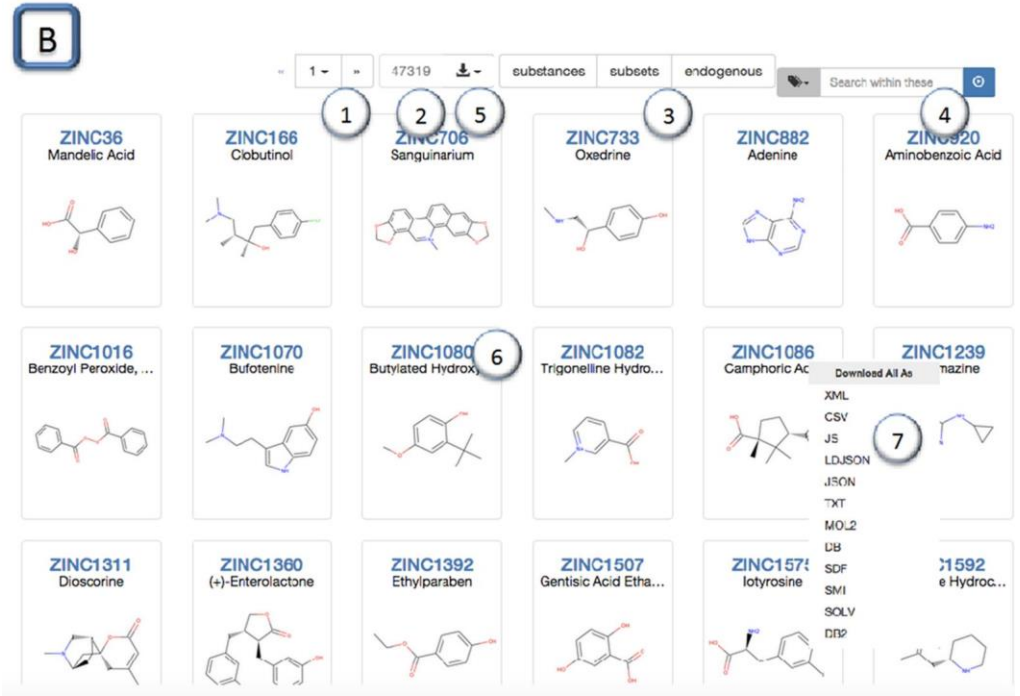
- Ingenuity Pathway Analysis (IPA) software
- KEGG pathway database
- MetaCore

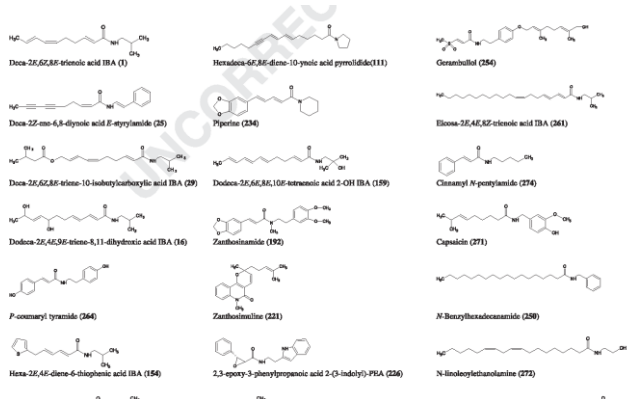
Different network visualization tools

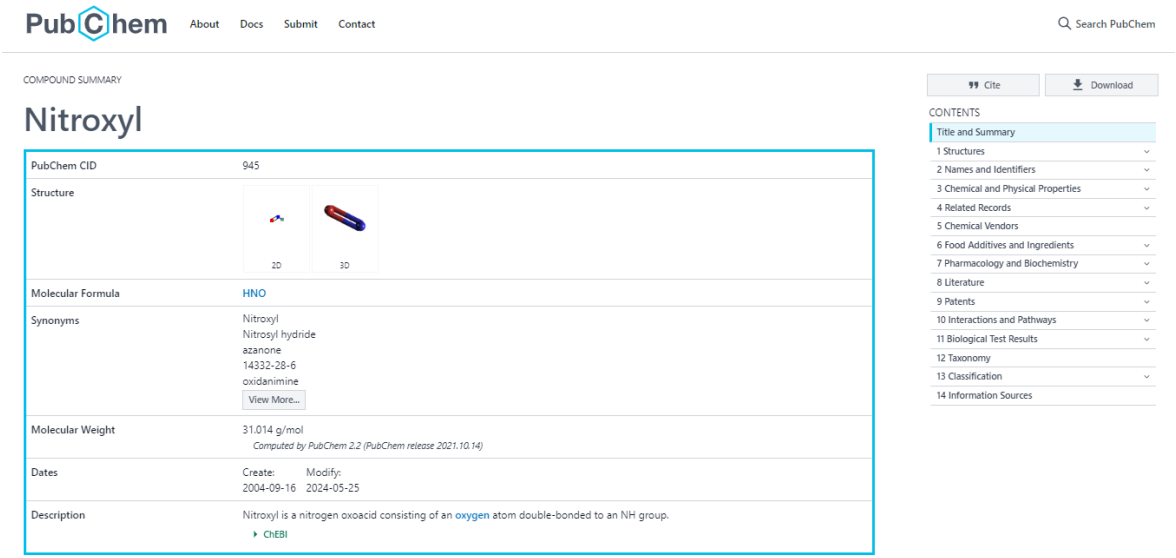
I. CADLIVE
II. Cytoscape
III. Graphviz
IV. Pajek
V. VANTED
VI. VisANT
VII. YANAsquare



Chemical compound information

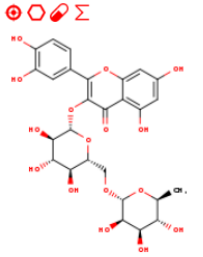


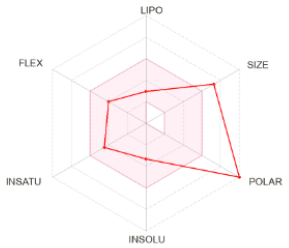




ADME/T

Molecule 1





SMILES Oc1cc(O)c2c(c1)oc(c(c2=O)O[C@@H]1O[C@H](CO[C@@H]2O[C@@H](C)[C@@H]([C@H]([C@H]2O)O)O)[C@H]([C@@H]([C@H]1O)O)O)c1ccc(c(c1)O)O

Physicochemical Properties	
Formula	C27H30O16
Molecular weight	610.52 g/mol
Num. heavy atoms	43
Num. arom. heavy atoms	16
Fraction Csp3	0.44
Num. rotatable bonds	6
Num. H-bond acceptors	16
Num. H-bond donors	10
Molar Refractivity	141.38
TPSA	269.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.46
Log $P_{o/w}$ (XLOGP3)	-0.33
Log $P_{o/w}$ (WLOGP)	-1.69
Log $P_{o/w}$ (MLOGP)	-3.89
Log $P_{o/w}$ (SILICOS-IT)	-2.11
Consensus Log $P_{o/w}$	-1.51

Water Solubility	
Log *S* (ESOL)	-3.30
Solubility	3.08e-01 mg/ml ; 5.05e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.87
Solubility	8.30e-03 mg/ml ; 1.36e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-0.29
Solubility	3.15e+02 mg/ml ; 5.15e-01 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-10.26 cm/s
Druglikeness	
Lipinski	No; 3 violations: MW>500, NorO>10, NHorOH>5
Ghose	No; 4 violations: MW>480, WLOGP<-0.4, MR>130, #atoms>70
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 4 violations: MW>600, TPSA>150, H-acc>10, H-don>5
Bioavailability Score	0.17
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	6.52

Physicochemical

Property	Value	DrugBank Percentile	Units
Molecular Weight	610.52	89.65%	Dalton
LogP	-1.69	11.55%	log-ratio
Hydrogen Bond Acceptors	16.00	96.37%	#
Hydrogen Bond Donors	10.00	96.55%	#
Lipinski Rule of 5	1.00	2.91%	# of 4
Quantitative Estimate of Druglikeness (QED)	0.14	8.10%	-
Stereo Centers	10.00	95.52%	#
Topological Polar Surface Area (TPSA)	269.43	95.04%	Å²

Absorption

Property	Prediction	DrugBank Percentile	Units
Human Intestinal Absorption	0.09	6.86%	-
Oral Bioavailability	0.18	3.45%	-
Aqueous Solubility	-3.86	34.28%	log mol/L
Lipophilicity	0.77	38.15%	log-ratio
Hydration Free Energy	-15.67	7.68%	kcal/mol
Cell Effective Permeability	-6.82	3.72%	cm/s
PAMPA Permeability	0.09	12.72%	-
P-glycoprotein Inhibition	0.14	55.45%	-

Distribution

Property	Prediction	DrugBank Percentile	Units
Blood-Brain Barrier Penetration	0.06	3.02%	-
Plasma Protein Binding Rate	84.88	63.32%	%
Volume of Distribution at Steady State	6.39	81.74%	L/kg

Metabolism

Property	Prediction	DrugBank Percentile	Units
CYP1A2 Inhibition	0.01	34.74%	-
CYP2C19 Inhibition	0.03	29.78%	-
CYP2C9 Substrate	0.03	9.42%	-
CYP2C9 Inhibition	0.02	36.91%	-
CYP2D6 Substrate	0.02	12.95%	-
CYP2D6 Inhibition	0.03	42.73%	-
CYP3A4 Substrate	0.41	42.50%	-
CYP3A4 Inhibition	0.01	33.11%	-

Excretion

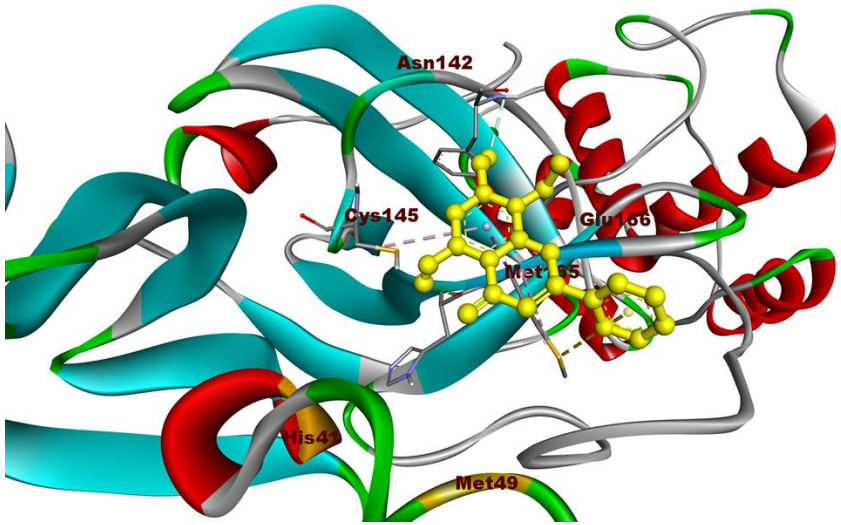
Property	Prediction	DrugBank Percentile	Units
Half Life	49.51	87.05%	hr
Drug Clearance (Hepatocyte)	25.57	38.66%	uL.min-1.(10^6 cells)-1
Drug Clearance (Microsome)	40.10	70.84%	mL.min-1.g-1

Toxicity

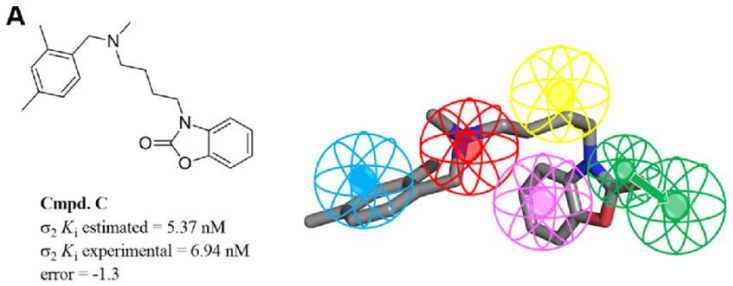
Property	Prediction	DrugBank Percentile	Units
hERG Blocking	0.65	69.99%	-
Clinical Toxicity	0.20	65.99%	-
Mutagenicity	0.60	88.02%	-
Drug Induced Liver Injury	0.75	67.74%	-
Carcinogenicity	0.02	10.62%	-
Acute Toxicity LD50	2.90	73.40%	log(1/(mol/kg))
Skin Reaction	0.21	22.64%	-
Androgen Receptor (Full Length)	0.08	83.68%	-
Androgen Receptor (Ligand Binding Domain)	0.12	91.47%	-
Aryl Hydrocarbon Receptor	0.11	73.09%	-

Virtual screening

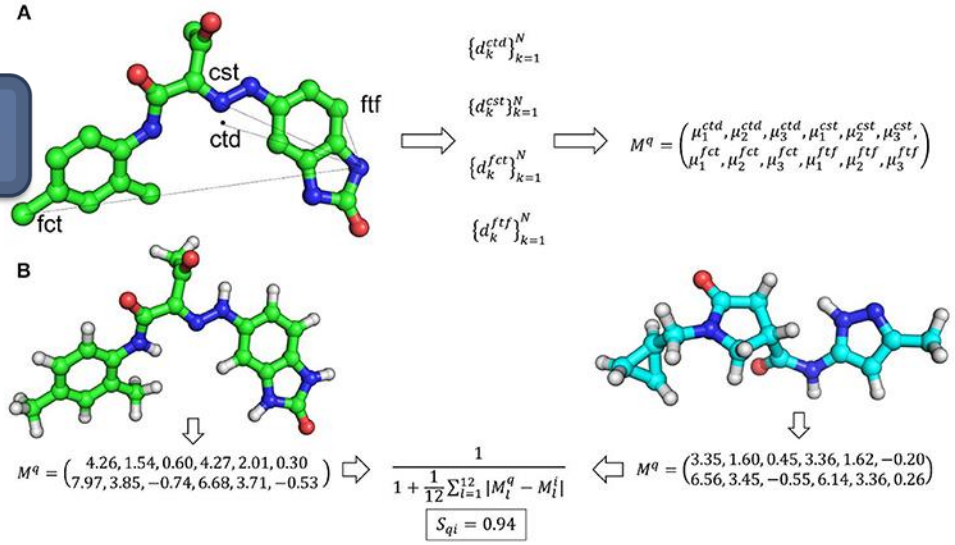
Molecular Docking



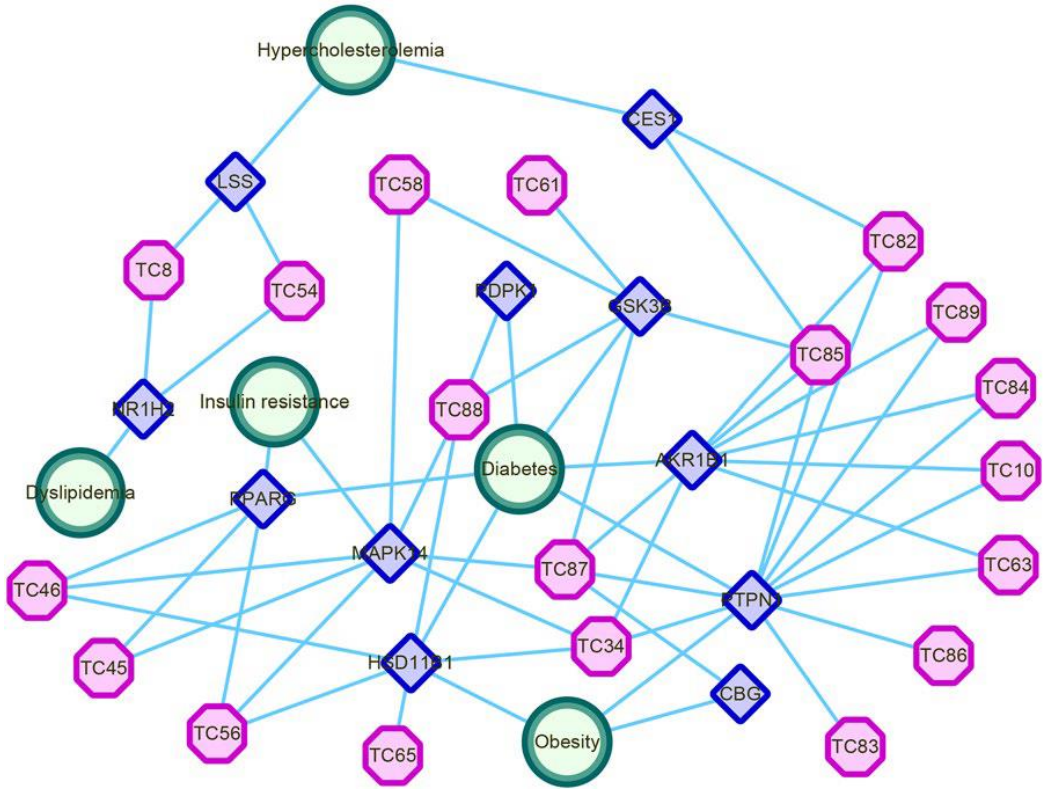
Pharmacophore modeling

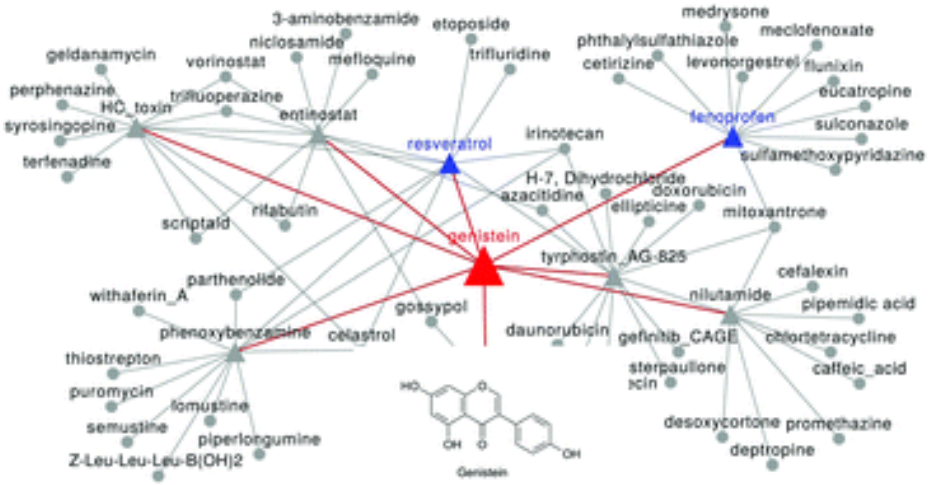


Small molecule shape similarity



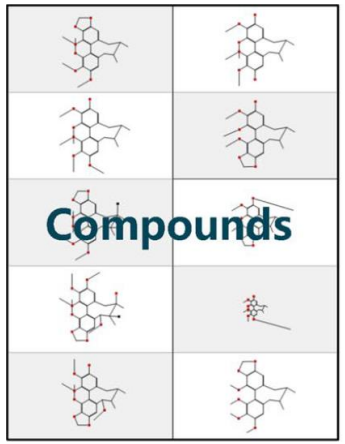
Network pharmacology





Conclusion

- This methodology is superior to conventional screening because it requires only structural information on compounds and can perform multi-target screening of a vast number of compounds in a relatively short period of time, which can drastically reduce the cost and time of drug development. Moreover, combining this in silico methodology with pertinent pharmacological experiments could significantly enhance the efficiency of medicinal plant research and new drug discovery.

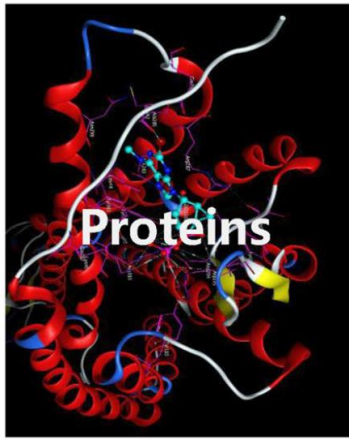


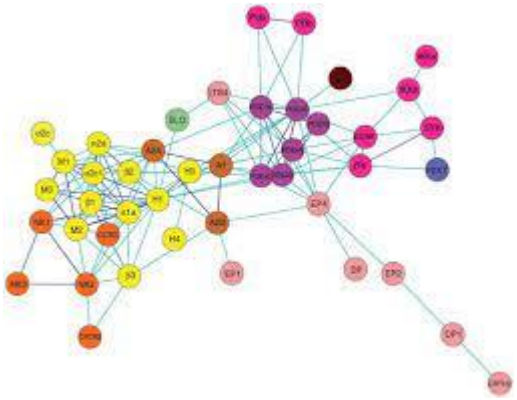
Virtual Screening Target Fishing

1 Molecular Docking

2 Pharmacophore Model

3 Molecular Shape Similarity





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