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In Silico Network Pharmacology Analysis of Bioactive Compounds from *Punica granatum* Pericarp

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Abstract:

Punica granatum, commonly known as pomegranate, is an important medicinal plant widely used in traditional systems of medicine due to its rich phytochemical composition and therapeutic potential. The pericarp (fruit peel) of the plant contains several biologically active phytoconstituents such as ellagic acid, gallic acid, quercetin, kaempferol, luteolin, punicalagin, and ursolic acid, which are reported to possess antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective activities. koThe present review article focuses on the network pharmacology-based evaluation of phytoconstituents present in the pericarp of Punica granatum. Network pharmacology is an emerging computational approach that helps in understanding the multi-component and multi-target therapeutic mechanisms of herbal medicines. In the present study, phytochemical information was collected from published scientific literature and databases such as Dr. Duke's Database and IMPPAT Database. Drug-likeness and pharmacokinetic properties of selected compounds were analyzed using MolSoft and SwissADME, while toxicity prediction was performed using Protox-II. The analysis suggested that major phytoconstituents of pomegranate pericarp exhibit favorable pharmacological properties and may interact with multiple biological targets associated with inflammation, oxidative stress, immune regulation, and cancer-related pathways. The study highlights the significance of network pharmacology in validating the traditional medicinal importance of pomegranate and provides scientific support for its future application in herbal drug discovery and development.

1. Introduction

Medicinal plants have been widely used since ancient times for the prevention and treatment of various diseases. Herbal medicines contain numerous bioactive compounds that exhibit therapeutic activities through multiple molecular mechanisms. In recent years, medicinal plants have gained considerable scientific attention due to their effectiveness, safety, affordability, and lower side effects compared to synthetic drugs. Punica granatum, commonly known as pomegranate or "Dalimb," is an important medicinal plant belonging to the family Lythraceae. The plant is widely cultivated in tropical and subtropical regions of the world and has been traditionally used in Ayurveda, Unani, and other traditional systems of medicine. Different parts of the plant including fruits, leaves, flowers, bark, and peel possess significant medicinal properties. Among them, the pericarp (fruit peel) is considered a rich source of bioactive phytochemicals with remarkable pharmacological activities.

The pericarp of Punica granatum contains several important phytoconstituents such as ellagic acid, gallic acid, quercetin, kaempferol, luteolin, punicalagin, and ursolic acid. These compounds are reported to possess antioxidant, anti-inflammatory, antimicrobial, anticancer, antiviral, hepatoprotective, and cardioprotective activities. The high polyphenolic content of pomegranate pericarp contributes significantly to its therapeutic potential and medicinal value. Conventional pharmacological approaches mainly focus on the interaction between a single drug and a single target. However, herbal medicines act through multiple compounds affecting numerous biological targets and signaling pathways simultaneously. Therefore, understanding the complex therapeutic mechanisms of medicinal plants requires an advanced systems-based approach.

Network pharmacology is an emerging interdisciplinary field that combines pharmacology, bioinformatics, systems biology, and computational science to study the interactions between phytoconstituents, target proteins, genes, and disease pathways. This approach helps in understanding the multi-component and multi-target therapeutic mechanisms of herbal medicines. Network pharmacology also assists in prediction of drug-likeness, toxicity, biological targets, and signaling pathways associated with bioactive compounds. In the present review article, a network pharmacology-based approach was employed to evaluate the therapeutic potential of phytoconstituents present in the pericarp of Punica granatum. Various bioinformatics databases and computational tools including Dr. Duke's Database, IMPPAT Database, MolSoft, SwissADME, and Protox-II were used for phytochemical analysis, drug-likeness prediction, pharmacokinetic evaluation, and toxicity assessment. The study aims to provide scientific evidence supporting the traditional medicinal uses of pomegranate pericarp and to explore its potential role in future herbal drug discovery and therapeutic development.

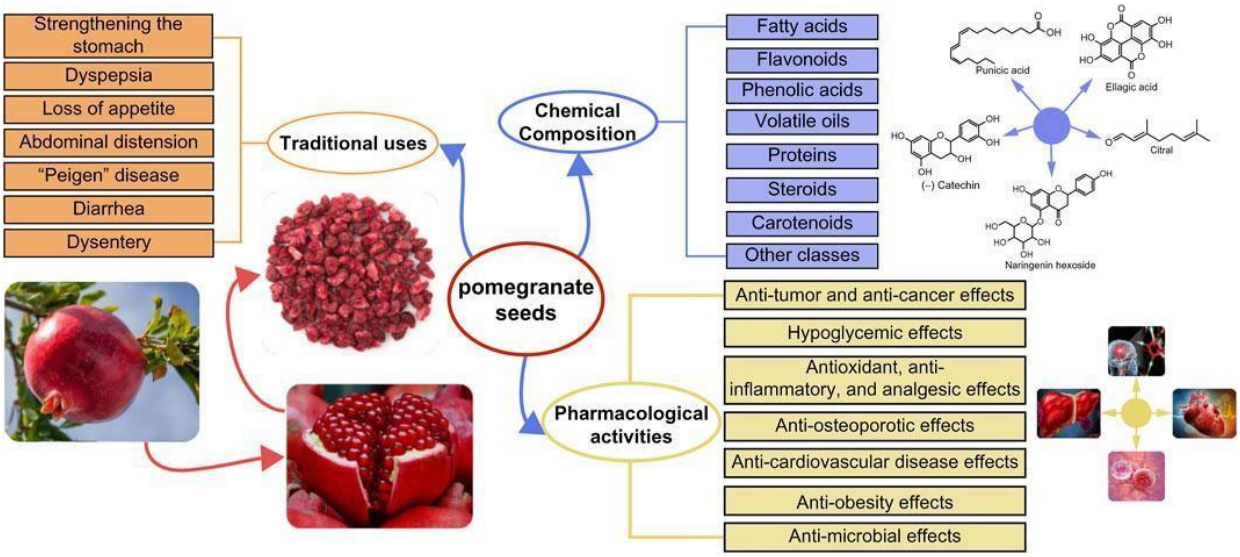
2. Uses

2.1 Medical Uses:

Traditional and Medicinal Uses of Punica granatum : Pomegranate has been used traditionally as a medicinal plant for several centuries. The fruit peel and bark are particularly valued because of their high tannin and polyphenol content. In Ayurveda, pomegranate is considered beneficial for maintaining digestive health and improving overall immunity.

Gastrointestinal Disorders :The peel extract has traditionally been used in the management of diarrhea, dysentery, intestinal worms, and gastric ulcers. The astringent nature of tannins helps reduce intestinal inflammation and fluid secretion.

Oral and Dental Care: Pomegranate peel preparations have been used as mouthwash and gargles to reduce dental plaque, gingivitis, and oral microbial infections. Antimicrobial compounds present in the peel inhibit the growth of oral pathogens.



Skin Disorders: Traditional medicine systems have utilized pomegranate extracts for wound healing, burns, acne, and skin infections due to their antimicrobial and antioxidant properties.

Cardiovascular Health: Consumption of pomegranate juice and peel extracts has been associated with reduction of oxidative stress and improvement of cardiovascular function. Polyphenols help reduce lipid peroxidation and improve endothelial health.

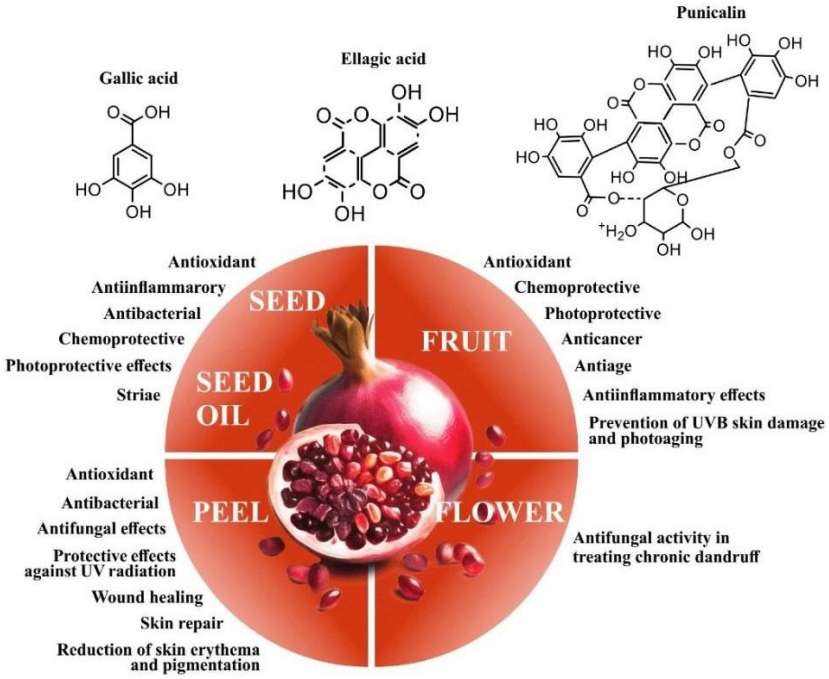
Diabetes Management: Studies suggest that pomegranate phytochemicals may help regulate blood glucose levels and reduce diabetic complications through antioxidant mechanisms.

2.2 Pharmacological Activities:

Pharmacological Activities of Punica granatum: Extensive pharmacological investigations have demonstrated that pomegranate peel exhibits multiple biological activities due to the synergistic action of its phytoconstituents.

Antioxidant Activity: Pomegranate pericarp contains abundant polyphenols and hydrolysable tannins that exhibit strong free radical scavenging activity. Ellagic acid and punicalagin help neutralize reactive oxygen species and protect cells against oxidative stress. Research studies have shown that pomegranate peel extract possesses higher antioxidant activity compared to pulp and seeds because of its elevated phenolic content.

Anti-inflammatory Activity: The phytochemicals present in pomegranate inhibit inflammatory mediators such as cyclooxygenase (COX), nitric oxide synthase, and pro-inflammatory cytokines. Punicalagin and ellagic acid suppress inflammatory pathways including NF-κB signaling. These activities may contribute to therapeutic benefits in arthritis, inflammatory bowel disease, and chronic inflammatory disorders.



Antimicrobial Activity: Pomegranate peel extracts exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and viruses. Studies have demonstrated inhibitory effects against pathogens such as:

- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida albicans*
- *Salmonella species*

The antimicrobial effect is mainly attributed to tannins and phenolic acids that disrupt microbial cell membranes.

Anticancer Activity: Several investigations have reported the anticancer potential of pomegranate phytoconstituents. Ellagic acid and punicalagin induce apoptosis, inhibit tumor proliferation, and reduce angiogenesis in different cancer cell lines.

Experimental studies have demonstrated activity against:

- breast cancer,
- prostate cancer,
- colon cancer,
- lung cancer.

Network pharmacology approaches indicate that pomegranate compounds can modulate multiple signaling pathways associated with cancer progression.

Antiviral Activity: Recent studies have highlighted antiviral properties of pomegranate peel compounds against influenza virus, herpes simplex virus, and SARS-CoV-2 related targets. Molecular docking investigations revealed strong binding affinity of punicalagin and ellagic acid toward viral proteins. This has increased scientific interest in the use of pomegranate phytochemicals for antiviral drug discovery.

Antidiabetic Activity: Pomegranate peel extracts may reduce hyperglycemia by improving insulin sensitivity and reducing oxidative stress. Polyphenolic compounds inhibit carbohydrate metabolizing enzymes and help regulate glucose metabolism.

Hepatoprotective Activity: The antioxidant-rich peel extract protects liver tissue from chemical-induced toxicity and oxidative damage. Studies indicate improvement in liver enzyme profiles following treatment with pomegranate extract.

2.3 Other Uses:

Other Applications of Punica granatum : Apart from medicinal significance, pomegranate peel has several industrial and commercial applications.

Food Industry: Pomegranate peel powder is used as a natural antioxidant and preservative in food products. It improves shelf life by preventing oxidative spoilage.

Cosmetic Industry: Due to its antioxidant and anti-aging properties, pomegranate extract is incorporated into creams, lotions, soaps, and skincare products.

Nutraceutical Applications: Pomegranate peel extracts are utilized in dietary supplements and herbal formulations because of their health-promoting effects.

Dye and Tanning Industry: The high tannin content of pomegranate peel makes it useful in leather tanning and natural dye production.

Agricultural Uses :Pomegranate peel waste has been explored for biofertilizer preparation and eco-friendly pest control formulations.

3. Aim and Objective of Work

Aim: The aim of the present review article is to evaluate the therapeutic potential of phytoconstituents present in the pericarp of Punica granatum using a network pharmacology approach.

Objectives:

1. To identify major phytochemical constituents present in the pericarp of Punica granatum.
2. To study the pharmacological and medicinal importance of selected phytoconstituents.
3. To evaluate drug-likeness properties of phytochemicals using MolSoft and SwissADME.
4. To predict toxicity profiles of phytoconstituents using Protox-II.
5. To understand the multi-target therapeutic mechanisms of pomegranate phytochemicals through network pharmacology.
6. To provide scientific support for the traditional medicinal uses of Punica granatum pericarp.

4. Plan of Work

Selection of Plant Material (Punica granatum Pericarp)
↓
Collection and Authentication of Plant
↓
Drying and Powder Preparation
↓ Extraction of Pericarp
↓ Identification of Phytoconstituents
using Dr. Duke's and IMPPAT Database
↓
Retrieval of Chemical Structures from PubChem Database
↓
Drug-Likeness Analysis using MolSoft and SwissADME
↓
Toxicity Prediction using Protox-II
↓
Target Prediction and Network Analysis
↓
Results and Discussion
↓
Conclusion and Future Scope

5. Methodology:

The present review article was carried out using a network pharmacology approach to evaluate the therapeutic potential of phytoconstituents present in the pericarp of Punica granatum. The methodology included plant procurement, authentication, extraction, phytochemical identification, drug-likeness analysis, and toxicity prediction using various bioinformatics databases and computational tools.

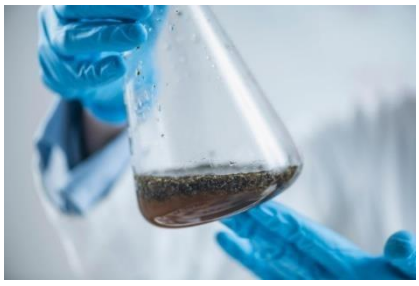
5.1 Plant Procurement and Authentication: Fresh fruits of Punica granatum were procured from local market sources and agricultural fields. Healthy and disease-free fruits were selected for the study. The plant material was authenticated using standard botanical characteristics and available botanical literature.

5.2 Collection and Preparation of Pericarp : The pericarp (fruit peel) was separated manually from fresh fruits and washed thoroughly with distilled water to remove dust and impurities. The peels were shade dried at room temperature for several days to preserve heat-sensitive phytoconstituents. After complete drying, the material was powdered using a mechanical grinder and stored in airtight containers for further studies.

5.3 Extraction of Plant Material: The dried pericarp powder was extracted using ethanol or methanol by maceration method. The powdered material was soaked in solvent for about 72 hours with occasional shaking to enhance extraction of phytochemicals. The extract was filtered using Whatman filter paper and concentrated at low temperature to obtain crude extract

5.4 Identification of Phytoconstituents:

Software/Database	Application
Dr. Duke's Database	Phytochemical identification
IMPPAT Database	Medicinal plant information
MolSoft	Drug-likeness prediction
SwissADME	ADMET analysis
Protox-II	Toxicity prediction
PubChem	Chemical structure retrieval



5.5 Network Pharmacology Analysis: Network pharmacology analysis was performed to understand the multi-target therapeutic mechanisms of phytochemicals. The study focused on identifying interactions

between phytoconstituents and biological targets associated with inflammation, oxidative stress, immune response, and cancer-related pathways.

Methodology Flowchart

Plant Procurement
↓
Authentication of Plant
↓
Collection of Pericarp
↓
Drying and Powder Preparation
↓
Extraction by Maceration
↓
Identification of Phytoconstituents
↓
Drug-Likeness Analysis
↓
ADMET Evaluation
↓
Toxicity Prediction
↓
Network Pharmacology Analysis

6. Preliminary Phytochemical Screening of Punica granatum Pericarp Extract: : Preliminary phytochemical screening was carried out to identify the presence of various bioactive phytoconstituents in the pericarp extract of Punica granatum. Qualitative chemical tests were performed using standard pharmacogenetic procedures to detect important secondary metabolites such as alkaloids, flavonoids, tannins, phenolic compounds, glycosides, saponins, carbohydrates, and proteins. The phytochemical constituents present in the extract are responsible for the diverse pharmacological activities of pomegranate pericarp including antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer properties.

6.1 Procedure for Phytochemical Screening: A small quantity of the concentrated pericarp extract was dissolved in suitable solvents and subjected to different qualitative chemical tests according to standard methods. The appearance of characteristic color changes or precipitates indicated the presence of specific phytoconstituents.

6.2 Qualitative Phytochemical Tests:

Phytoconstituent	Test Performed	Observation	Result
Alkaloids	Dragendorff's test	Reddish-brown precipitate	Present
Flavonoids	Alkaline Reagent test	Yellow color disappears	Present
Phenolics	Ferric chloride test	Blue-green color	Present
Tannins	Ferric chloride test	Blue black color	Present
Saponins	Foam test	Stable foam	Present
Glycosides	Keller–Killiani test	Brown ring	Present
Carbohydrates	Molisch's test	Violet ring	Present
Proteins	Biuret test	Violet color	Present

6.3 Significance of Phytochemical Screening: The preliminary phytochemical analysis confirmed the presence of several important secondary metabolites in the pericarp extract of Punica granatum. These phytochemicals contribute significantly to the medicinal and pharmacological properties of the plant. Polyphenols and tannins such as punicalagin and ellagic acid are considered major bioactive constituents responsible for antioxidant and therapeutic activities. The identified phytoconstituents may interact with multiple biological targets, supporting the use of network pharmacology and molecular docking studies for further investigation.

Flowchart:

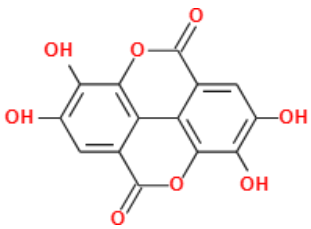
Extract Preparation
↓
Addition of Specific Reagents
↓
Color Change/Precipitate Formation
↓
Identification of Phytoconstituents
↓
Interpretation of Results

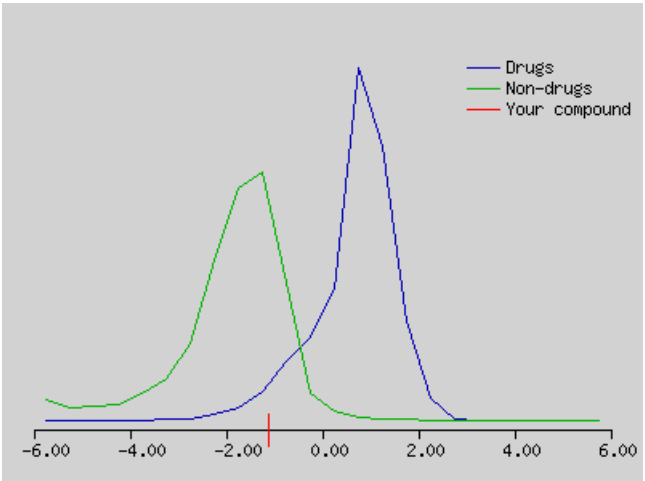
Summary Table of Phytochemicals

Phytochemical	Chemical Class	Major Pharmacological Activity
Ellagic acid	Polyphenol	Antioxidant, anticancer
Gallic acid	Phenolic acid	Antimicrobial, antioxidant
Punicalagin	Tannin	Anti-inflammatory, antioxidant
Quercetin	Flavonoid	Antiviral, antioxidant
Kaempferol	Flavonoid	Cardioprotective, anticancer
Luteolin	Flavonoid	Neuroprotective,anti-inflammatory
Ursolic acid	Triterpenoid	Hepatoprotective, anticancer
Catechin	Flavanol	Antioxidant, cardioprotective

7. Toxicity Predication:

1. ELLAGIC ACID





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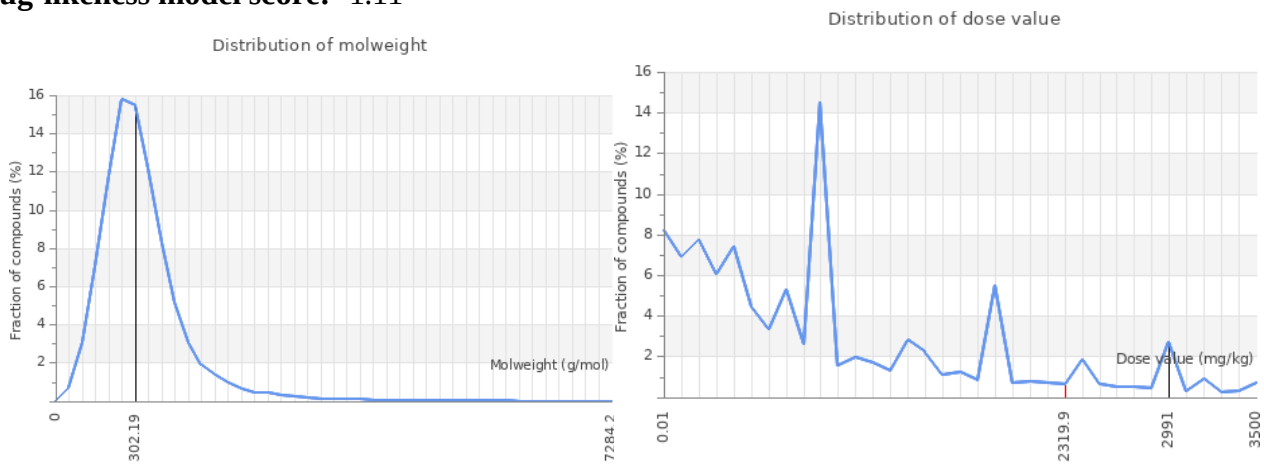


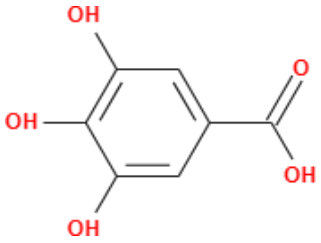
Predicted LD50: 2991mg/kg Predicted Toxicity Class: 4 Average similarity: 83.33% Prediction accuracy: 70.97%

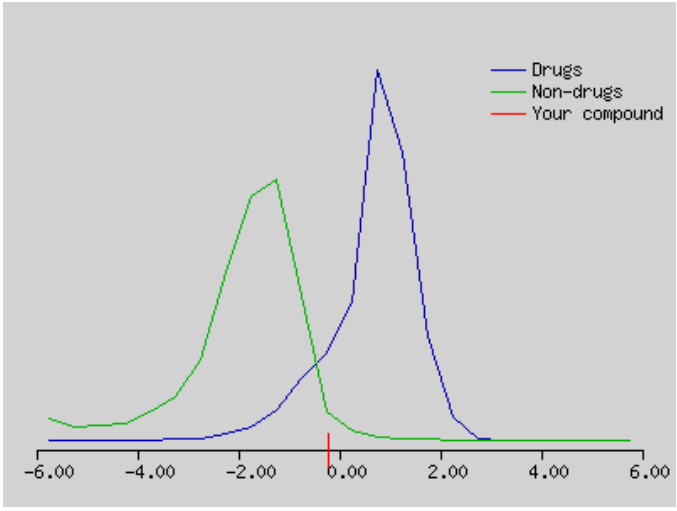
ProTox-3.0 - Prediction of Toxicity of chemicals

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.83
Organ toxicity	Neurotoxicity	neuro	Inactive	0.91
Organ toxicity	Nephrotoxicity	nephro	Active	0.58
Organ toxicity	Respiratory toxicity	respi	Active	0.84
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.76
Toxicity end points	Carcinogenicity	carcino	Active	0.59
Toxicity end points	Immunotoxicity	immuno	Inactive	0.81
Toxicity end points	Mutagenicity	mutagen	Inactive	0.84
Toxicity end points	Cytotoxicity	cyto	Inactive	0.90
Toxicity end points	BBB-barrier	bbb	Active	0.60
Toxicity end points	Ecotoxicity	eco	Inactive	0.67
Toxicity end points	Nutritional toxicity	nutri	Active	0.71
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.87
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99

Tox21-Nuclear signalling pathways	receptor	Androgen Receptor Ligand Binding Domain (AR-LBD)	Nr ar_lbd	Inactive	0.81
Tox21-Nuclear signalling pathways	receptor	Aromatase	nr_aromatase	Inactive	0.99
Tox21-Nuclear signalling pathways	receptor	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.94
Tox21-Nuclear signalling pathways	receptor	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.95
Tox21-Nuclear signalling pathways	receptor	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress pathways	response	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress pathways	response	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress pathways	response	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.86
Tox21-Stress pathways	response	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.95
Tox21-Stress pathways	response	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.97
Molecular Initiating Events		Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Initiating Events		Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Initiating Events		Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Initiating Events		Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Initiating Events		GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Initiating Events		Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmda r	Inactive	0.92

2. GALLIC ACID





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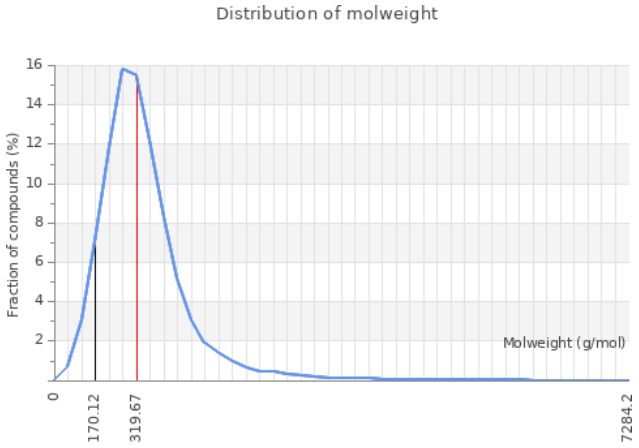
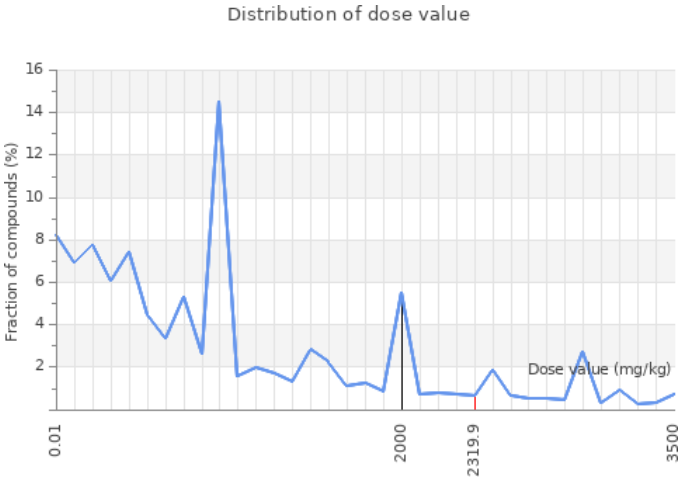
Drug-likeness model score: -0.22





Predicted LD50: 2000mg/kg

Predicted Toxicity Class: 4

Average similarity: 84.82%

Prediction accuracy: 70.97%

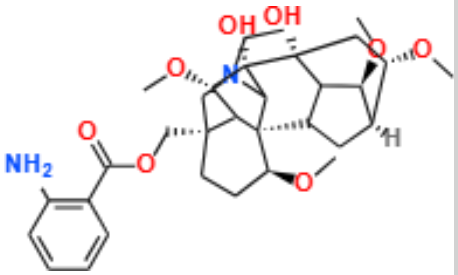
ProTox-3.0 - Prediction of Toxicity of chemicals

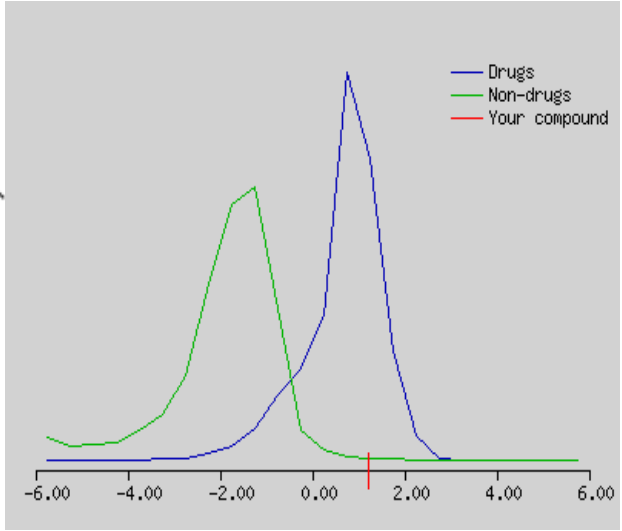
Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.61
Organ toxicity	Neurotoxicity	neuro	Inactive	0.88

Organ toxicity	Nephrotoxicity	nephro	Active	0.69
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.89
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.94
Toxicity end points	Cytotoxicity	cyto	Inactive	0.91
Toxicity end points	BBB-barrier	bbb	Active	0.67
Toxicity end points	Ecotoxicity	eco	Inactive	0.80
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.83
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.90
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.89
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.90
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.85
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.85
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.97
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.97
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.96

Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92

3. INULIN





Drug-likeness model score: 1.23

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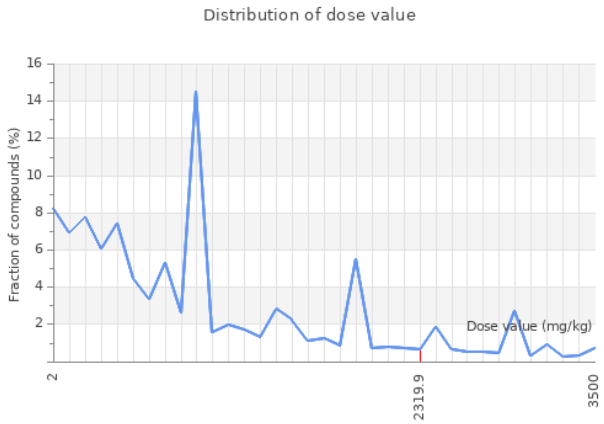
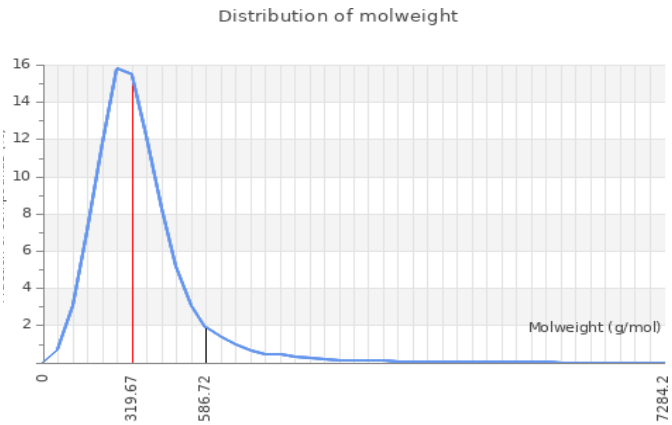




Predicted LD50: 2mg/kg

Predicted Toxicity Class: 1

Average similarity: 81.73%

Prediction accuracy: 70.97%

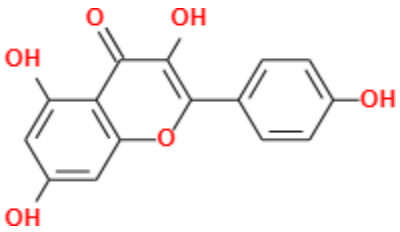
ProTox-3.0 - Prediction of Toxicity of chemicals

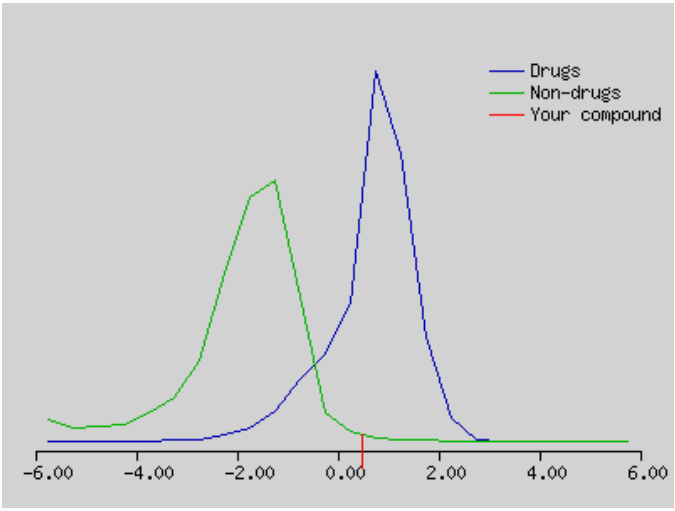
Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.69
Organ toxicity	Neurotoxicity	neuro	Active	0.87
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.90
Organ toxicity	Respiratory toxicity	respi	Active	0.98
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.77
Toxicity end points	Carcinogenicity	carcino	Inactive	0.62
Toxicity end points	Immunotoxicity	immuno	Active	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.97
Toxicity end points	Cytotoxicity	cyto	Inactive	0.93
Toxicity end points	Ecotoxicity	eco	Active	0.73
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.74
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.99
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.88
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.88
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.70
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.96
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.55
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.75
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.75
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.93

Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.76
Molecular Initiating Events	Glutamate receptor (NMDAR)	N-methyl-D-aspartate mie_nmdar	Inactive	0.89

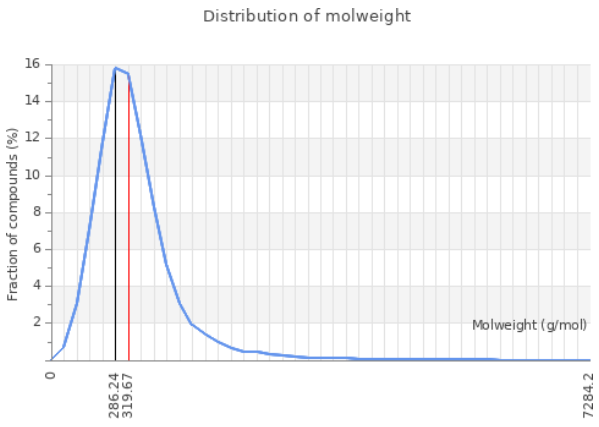
Value of input compound
Mean value of dataset

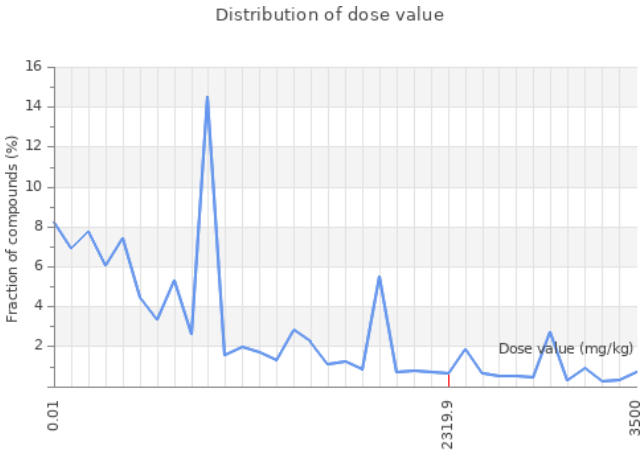
4. KAEMPFEROL





Drug-likeness model
score: 0.50





Predicted LD50: 3919mg/kg

Predicted Toxicity Class: 5

Average similarity: 82.46%

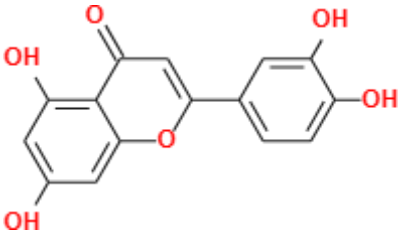
Prediction accuracy: 70.97%

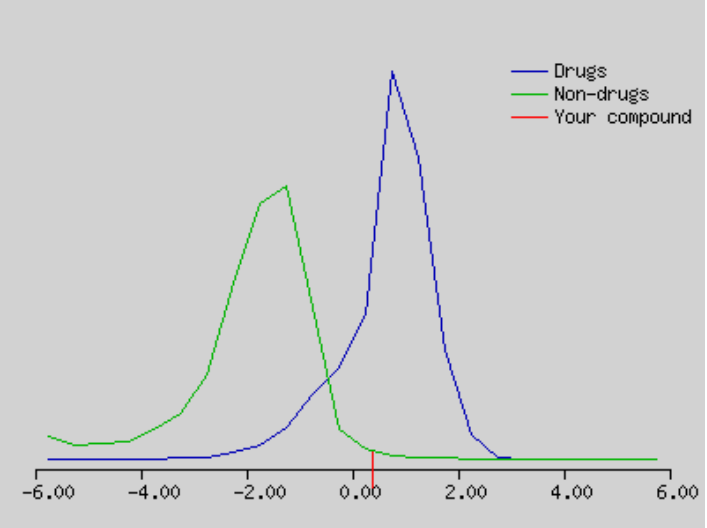
ProTox-3.0 - Prediction of Toxicity of chemicals

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.68
Organ toxicity	Neurotoxicity	neuro	Inactive	0.89
Organ toxicity	Nephrotoxicity	nephro	Active	0.62
Organ toxicity	Respiratory toxicity	respi	Active	0.83
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.91
Toxicity end points	Carcinogenicity	carcino	Inactive	0.72
Toxicity end points	Immunotoxicity	immuno	Inactive	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.52
Toxicity end points	Cytotoxicity	cyto	Inactive	0.98
Toxicity end points	BBB-barrier	bbb	Active	0.57
Toxicity end points	Ecotoxicity	eco	Inactive	0.51
Toxicity end points	Clinical toxicity	clinical	Inactive	0.54
Toxicity end points	Nutritional toxicity	nutri	Active	0.66
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Active	0.96
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Active	0.95
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	1.0
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.92
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.92
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.97

Molecular Events	Initiating	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Events	Initiating	GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Events	Initiating	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92

5. LUTEOLIN

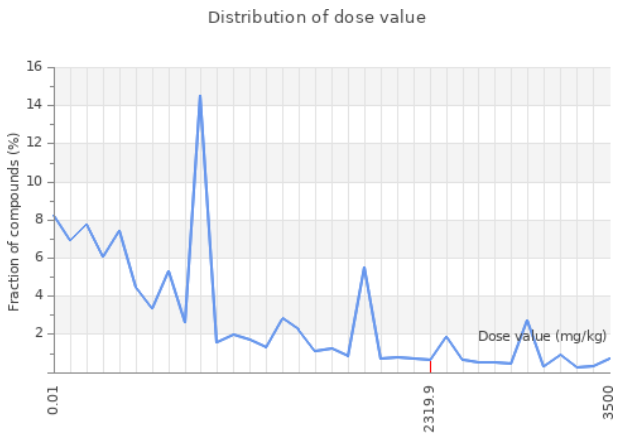


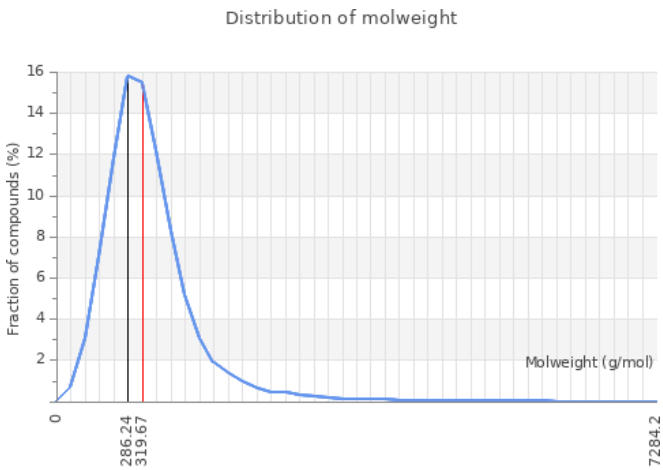


Drug-likeness model score: 0.38

Value of input compound

Mean value of dataset





Predicted LD50: 3919mg/kg

Predicted Toxicity Class: 5

Average similarity: 80.53%

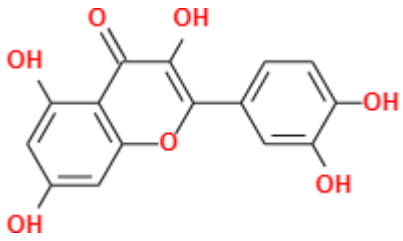
Prediction accuracy: 70.97%

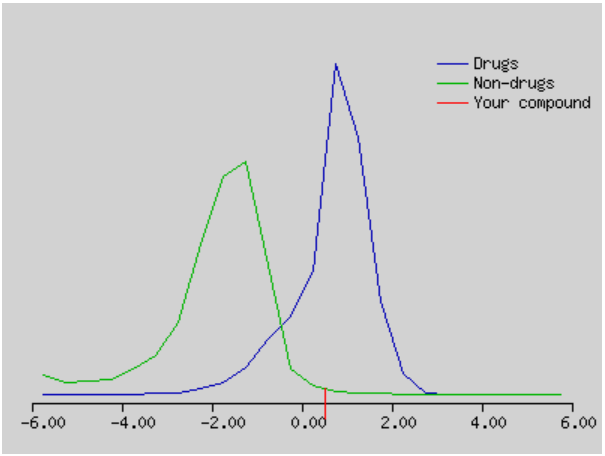
ProTox-3.0 - Prediction of Toxicity of chemicals

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.69
Organ toxicity	Neurotoxicity	neuro	Inactive	0.89
Organ toxicity	Nephrotoxicity	nephro	Active	0.62
Organ toxicity	Respiratory toxicity	respi	Active	0.83
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.99
Toxicity end points	Carcinogenicity	carcino	Active	0.68
Toxicity end points	Immunotoxicity	immuno	Inactive	0.97
Toxicity end points	Mutagenicity	mutagen	Active	0.51
Toxicity end points	Cytotoxicity	cyto	Inactive	0.99
Toxicity end points	BBB-barrier	bbb	Active	0.53
Toxicity end points	Ecotoxicity	eco	Inactive	0.53
Toxicity end points	Clinical toxicity	clinical	Inactive	0.53
Toxicity end points	Nutritional toxicity	nutri	Active	0.63
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Active	0.91
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97

Tox21-Nuclear receptor signalling pathways		Aromatase	nr_aromatase	Inactive	0.91
Tox21-Nuclear receptor signalling pathways		Estrogen Receptor Alpha (ER)	nr_er	Active	0.87
Tox21-Nuclear receptor signalling pathways		Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Active	0.95
Tox21-Nuclear receptor signalling pathways		Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.98
Tox21-Stress pathways	response	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress pathways	response	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress pathways	response	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	1.0
Tox21-Stress pathways	response	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.97
Tox21-Stress pathways	response	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Events	Initiating	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Events	Initiating	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Events	Initiating	Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Events	Initiating	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Events	Initiating	GABA receptor (GABAR)	mie_gabar	Inactive	0.96

6 .QUERCETIN

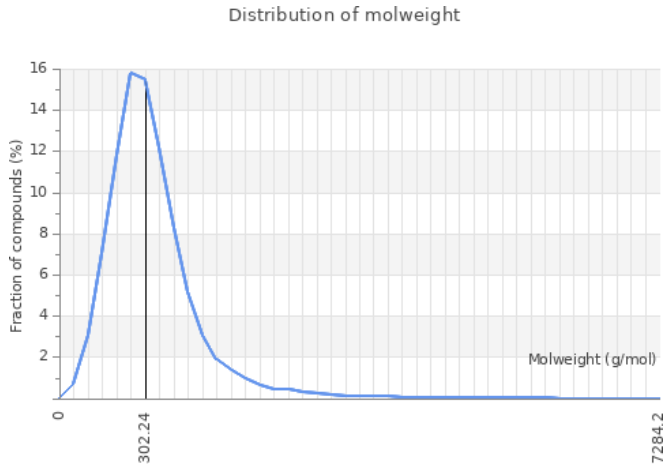


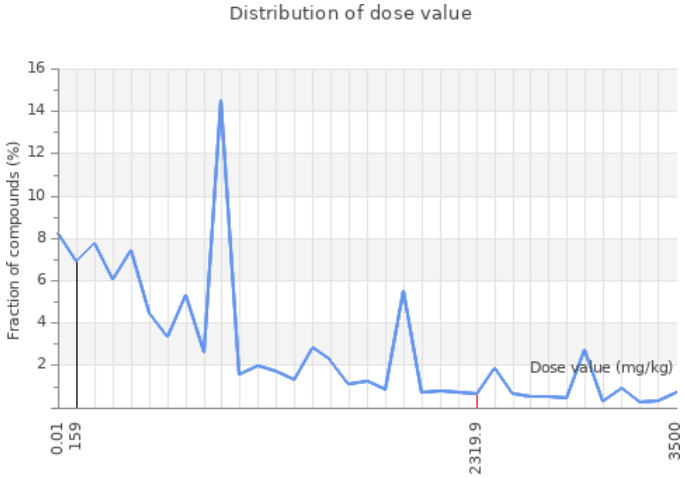


Drug-likeness model score: 0.5

Value of input compound

Mean value of dataset





Predicted LD50: 159mg/kg

Predicted Toxicity Class: 3

Average similarity: 100%

Prediction accuracy: 100%

ProTox-3.0 - Prediction of Toxicity of chemicals

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.69

Organ toxicity	Neurotoxicity	neuro	Inactive	0.89
Organ toxicity	Nephrotoxicity	nephro	Active	0.62
Organ toxicity	Respiratory toxicity	respi	Active	0.83
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.99
Toxicity end points	Carcinogenicity	carcino	Active	0.68
Toxicity end points	Immunotoxicity	immuno	Inactive	0.87
Toxicity end points	Cytotoxicity	cyto	Inactive	0.99

Toxicity end points	BBB-barrier	bbb	Active	0.53
Toxicity end points	Ecotoxicity	eco	Inactive	0.53
Toxicity end points	Clinical toxicity	clinical	Inactive	0.53
Toxicity end points	Nutritional toxicity	nutri	Active	0.63
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Active	0.91
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.87
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Active	0.95
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.98
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Active	1.0
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.97
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Events	Initiating Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Events	Initiating Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Events	Initiating Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Events	Initiating Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Events	Initiating GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Events	Initiating Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92

6.2Toxicity Predication Result:

Phytochemical	Drug-Likeness Score	Toxicity Class	Major Toxicity Prediction
Ellagic Acid	-1.11	Class IV	Slight nephrotoxicity and respiratory toxicity predicted
Gallic Acid	-0.22	Class IV	Mild nephrotoxicity observed
Inulin	1.23	Class I	High toxicity with hepatotoxicity and neurotoxicity
Kaempferol	0.50	Class V	Low toxicity profile
Luteolin	0.38	Class V	Low toxicity with mild carcinogenicity prediction
Quercetin	0.50	Class III	Moderate toxicity with respiratory toxicity prediction

7. Interpretation of Toxicity Classes:

Toxicity Class	Toxicity Level
Class I	Extremely toxic
Class III	Moderately toxic
Class IV	Slightly toxic
Class V	Practically non-toxic

The toxicity prediction study revealed that kaempferol and luteolin possess comparatively safer toxicity profiles with high LD50 values and low toxicity classes. Ellagic acid and gallic acid showed slight toxicity with limited organ toxicity effects. Quercetin demonstrated moderate toxicity, whereas inulin showed high predicted toxicity with multiple active toxicological endpoints. Overall, most phytochemicals exhibited acceptable safety profiles for further pharmacological and network pharmacology studies.

8. Result and Discussion

8.1 Result:

Parameter	Observation
Major phytochemicals identified	Ellagic acid, quercetin, gallic acid, kaempferol, luteolin
Drug-likeness analysis	Favorable molecular properties observed
ADMET evaluation	Good pharmacokinetic characteristics
Toxicity prediction	Low toxicity profile
Network pharmacology findings	Multi-target therapeutic interactions

8.2 Discussion:

The present review article highlights the therapeutic significance of phytoconstituents present in the pericarp of Punica granatum and their importance in network pharmacology studies. Pomegranate pericarp is rich in polyphenols, flavonoids, tannins, and phenolic acids which contribute significantly to its medicinal properties. Major phytochemicals such as ellagic acid, gallic acid, quercetin, kaempferol, luteolin, and ursolic acid were identified through literature survey and phytochemical databases including Dr. Duke's Database and IMPPAT Database. These compounds are reported to exhibit strong antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective activities. Drug-likeness and pharmacokinetic evaluation performed using MolSoft and SwissADME suggested that several phytochemicals possess favorable molecular properties and acceptable bioavailability. Compounds such as quercetin,
kaempferol, and luteolin showed good compliance with Lipinski's rule of five, indicating their potential suitability as therapeutic agents. Toxicity prediction studies carried out using Protox-II indicated that most selected phytochemicals possess comparatively low toxicity profiles, supporting their safety for further pharmacological investigations. The network pharmacology approach demonstrated that pomegranate phytoconstituents may interact with multiple molecular targets involved in inflammation, oxidative stress, apoptosis, immune regulation, and cancer-associated pathways. This supports the concept that herbal medicines exert therapeutic effects through multi-component and multi-target mechanisms rather than single-target interactions. Overall, the present findings scientifically validate the traditional medicinal importance of Punica granatum pericarp and highlight its potential role in herbal drug discovery and future therapeutic development

9. Conclusion:

The present review article highlighted the therapeutic importance of phytoconstituents present in the pericarp of Punica granatum through a network pharmacology approach. Pomegranate pericarp was found to contain several important bioactive compounds including ellagic acid, gallic acid, quercetin, kaempferol, luteolin, punicalagin, and ursolic acid, which possess significant antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective activities.
Computational analysis using various bioinformatics tools such as Dr. Duke's Database, IMPPAT Database, MolSoft, SwissADME, and Protox-II demonstrated favorable drug-likeness, pharmacokinetic properties, and acceptable toxicity profiles of selected phytoconstituents. The network pharmacology approach further suggested that these phytochemicals interact with multiple biological targets and signaling pathways associated with inflammation, oxidative stress, immune response, and cancer-related mechanisms. The study scientifically supports the traditional medicinal uses of pomegranate pericarp and emphasizes its potential role in herbal drug discovery and therapeutic development.

10. Future Scope:

1. Advanced network pharmacology studies can be carried out to identify additional molecular targets and signaling pathways associated with pomegranate phytoconstituents.
2. Experimental in vitro and in vivo studies may be performed to validate the predicted pharmacological activities.
3. Clinical investigations can be conducted to evaluate the therapeutic efficacy and safety of pomegranate-based herbal formulations in humans.
4. Novel herbal products and nutraceutical formulations may be developed using bioactive compounds present in Punica granatum pericarp.
5. Further studies on synergistic interactions among phytochemicals may provide better understanding of multi-target therapeutic mechanisms.
6. Computational approaches such as molecular docking and pathway enrichment analysis may be incorporated in future studies for deeper pharmacological evaluation.

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