A Network Pharmacology Approach to Elucidate the Anti-inflammatory Effects of Ellagic Acid

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Abstract

Ellagic acid (EA) is a naturally occurring polyphenolic compound with antioxidant properties found in a variety of fruits and vegetables, including strawberries, raspberries, pomegranates, and nuts such as pecans and walnuts. EA appears to have potential health benefits, but more research is needed to fully understand its effects and mechanisms and how it can be used safely and effectively as a complimentary medicine. Notably, accumulating evidence demonstrates the anti-inflammatory effects of EA, but a unified mechanism is not well understood. A network pharmacology approach was used to understand the anti-inflammatory effects of EA. It was revealed that there are 52 targets of EA that are related to inflammation. GO and KEGG revealed many relevant signaling pathways, diseases relevant to inflammation. Topological analysis determined 10 important targets that are AKT1, VEGFA, TNF, MAPK3, ALB, SELP, MMP9, MMP2, PTGS2, and ICAM1. Molecular docking and molecular dynamics simulations were employed to help determine AKT1, PTGS2, VEGFA, MAPK3 as the most probable targets of EA with molecular mechanics Poisson-Boltzmann surface area binding energies of -82.37 ± 159.8, -52.06 ± 171.4, -19.24 ±79.02, and -13.98 ± 149.6 kcal/mol, respectively. Overall, this paper confirmed the anti-inflammatory effects of EA demonstrated in previous studies and pinpointed very probably targets of EA.

Abbreviations

AKT1	AKT serine/threonine kinase 1
ALB	Albumin
DMNC	Density of Maximum Neighborhood Component
EA	Ellagic Acid
EPC	Edge Percolated Component
GO	Gene Ontology
HIF	Hypoxia-inducible Factor
ICAM	Intercellular Adhesion Molecule
IL	Interleukin
KEGG	Intercellular Adhesion Molecule
MAPK	Mitogen-activated Protein Kinase
MCC	Maximal Clique Centrality
MMP	Matrix Metallopeptidase
MM-PBSA	Molecular Mechanics Poisson-Boltzmann Surface Area
MNC	Maximum Neighborhood Component
NF-κB	Nuclear factor kappa B
PPI	Protein Protein Interaction
PTGS	Prostaglandin-endoperoxide Synthase 2
SELP	Selectin P
TNF	(TNF-α) Tumor Necrosis Factor alpha
VEGFA	Vascular Endothelial Growth Factor A

Introduction

Ellagic acid (EA) is a naturally occurring polyphenolic compound with antioxidant properties found in a variety of fruits and vegetables, including strawberries, raspberries, pomegranates, and nuts such as pecans and walnuts (Baliga et al., 2019; Sharifi-Rad et al., 2022). EA has been studied for its potential health benefits, including its ability to support the immune system and protect cells from damage (Sharifi-Rad et al., 2022). Some research has suggested that EA may have anti-inflammatory and chemopreventive effects, which could potentially help to reduce the risk of chronic diseases such as heart disease and cancer (BenSaad et al., 2017; Päivärinta et al., 2006; Ridker, 2017). For instance, in a study model of culture of primary human gingival epithelial cells, EA was demonstrated to regulate the oral innate immunity via increasing the expression of chemokine ligand 5, IL-2, IL-1β and decreasing the expression of IL-6, IL-8, and TNF (Promsong et al., 2015). In terms of its potential anticancer effects, some research has suggested that ellagic acid may help to inhibit the growth of cancer cells and induce cell death in certain types of cancer, such as breast, colon, and prostate cancer (Ceci et al., 2018). In another instance, transcriptional profiling using microarray and functional analysis on Caco-2 cells exposed to EA revealed that EA could affect the expression of growth factor receptors (fibroblast growth factor receptor 2, epidermal growth factor receptor), oncogenes (K-Ras, c-Myc), and tumor suppressors (dual specificity phosphatase 6, Fos) and of genes involved in cell cycle (cyclin B1, cyclin B1 Interacting Protein 1) (González-Sarrías et al., 2009). EA is also claimed to support a variety of other health goals, including weight loss, cardiovascular health, and improved digestion (Kang et al., 2016). More research into the mechanism of this compound is needed to fully understand these potential effects and how anti-inflammatory, anti-cancer, or metabolic syndrome preventive effects of EA can be utilized. Overall, EA appears to have

potential health benefits, but more research is needed to fully understand its effects and how it can be used safely and effectively as a complimentary medicine.

On another note, inflammation is a natural process that occurs in the body in response to injury or infection (L. Chen et al., 2018). It is characterized by swelling, redness, warmth, and pain, and is a crucial part of the body's immune response (Scott, 2004). When the body is injured or infected, immune cells are activated to help fight off the infection or repair the damage (Fang et al., 2018; Luster et al., 2005). This process involves the release of various chemicals and signaling molecules that cause inflammation in the affected area. Inflammation is important because it helps to protect the body from harm and promote healing. However, chronic inflammation, which is a long-term, persistent form of inflammation, can be harmful and contribute to the development of chronic diseases such as heart disease, diabetes, and cancer (Furman et al., 2019). Chronic inflammation is often caused by underlying conditions such as obesity, smoking, and high levels of stress, and can also be triggered by certain foods and environmental factors (Bosma-den Boer et al., 2012). There is increasing evidence to suggest that chronic inflammation is a key factor in the development of many chronic diseases. For instance, cardiovascular diseases are often caused by inflammation in the arteries, which can lead to the build-up of plaque and eventually cause a heart attack or stroke (Kabbany et al., 2016). Similarly, inflammation in the pancreas may contribute to the development of diabetes, and inflammation in the colon may increase the risk of colon cancer (Terzić et al., 2010). Studying inflammation is important because it helps to understand the underlying causes of chronic diseases and may lead to the development of new treatments and prevention strategies. Certain medications, such as nonsteroidal anti-inflammatory drugs and corticosteroids, can help to reduce inflammation and pain or may be used to treat conditions such as arthritis (Del Grossi

Moura et al., 2018). However, their misusage has been associated with adverse events such as gastrointestinal ulcers, serious cardiovascular events, or hypertension (Vonkeman & van de Laar, 2010; Yasir et al., 2022). It should be noted that lifestyle changes such as eating a healthy diet, exercising regularly, and managing stress may also help to reduce inflammation and lower the risk of chronic diseases (Margină et al., 2020). EA, with accumulating evidence of anti-inflammatory properties, can be easily found as a part of a healthy, plant-based diet (Kang et al., 2016). Herein, a network pharmacology approach, integrated with molecular docking and molecular dynamics simulation, is utilized to elucidate the mechanisms underlying anti-inflammatory properties of EA.

Results and Discussion

1. Network Construction and Analysis

The retrieval of EA target proteins and target proteins for inflammation results in 157 and 886 target proteins, respectively (**Figure 1**). There were 52 overlapped proteins, representing potential therapeutic targets of EA for its anti-inflammatory properties. A PPI network of 52 overlapped was constructed and resulting in 325 number of edges, 12.5 average node degree, 0.688 average local clustering coefficient, as well as a PPI enrichment p-value of less than 1.0e-16, indicating that the proteins are biologically connected (**Figure 1**).

The 5 most significant GO Biological Process enriched pathways include: response to organic substance, response to oxygen-containing compound, response to lipid, and response to chemical (**Figure 2A**). The 5 most significant GO Molecular Function enriched pathways include: identical protein binding, protein binding, signaling receptor binding, enzyme binding, ion binding (**Figure 2A**). The 5 most significant GO Cellular Component enriched pathways include: vesicle lumen, endomembrane system, secretory granule, secretory granule lumen, and

membrane raft (**Figure 2A**). Interestingly, lipid regulation and inflammation have an intimate relationship. Particularly, abnormalities in lipid profile or regulation can lead to abnormalities in inflammatory responses, and the reverse is also true in that alterations of inflammatory signaling (in the context of metabolic diseases such as diabetes or atherosclerosis) can result in changes of lipid metabolism in liver, skeletal muscle, macrophage, or adipose tissue (Glass & Olefsky, 2012). In a murine basal diet model, EA supplementation decreased total cholesterol, low-density lipoprotein, and the abundance of acetyl-CoA carboxylase while increasing high-density lipoprotein and the abundances of phospho-hormone-sensitive lipase, carnitine palmitoyl transferase 1B, and peroxisome proliferator-activated receptor alpha protein (Xu et al., 2021). In a randomized double-blind clinical trial, patients with type 2 diabetes consuming 180 mg of EA daily for 8 weeks demonstrated a decrease in inflammatory markers (i.e, TNF, and IL-6), total cholesterol, triglycerides, as well as low-density lipoprotein and an increase in total antioxidant capacity, glutathione peroxidase activity, as well as superoxide dismutase enzymes (Ghadimi et al., 2021).

The 30 most significant KEGG enriched pathways are illustrated in **Figure 2B**. Notably, cancer-related pathways include: pathways in cancer, prostate cancer, microRNAs in cancer, chemical carcinogenesis, pancreatic cancer, acute myeloid leukemia, chronic myeloid leukemia, bladder cancer, breast cancer, and small cell lung cancer (**Figure 2B**). Cancer and inflammation have a uniquely inseparable relationship: cancer growth and progression are strongly associated with inflammation, which, in turn, can affect cancer formation, metastasis or response to therapy (Singh et al., 2019; Zhao et al., 2021). Recent evidence from *in vitro* and *in vivo* studies have suggested that EA may be able to inhibit tumor cell proliferation, induce apoptosis, break DNA binding to carcinogens, block virus infection, and disturb inflammation, angiogenesis, and drug-

resistance processes, which are all important factors in the development and progression of cancer (Zhang et al., 2014). Other pathways relevant to inflammation also include Hepatitis B, FoxO, TNF, and HIF-1 signaling pathways. In conjunction, it was demonstrated that EA could effectively inhibit Hepatitis B-infected HepG2 2.2.15 cells from secreting hepatitis B e-antigen (Shin et al., 2005). In a model of high glucose-induced injury in rat mesangial cells, EA was demonstrated to inhibit the activation of the PI3K/Akt signaling pathway and reduce the expression levels of downstream transcription factor FOXO3a (W. Lin et al., 2021). In a model of 1,2-dimethylhydrazine-induced rat colon carcinogenesis, EA downregulated iNOS, PTGS2, TNF and IL6 via inhibition of NF-kB and demonstrated chemopreventive effects on colon carcinogenesis (Umesalma & Sudhandiran, 2010). Lastly, in a study using *in vitro* model of lung cancer (i.e., HOP62 and H1975 cell lines) EA decreased both mRNA expression of target genes of HIF-1 as well as the protein level of HIF-1, whose inhibition may enhance the effectiveness of a vast variety of innovative and established anticancer medicines (Duan et al., 2020).

To further determine critical proteins in EA's anti-inflammatory activity, topological analysis was performed (**Figure 2C-F**) using cytoHubba MCC, DMNC, MNC, and EPC algorithms. The MCC algorithm determined PTGS2, MMP9, ALB, and TNF as the 4 most essential proteins of the network (**Figure 2C**). Alternatively, the DMNC algorithm determined ICAM1, MMP2, SELP, and MMP9 as the 4 most essential proteins of the network (**Figure 2D**). Furthermore, the MNC algorithm determined MAPK3, TNF, AKT1, and VEGFA as the 4 most essential proteins of the network (**Figure 2E**). Lastly, the EPC algorithm determined MAPK3, TNF, AKT1, and VEGFA as the 4 most essential proteins of the network (**Figure 2F**). In essence, per the recommendation of Chin et al., 2014, combining the results of these 4 algorithms determined that the top 10 most important proteins of the network are PTGS2,

MMP9, MMP2, ALB, TNF, ICAM1, SELP, MAPK3, VEGFA, and AKT1. PTGS2 is an enzyme that plays a role in bio-transforming arachidonic acid to prostaglandins, which are signaling molecules that have various functions in the body, including the regulation of inflammation (Simon, 1999). MMP9, in the context of inflammation, is often upregulated and released by both immune cells (i.e, neutrophils and monocytes) as well as endothelial or fibroblast cells (Al-Sadi et al., 2021; Yabluchanskiy et al., 2013). The upregulation and release of MMP9 can eventually contribute to the breakdown of extracellular matrix proteins and other proinflammatory molecules, leading to tissue damage. In a similar manner, MMP2 is a protease that can cleave several extracellular matrix proteins, including collagens, laminins, and elastins and is important for various physiological processes, such as tissue repair and remodeling, as well as pathological processes such as cancer cell invasion and metastasis (Maybee et al., 2022; Song et al., 2021). Inadequacy of ALB is associated with inflammatory conditions (Soeters et al., 2019); a clinical study demonstrated that ALB is negatively correlated with inflammatory indices (i.e, C-reactive protein and white blood cell count), implying a potential role of ALB in the regulation of inflammatory and immune responses (Sheinenzon et al., 2021). TNF mediates inflammation by activating immune cells and inducing the expression of other cytokines, chemokines, and adhesion molecules and eventually clears infections and in the process of tissue repair after injury, but TNF can also be the driving force of chronic inflammation, leading to tissue damage and the development of autoimmune diseases (Chu, 2013; Kalliolias & Ivashkiv, 2016). ICAM1 is a type of cell adhesion molecule that is expressed on the surface of various types of cells, including epithelial cells, endothelial cells, and immune cells and plays a critical role in the inflammatory response by mediating the adhesion of leukocytes to the endothelium (Bui et al., 2020). SELP is a type of cell adhesion molecule that is expressed on the surface of stimulated

endothelial cells and activated platelets; SELP can mediate the interaction between leukocytes and endothelial cells, allowing leukocytes to "roll" along the surface of the endothelium, which is important for the recruitment of leukocytes to sites of inflammation (M. Chen & Geng, 2006). MAPK3 plays a key role in regulating various cellular processes, including cell proliferation, differentiation, and survival and has been shown to be upregulated in immune cells during inflammation, and its activation also is associated with the production of pro-inflammatory mediators, such as cytokines and chemokines (Lucas et al., 2022). In inflammation, VEGFA is important for recruiting of immune cells to the site of inflammation, forming of new blood vessels, maintaining the integrity of blood vessels, wound healing, and the development of the placenta during pregnancy; however, excessive, or uncontrolled production of VEGFA can contribute to the development of certain diseases, such as cancer (Scaldaferri et al., 2009; Shaik-Dasthagirisaheb et al., 2013). Lastly, activation of AKT1 is known to lead to the activation of NF-κB, which in turn upregulates and encodes cytokines, chemokines, and adhesion molecules that play critical roles in inflammatory responses (Luthra et al., 2008; Zhou et al., 2013). EA might very well directly interact with these targets to exert its anti-inflammatory effects, as previous studies demonstrated that EA could affect the gene as well as protein expression of these targets (Attilio et al., 2010; Kowshik et al., 2014; C. Lin et al., 2019; Pattanayak et al., 2017; Umesalma & Sudhandiran, 2010; Yu et al., 2007). Therefore, molecular docking and molecular dynamics simulations were utilized to validate said speculation.

2. Molecular Docking and Molecular Dynamics Simulation Studies

Table 1. Results of molecular docking studies, sorted by binding affinities from strongest to weakest.

Target	Binding Affinity (kcal/mol)	Predicted Dissociation	Contact surface ($Å^2$)

		Constant (pM)	
AKT1 (PDB: 6HHG)	-9.894	55,924.5	249.81
MAPK3 (PDB: 4QTB)	-9.452	117,921.3	254.77
PTGS2 (PDB: 5F19)	-9.359	137,962.8	255.40
MMP9 (PDB: 1L6J)	-8.916	291,397.3	230.30
ALB (PDB: 6M4R)	-8.502	586,072.6	265.98
MMP2 (PDB: 7XJO)	-7.111	6,131,516.5	208.28
SELP (PDB: 1G1S)	-6.900	8,754,532.0	159.0
ICAM1 (PDB: 1IAM)	-6.871	10,054,020.0	169.00
TNF (PDB: 2AZ5)	-6.479	17,816,814.0	173.73
VEGFA (PDB: 4KZN)	-6.160	30,525,314.0	154.23

Results of molecular docking (binding affinity, predicted Ki, and contact surface) are summarized in **Table 1**. In brief, from the molecular docking results, EA had the strongest binding affinities for AKT1, MAPK3, PTGS2 (with -9.894, -9.452, and -9.359 kcal/mol, respectively) and weakest binding affinities for ICAM1, TNF, and VEGFA (with -6.871, -6.479, -6.160 kcal/mol, respectively) (**Table 1**).However, the crucial analyses of this study rely on the ligand contact analysis (**Figure 3**) and MM/PBSA-calculated binding energies (**Figure 4A**) by means of molecular dynamics simulations. EA was able to maintain continuous contacts with all important target protein throughout 100 ns of molecular dynamics simulations (**Figure 3**). From MM-PBSA binding energy calculations, EA demonstrated strongest binding affinities with AKT1, PTGS2, VEGFA, MAPK3 with -82.37 ± 159.8, -52.06 ± 171.4, -19.24 ±79.02, and -13.98 ± 149.6 kJ/mol, respectively (**Figure 4A**). EA demonstrated weaker binding with ALB, MMP9, ICAM1, TNF, MMP2, and SELP with -9.597 ± 223.9, 16.84 ± 169.2, 29.11 ± 169.2,

46.92 ± 80.85, 54.92 ± 81.22, and 59.51 ± 92.92 kJ/mol, respectively (**Figure 4A**). However, these results do not necessarily negate ALB, MMP9, ICAM1, TNF, MMP2, and SELP as potential targets of EA, as it only highlights that AKT1, PTGS2, VEGFA, and MAPK3 are the most likely targets of EA. To reiterate, AKT1, PTGS2, VEGFA, MAPK3 had been demonstrated to play critical roles in progression of cancer, inflammation, HIF-1 signaling, and TNF signaling (Faurschou & Gniadecki, 2008; Fojtík et al., 2021; Guadagni et al., 2007; Lee et al., 2010; C.-C. Lin et al., 2004; Ramakrishnan et al., 2014; Siddappa et al., 2015; Stegeman et al., 2016). Thus, they, through topological analysis and molecular dynamics simulations, are most likely to be targets of EA for its anti-inflammatory activities and are included in the illustration of putative anti-inflammatory mechanism of EA (**Figure 4B**).

Conclusion

In summary, a network pharmacology approach was used to understand the anti-inflammatory effects of EA. It was revealed that there are 52 targets of EA that are related to inflammation. Topological analysis determined 10 important targets that are AKT1, VEGFA, TNF, MAPK3, ALB, SELP, MMP9, MMP2, PTGS2, and ICAM1. Molecular docking and molecular dynamics simulations helped determine AKT1, PTGS2, VEGFA, MAPK3 as the most probable targets of EA.

Methods

1. Retrieval of EA target proteins

Target proteins of EA were retrieved from SwissTargetPrediction (Daina et al., 2019) and SymMap v2 (Wu et al., 2019) in UniProt ID format. String-db.org (Szklarczyk et al., 2021) was used to exclude any duplicate and resulted in a total of 157 EA target proteins.

2. Retrieval of target proteins for inflammation

DisGeNET (Piñero et al., 2019) was used to retrieve target inflammation proteins in UniProt ID format via the following accession numbers: C0021368, C0234251, and C1290884. String-db.org was also used to exclude any duplicate and resulted in a total of 886 target proteins for inflammation.

3. Constructing PPI network of EA target proteins for anti-inflammatory properties

After two networks of 157 EA target proteins and 886 target proteins for inflammation were constructed on string-db.org, they were then sent to Cytoscape 3.9.1 (Shannon et al., 2003) to find mutual proteins between the two networks via the Merge-Intersection function, resulting in 52 EA target proteins that are also relevant for its anti-inflammatory properties. This visualization of this network and its basic topological analysis were then provided through string-db.org at a moderate confidence score of 0.55. Within string-db.org, GO enrichment analysis was also retrieved; 15 selected enriched terms were presented. On the other hand, ShinyGO 0.76.3 (Ge et al., 2020) was used to perform and visualize KEGG enrichment analysis.

4. Topological analysis of the PPI

Both local-based (i.e, MCC, DMNC, and MNC) and global-based (i.e, EPC) algorithms from the cytoHubba plug-in of Cytoscape were used to determine the most critical target proteins. The mathematical basis for these algorithms can be found at Chin et al., 2014.

5. Molecular Docking

YASARA Structure (Land & Humble, 2018) was used to perform both molecular docking and molecular dynamics simulations. The dock_run.mcr script, which utilized Vina algorithm, was employed to perform molecular docking for EA towards important protein targets for inflammation. For each protein target, 100 docking runs were performed, and the docked pose

with the most negative binding affinity (ΔG) in kcal/mol was selected for further validation through molecular dynamics simulations.

6. Molecular Dynamics Simulations

The md_run.mcr script was employed to perform molecular dynamics simulations for docked complexes to investigate the interactions between EA and its critical target proteins. In brief, the important parameters for the simulations are as follows: pH is 7.4; ion concentration is 0.9% NaCl; temperature is 298 K; water density is 0.997 g/ml; pressure control mode is solvent probe; cell shape is cube with periodic boundary; force field is AMBER14. The simulation is speed is 'normal,' in which a mixed-multiple timestep (of 2*1.25 femtoseconds) algorithm combined with LINCS algorithm is utilized. Eventually, analyses of contacts between EA and target proteins as well as movement RMSD of EA were retrieved through the md_analyze.mcr script. Binding energies derived from MM/PBSA were calculated using md_analyzebindenergy.mcr script, based on the following premise:

$$\Delta G\text{-binding} = \Delta G\text{-complex} - (\Delta G\text{-protein} + \Delta G\text{-ligand}) \text{ (in kJ/mol)}$$

In which, ΔG-complex is calculated based on the solvation and potential energies of the complex; ΔG-protein is calculated based on the solvation and potential energies of the protein, and ΔG-ligand is calculated based on the solvation and potential energies of the ligand. More negative energies indicate better binding; positive energies do not indicate no binding.

Figure Legends

Figure 1. Venn diagram showing the overlap between 157 target proteins of ellagic acid (EA) and 886 target proteins for inflammation as well as the protein-protein interaction network of 52 overlap proteins.

Figure 2. Enrichment analysis and topological analysis of the protein-protein interaction. network. (A) Gene Ontology (GO) enrichment analysis. (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. Topological analysis to determine important proteins of the network via (C) Maximal Clique Centrality (MCC) (D) Density of Maximum Neighborhood Component (DMNC) (E) Maximum Neighborhood Component (MNC) (F) Edge Percolated Component (EPC)

Figure 3. Residue contacts between ellagic acid (EA) and important proteins of the network determined through topological analysis. Red, green, and yellow colors denote hydrophobic interaction, hydrogen bonding, and the simultaneous combination of hydrophobic interaction and hydrogen bonding, respectively.

Figure 4. (A) Binding energy calculated through molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method, represented in violin plots. (B) Illustration of putative anti-inflammatory mechanism of ellagic acid (EA) based on 4 proteins with strongest binding energies for EA.

Disclosure Statement

The author declares no conflict of interest and being the sole contributor of this work.

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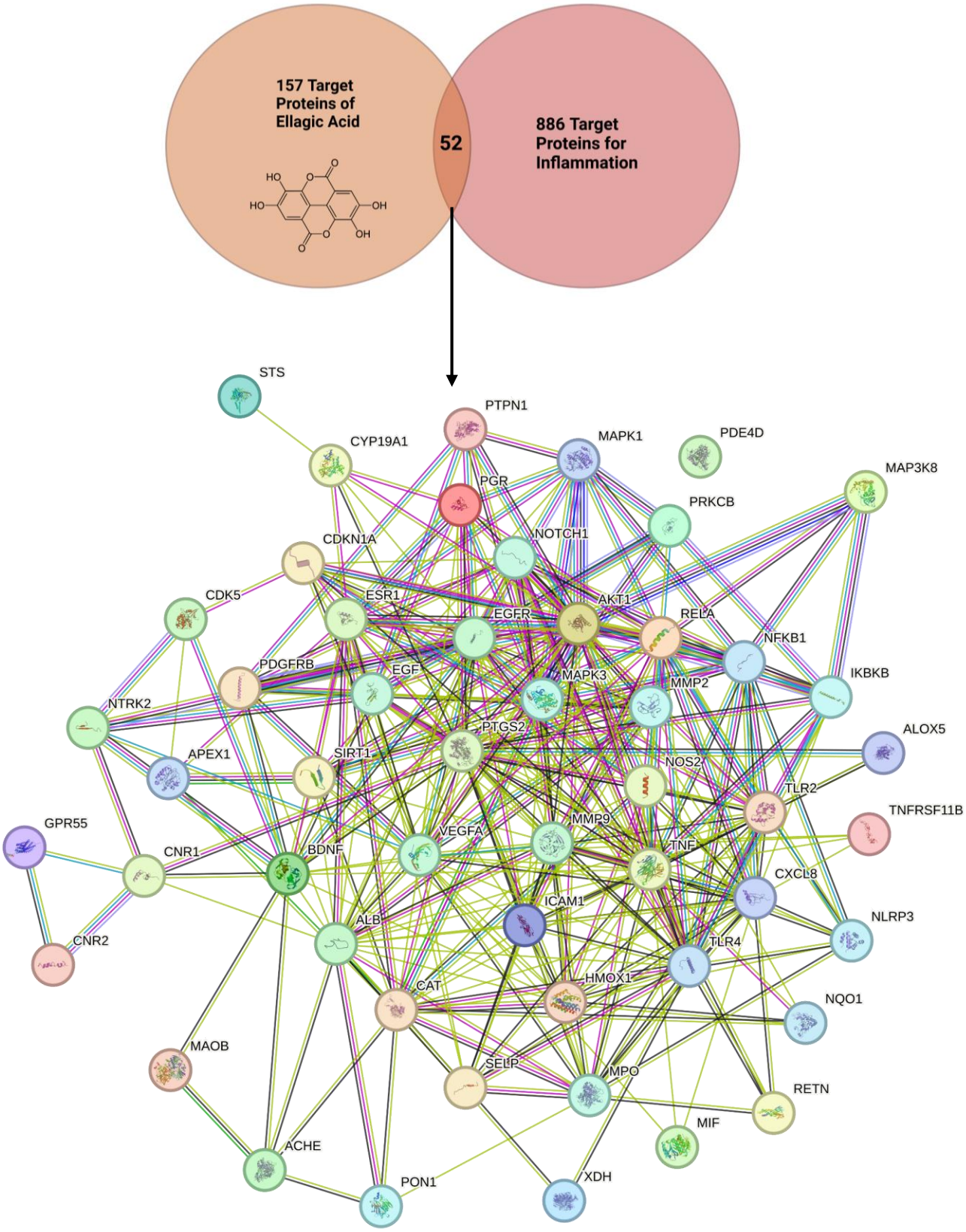
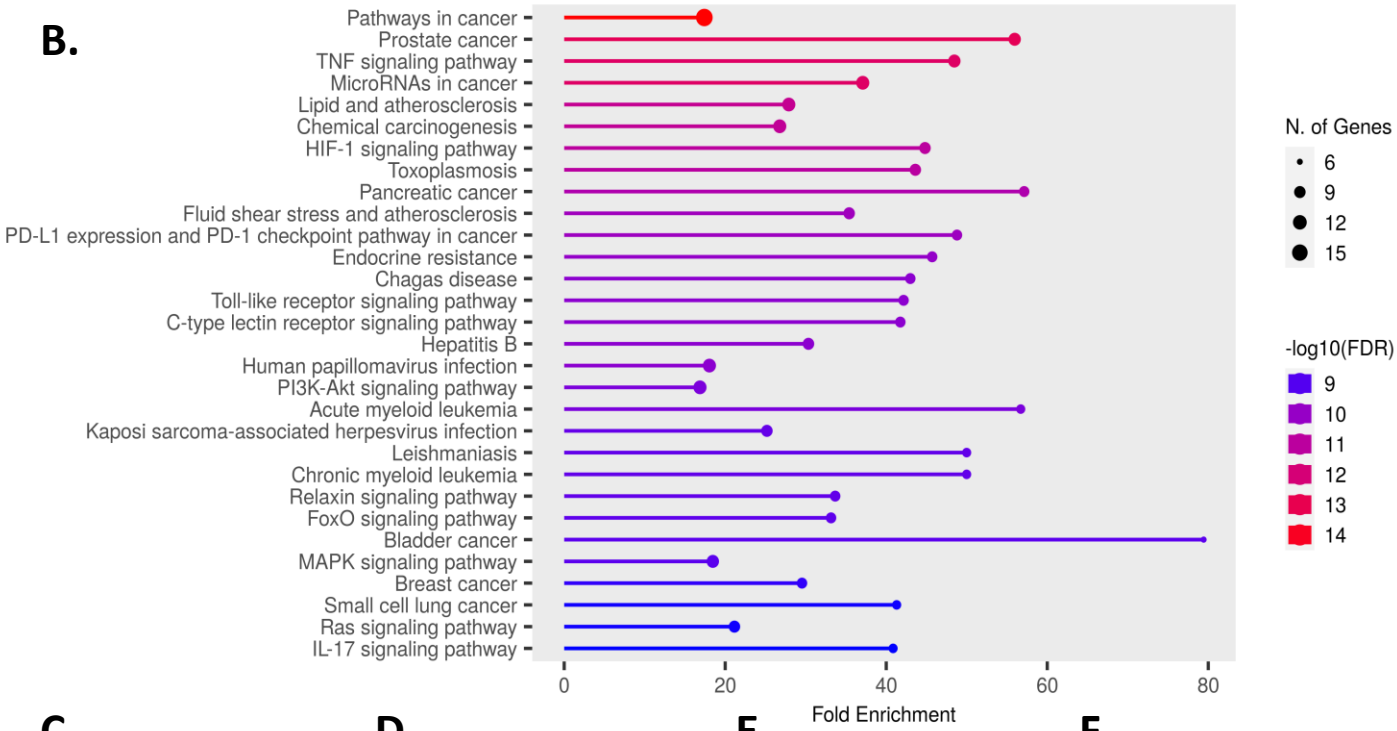

157 Target Proteins of Ellagic Acid
52
886 Target Proteins for Inflammation
HO
HO
OH
OH
STS
PTPN1
CYP19A1
MAPK1
PDE4D
MAP3K8
PGR
PRKCB
NOTCH1
CDKN1A
CDK5
ESR1
AKT1
EGFR
RELA
NFKB1
PDGFRB
EGF
MAPK3
MMP2
IKBKB
NTRK2
PTGS2
ALOX5
APEX1
SIRT1
NOS2
TLR2
TNFRSF11B
GPR55
MMP9
VEGFA
TNF
CNR1
BDNF
CXCL8
ICAM1
NLRP3
ALB
CNR2
TLR4
HMOX1
CAT
NQO1
MAOB
SELP
MPO
RETN
MIF
ACHE
PON1
XDH

A.

GO-term	Description	Count in network	False discovery rate
Biological Processes			
GO:0010033	Response to organic substance	46 of 3011	5.36e-27
GO:1901700	Response to oxygen-containing compound	38 of 1567	1.18e-26
GO:0033993	Response to lipid	29 of 858	3.61e-22
GO:0042221	Response to chemical	47 of 4333	5.03e-22
GO:0070887	Cellular response to chemical	41 of 2919	4.58e-21
Molecular Function			
GO:0042802	Identical protein binding	29 of 1896	5.70e-13
GO:0005515	Protein binding	44 of 7026	1.11e-09
GO:0005102	Signaling receptor binding	22 of 1581	2.71e-08
GO:0019899	Enzyme binding	24 of 2239	3.71e-07
GO:0043167	Ion binding	38 of 6188	7.10e-07
Cellular Component			
GO:0031983	Vesicle lumen	11 of 330	1.29e-06
GO:0012505	Endomembrane system	33 of 4542	1.30e-06
GO:0030141	Secretory granule	15 of 845	2.09e-06
GO:0034774	Secretory granule lumen	10 of 324	4.25e-06
GO:0045121	Membrane raft	10 of 324	4.26e-06

B.



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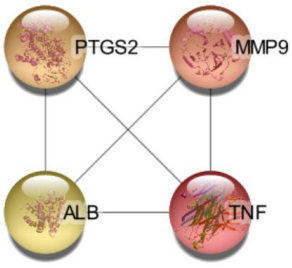
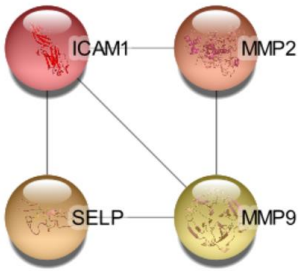


MCC

D.



DMNC

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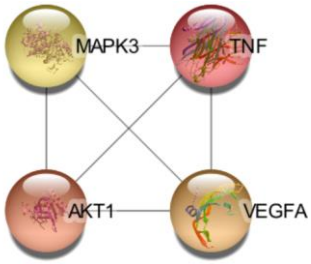
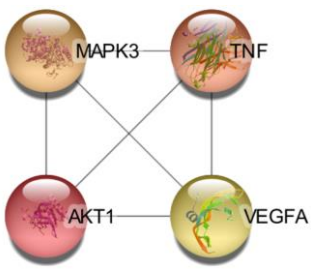


MNC

F.



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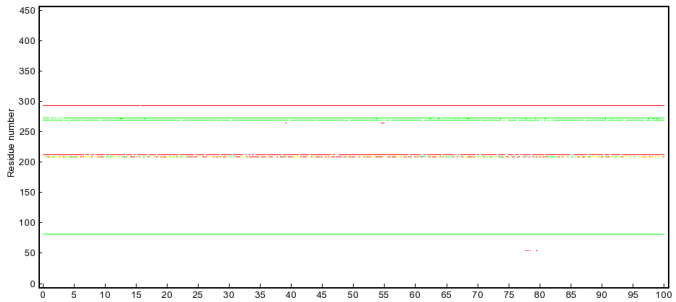
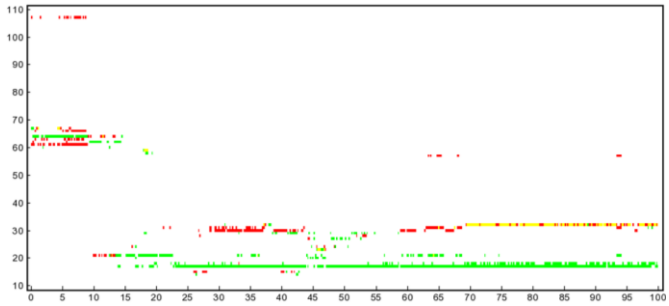


AKT1



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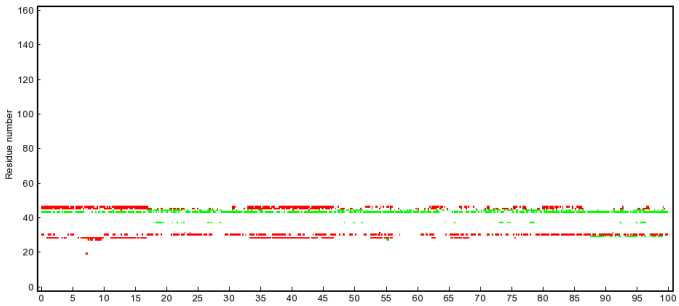
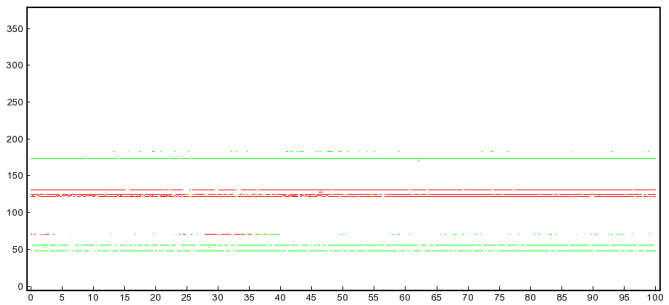
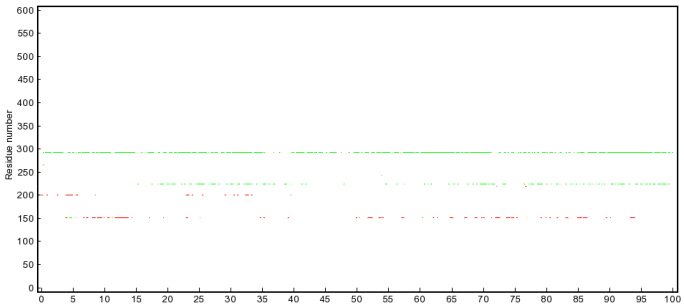


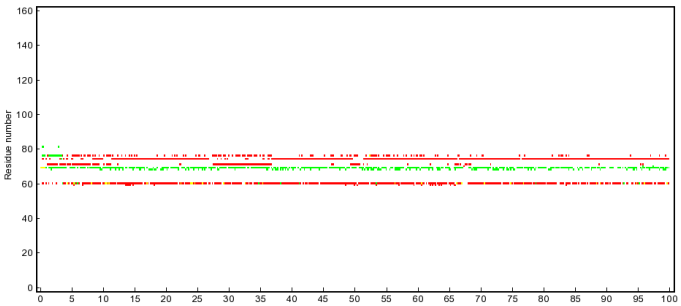
TNF



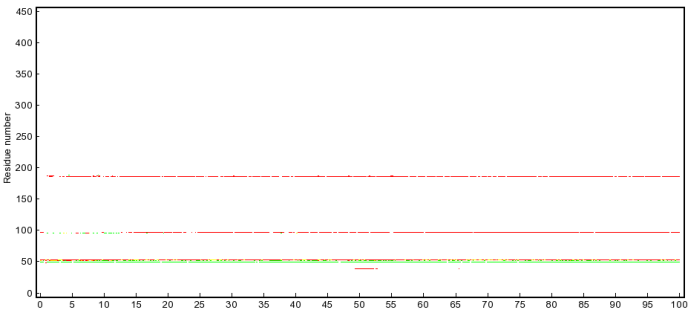
MAPK3



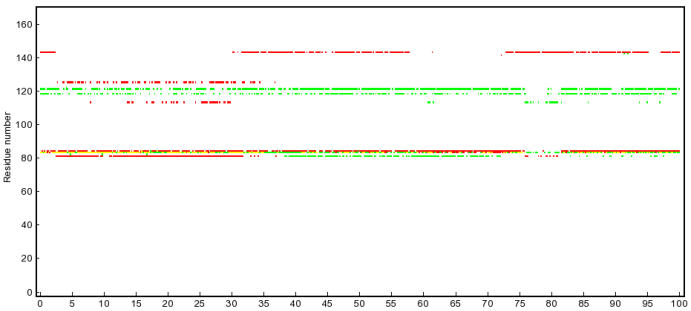
ALB



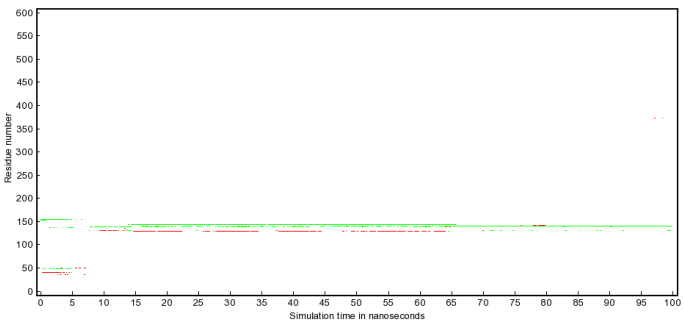
SELP



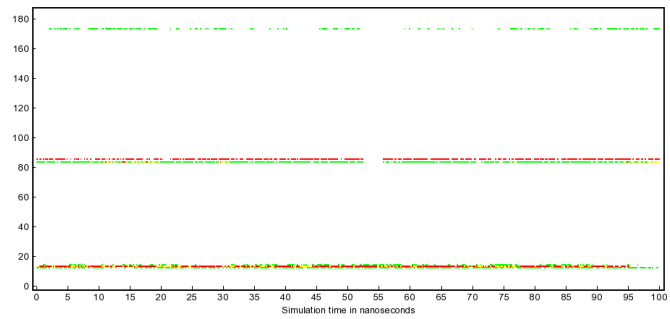
MMP9



MMP2

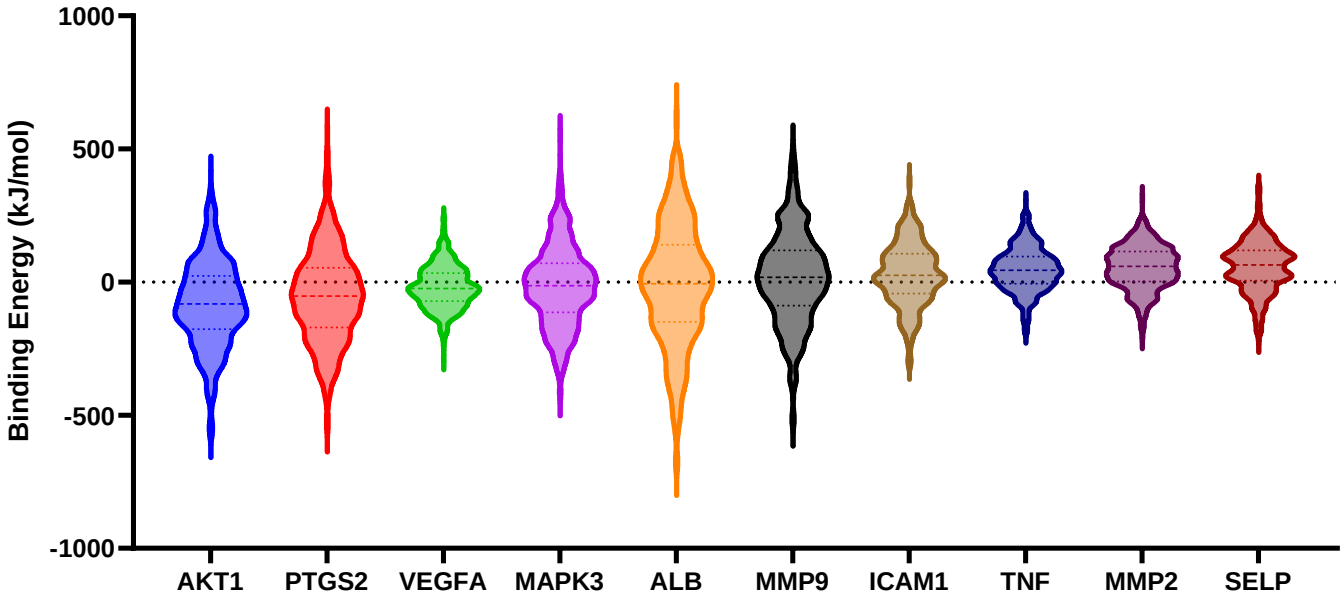


PTGS2

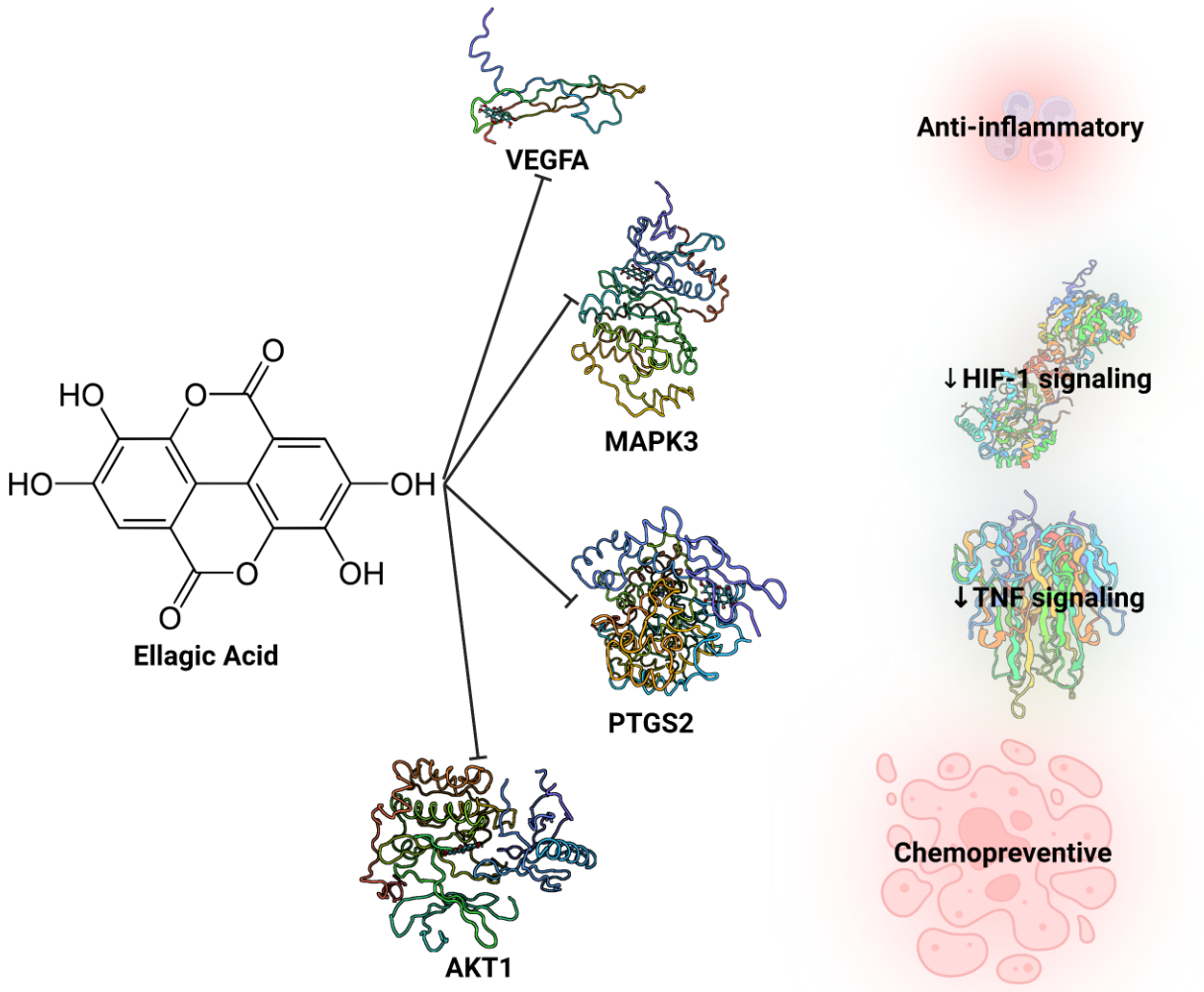


ICAM1

A.


1000
500
0
-500
-1000
Binding Energy (kJ/mol)
AKT1
PTGS2
VEGFA
MAPK3
ALB
MMP9
ICAM1
TNF
MMP2
SELP

B.


VEGFA
MAPK3
PTGS2
AKT1
HO
HO
O
O
O
O
OH
OH
Ellagic Acid
Anti-inflammatory
↓HIF-1 signaling
↓TNF signaling
Chemopreventive