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Computational Analysis For The Prediction Of Key Genes Affected By The Exposure Of Microplastics

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ABSTRACT:

Humans and other biological entities are at a great risk from microplastics, which are ubiquitous in both marine and terrestrial ecosystems. Their capacity to transport and absorb harmful substances is demonstrated by recent research, which suggests that they may be the source of a number of health problems. By offering insights into the fundamental molecular processes and aiding in the development of abatement techniques, computational biology has emerged as a critical method for identifying important genes impacted by microplastic exposure. This work uses databases and bioinformatics methods, such as MalaCard, GeneCard, and OMIM to find and examine the genes that are affected by exposure to microplastics. Additionally, utilizing 12 distinct cytohubba characteristics, the protein-protein interaction networks were examined in order to identify the hub gene. "TNF" protein was identified as the key regulator of the network. A list of phytochemicals was also carefully selected after a thorough review of the literature in order to determine which ones would be useful in protecting against the exposure to microplastics. Using ADMETLab 3.0, the drug-like properties of these phytochemicals were tested. The structure of the key hub gene, that is, TNF was modeled using Swiss-Model. Molecular docking studies were done to explore the potential of phytochemicals against TNF. Molecular docking studies revealed the potential role of "Ellagic Acid" that has the highest binding energy of "-9.36" in the management of microplastics exposure in human. This study underscores the pervasive threat of microplastics to both human health and the environment, highlighting their ability to transport harmful substances. Computational biology has played a pivotal role in identifying key genes affected by microplastic exposure, with TNF emerging as a critical regulator. Through molecular modeling and docking studies, Ellagic Acid shows promising potential as a therapeutic agent against microplastic-induced health risks.

Keywords: Network biology, Computational biology, TNF, Mircoplastic, Molecular modeling, Exposure management, Gingerol, Binding energy.

INTODUCTION:

At the moment, microplastics stand to be one of the most pervasive environmental problems, with some potential adverse impacts on ecosystems and human health. These small plastic particles, less than 5 mm in size, come from sources similar to breaking down larger plastic items, industrial activities, and decaying of plastic wastes. Because they are so small and nondigestible, microplastics can easily be consumed by many organisms at all trophic levels of the food chain, fast becoming of concern to the environment.

While the physical and chemical consequences of microplastic pollution have been extensively studied, their biological effects, particularly at the molecular level, remain largely unexplored. Understanding how microplastics influence gene expression in organisms is crucial for assessing their ecological ramifications comprehensively. Traditional experimental approaches are often limited in their ability to capture the complex and dynamic nature of gene expression alterations induced by microplastic exposure across diverse species and environmental conditions.

Environmental MPs are able to enter the human body, pass through biological barriers, and be further distributed in the organism. [R. Dris et al., M. Bläsing et al.] The accumulation of MPs in tissues can lead to a variety of adverse effects: from oxidative stress and immunological inflammation to cellular damage, endothelial leakiness, neurotoxicity, and metabolic problems. The MPs' unique features in physical and chemical characteristics can make the central nervous system sensitive to them even with the blood-brain barrier. The reports by [B. Chai et al., S. Feng et al., and T.A. Kurniawan et al.] relate that the damaging of the BBB, neurological function impairment, and transfer of MPs into the brain can occur. These effects may potentially accelerate the development and progression of neurodevelopmental and neurodegenerative diseases. Nevertheless, most of the research works have focused on the general risks of microplastics to the human body, with few studies involving their neurotoxic effects. The more recent reviews focus mainly on summarizing the neurotoxic effects either in different test subjects or the behavior of microplastics within a cell. [C.G. Avio et al.], [G. Erni-Cassola et al.] Further research into the neural diseases MPs can provoke is required.

Literature published between 2000 and 2024 was retrieved by an online search of the Web of Science databases with the support of the following keywords: Microplastics, nanoplastics, environmental risk, neurotoxicity, human exposure, and neurological illnesses compose a series of interconnected concerns. In this work, focusing on neurotoxic effects on human health as a result of MPs and NPs, we have done an overview of the literature. A general overview on MPs and NPs as a risk for human health and the environment by [J.C. Prata], mechanisms opening MPs' and NPs' passage into the brain by [H.A. Leslie et al.], neurotoxic effects of MPs and NPs on abnormalities in neurodevelopment and neurodegeneration by [K. Yin et al.], and lastly, by [J.Q.

Jiang], possible mechanisms by which MPs and NPs cause neurotoxicity. This will help in increasing the knowledge regarding the strength of connection of MPs and NPs with the developing neurodevelopmental and neurodegenerative disorders. Plastic pollution and its health effects are a concern not just for human health but for sustainable development of the ecosystem itself.

We hereby propose a computational framework for predicting key genes affected by microplastic exposure. Our approach will harness the power of bioinformatics, equipped with cutting-edge data-driven methodologies, to integrate multi-omics information. It applies transcriptomics, proteomics, and metabolomics in the study of molecular mechanisms underlying microplastic toxicity. This large dataset, acquired either from model organisms or environmental samples, will be analyzed to identify conserved molecular signatures associated with microplastic exposure that would facilitate cross-species comparisons and generalizations.

The utilization of computational methods offers several advantages in studying microplastic-induced gene expression changes. Firstly, it enables the simultaneous analysis of multiple datasets, allowing for a comprehensive assessment of gene expression alterations across different biological systems. Secondly, by employing machine learning algorithms and network-based approaches, we can uncover hidden patterns and interactions within complex biological data, elucidating the intricate regulatory networks modulated by microplastic exposure. Lastly, computational predictions can guide experimental studies by prioritizing candidate genes and pathways for further validation, thereby accelerating the discovery of novel biomarkers and therapeutic targets for mitigating microplastic pollution.

In summary, this computational analysis holds promise in advancing our understanding of the molecular responses to microplastic exposure, shedding light on the potential risks posed by microplastics to environmental and human health. By elucidating the underlying mechanisms driving microplastic toxicity, our findings may inform regulatory policies and management strategies aimed at mitigating the impacts of microplastic pollution on ecosystems worldwide.

Plastic contamination has been one of the most challenging materials in the world over the recent past. Ten percent of the globally produced plastics each year end up in water as wastes. According to Borrelle et al., plasty can fragment slowly, resulting in secondary microplastics measuring between 0.1 µm and 5 mm and secondary nanoplastics of less than 100 nm. It has recently been demonstrated that up to 16 million nano- and microplastic particles per liter can be detected in polypropylene baby feeding bottles.[Li and associates], While A single source can release 3.1 billion nanoplastics and 11.6 billion microplastic teabag in boiling water.[Hernandez and others], [A. Mirzaie et al.] Besides, very usual food packaging, such as paper cups, take-out boxes, and instant noodle packets releases the nanoplastics into the environment.[Li and co-workers], These nanoparticles, following their ingestion, become capable of entering the body tissues and producing devastating toxicological effects[Li et al.]., [S.-L. Hsieh et al.], [W. Lin *et al.*], Nano- and microplastics have just been identified in human blood, organs, placenta, and breast milk and in the gastrointestinal tract pointing to a worrisome association with major health disorders, such as diabetes and obesity, cognitive impairment,

and neurodegenerative diseases like PD and AD [N. Benseny-Cases *et al.*], [C. Lazzari *et al.*], and. With about 6 million cases in the With 30 million cases worldwide and a considerable number in the United States, Alzheimer's disease is the most common neurological condition. [N. Benseny-Cases et al.]. The second most common type of dementia, Parkinson's disease, affects 6 million adults over 65 and is projected more than to quadruple to 12 million cases in the world by 2040. [Dorsey et al.], [C. Lazzari et al.] Dorsey et al. More than 90% of the huge population affected by these diseases consists of sporadic cases. Though Aβ in Alzheimer's disease and α-synuclein in Parkinson's disease have been demonstrated to be the main causes due to abnormal aggregation of amyloid proteins, there is a growing consensus that exposure to common but ill-defined environmental toxins could be the cause for the steep rise of these neurological disorders.A variety of biota, including fish, mollusks, crustaceans, nematodes, and rats, have recently had the neurotoxicity of nanoplastics clarified [M. Pang *et al.*], [Dorsey et al.], [Hernandez], [A. Mirzaie et al.], [W. Lin et al.], [H.A. Leslie *et al.*]. Neurotoxic effects, for instance, have been reported when fish and bivalves are directly exposed to nanoplastics through the food chain. [W. Li et al.], [Kopatz and associates] When nanoplastic particles were introduced into drinking water in mice, they were able to pass through the blood-brain barrier and reach brain in just two hours—something that was not the case with bigger particles. Kopatz and associates, 15 It has been discovered that tiny polystyrene (PS) nanoparticles exhibit clear neurotoxicity by blocking AChE activities, leading to a considerable how the particles are absorbed by cells and accumulate in the mouse brain.[S.-L. Hsieh *et al.*] The neurotoxicity of nanoplastics has been shown to be dose-dependent, with low-dose nanoplastics either showing no neurotoxicity at all or very little. There is now no information available on how much nanoplastics are present in the brain, influenced by the capabilities of detection methods. On on the other hand, it is expected that the brain would have very little nanoplastic due to the blood-brain barrier. The association between the neurotoxicity of nanoplastics and their impact in brain illnesses is left with a significant information gap. In order to close this gap, research on the neurotoxicity of nanoplastics themselves must go beyond where it is at the moment. Rather, it is necessary to study the regulation mechanism pertaining to the the in vivo effects and roles of amyloid proteins in the brain diseases, with a focus on the impact of naturally low-toxic nanoplastics. More crucially, our research has highlighted the fact that by interacting with essential proteins, even less harmful exogenous chemicals can have a very toxic effect. In order to clarify the complex interactions between environmental toxins and brain illnesses, it provides a useful basis for future research initiatives.

LITERATURE REVIEW:

Numerous technologies for networking are constantly being created as the information era progresses. Network drug discovery is gaining pace as an integration of pharmacology and information network, based on system biology, bioinformatics, and high-throughput histology [Z. H. Liu, .Q. Zhang et al.]. In 2007, Andrew L. Hopkins introduced the idea of network pharmacology [A. L. Hopkins]. In accordance with the low effectiveness of highly selective single-target medications, it blends network biology with polypharmacology [A. L. Hopkins]. From a vast quantity of data, network pharmacies allows us to immediately discover

medications and disease targets as well as comprehend the processes and routes that connect them [B. Zhang, X. Zhu et al.]. It is a useful approach. These days, the range of applications for network pharmacology is growing and includes investigating the fundamental pharmacologic effects of medications on illnesses and their causes [S. Y. Guo et al., R. Wu et al.], examine the practical significance of TCM [L. L. Zhan et al.] and its implementation of TCM [S. Han et al., C. Y. Ung et al.].

DrugBank [D. S. Wishar et al.], STITCH [M. Kuhn et al.], and TCM chemical knowledge databases [M. Zhang et al.] are examples of common tools used in network pharmacology. These databases contain information about pharmaceutical molecules, and other databases related to active ingredients include PubChem [T. Cheng et al.], ChEMBL [G. Papadatos et al.], KEGG [J. Wixon et al.], and Target database. Gene-related databases include OMIM [A. Hamosh et al.], protein-related databases like HPRD [. S. Keshava Prasad et al.], BioGRID [B. Lehne et al.],and DIP [K. R. Brown et al.], and databases related to biomolecular interactions include HPRD, BIND [. Jurisica et al.], DIP, HAPPI [J. Y. Chen et al.], MINT [T. Schlitt et al.], STRING [D. Szklarczyk et al.], and PDZBase [L. Skrabane et al.]. You may utilize any of them to locate the information you need. Additional tools, such as Cytoscape, Pajek, VisANT, GUESS, WIDAS, PATIKA, PATIKAweb, and CADLIVE, are required in addition to these databases [. Shannon, E. Adar et al.]. Currently, VisANT, GUESS, Pajek, and Cytoscape are the most used network evaluation programs in the field of TCM research.

Designing incredibly selective ligands that can prevent side effects has been the primary emphasis of drug development over the past few decades, according to the prevalent paradigm of "one gene, one drug, one disease" [F. Sams-Dodd]. Yet, the clinical attrition rate of novel therapeutic candidates might approach 30% due to their lack of safety and effectiveness [I. Kola et al.]. Further research using large-scale functional genomics investigations has shown that just 34% of single-gene knockouts resulted in illness or death [M. E. Hillenmeyer et al.], while many single-gene knockouts have no influence on the phenotype [B. P. Zambrowicz et al.]. Changes to a single molecular component are not the focus of systems biology, a contemporary trend in neuroscience study that looks at the intricate relationships within biological structures holistically [H. Kitano, U. Sauer et al.].

Network phârmâcology is a system biology-based methodology; it replaces, according to A. L. Hopkins and A. L. Hopkins, the corollary of rational drug design of "magic bullets" with the search for multitarget drugs that act on biological networks as "magic shotguns". It challenges the dominant assumption of single-target drug discovery because of increased understanding of the role of network biology systems. Chinese herbal medicines include natural medicines discovered by the ancient Chinese, evolved through at least 3000 years of uninterrupted clinical practice. Generally, CHM can cure diseases only through the synergistic effects of a great deal of compounds and herbal formulae, which mainly work on integrative and holistic ways [G. A. Luo et al.]. The rising need for elucidating pharmacologic processes, possible therapeutic effectiveness, and clinical toxicity are significant concerns that must be addressed, nevertheless, given the expanding acceptance and

immense possibility of CHM. The concept of drug discovery based on thorough investigation and synthetic evaluation may be integrated in a novel way with the technique and technologies of network pharmacology. Undoubtedly, this idea aligns with the traits of TCM's syndrome distinction and the holistic approach to treating CHM [Z. H. Liu et al.].

The computational study of alterations in gene expression brought on by exposure to microplastics has become a growing area of interest in recent studies. Smaller than 5 mm plastic particles are known as microplastics, and they are a major environmental hazard to human health and marine life alike. Studies have indicated that these particles have the ability to cause inflammation, oxidative stress, and other detrimental effects on cells. Some of the most important recent advances in civilization, such as contemporary technology and medical enhancements like single-use syringes and modern prostheses, can be attributed to plastics since they are strong, affordable, and manufactured quickly [Kautish et al.]. Yet, because up to 70% of the world's plastic gets disposed of improperly in landfills or the environment, the enormous rise in plastic manufacturing has also resulted in a serious pollution issue [Jabeen, F et al.]. It is known that plastics in the environment may absorb toxic substances [5,6,7], harbor invasive species like viruses [Prata, J.C, Cole, M et al.], and be consumed by marine life [Wright, S.L, Duarte, A.C et al.].

Apart from the aforementioned detrimental effects, it has been demonstrated that plastics subjected to environmental variables including ultraviolet light, oxidation, and physical abrasion lead to the creation of microplastics, [da Costa, J.P]. Microplastics enter the human body through inhalation of textiles, synthetic rubber tires, and plastic covers. One can consume MPs straight with the intake of water, seafood, and consumer goods like apparel, toothpaste, salt, sugar, honey, beer, and all types of food stored in plastic bottles, plastic wraps, or cans-cartons. In addition to other detrimental effects, MPs have been shown to upregulate pro-inflammatory cytokines [Li, B, Wang, X et al.], impair cell viability [Halimu, G, Palaniappan, S et al.], cause oxidative stress [Qiao, R, Gonzalez-Gil, G et al.], and change energy metabolism [Limonta, G, Jin, Y. et al.].

The lungs [Jenner, L.C, Carvalho-Oliveira, R et al.], blood [Leslie, H.A, Guan, Q et al.], cirrhotic liver tissues [Tamminga, M], human feces [Köppel, S, Luo, T et al.], and even breastmilk [Ragusa, A et al.] have all been found to include MPs more recently. It has become more crucial to comprehend the health effects of microplastics exposure in mammals as a result of these findings and the fact that a significant amount of MPs research is still conducted in marine models. Age is another factor that may affect the outcome of MP exposure, but there are currently very few research that address the potential negative consequences of MP exposure on mammal brain health. Therefore, we offered to study the impact of MP exposure on C57BL/6J mice of different ages, with a particular emphasis on the impacts on neurobehavior, inflammatory response, translocation, and MP build-up in several tissues, including the brain.

Since their invention and subsequent widespread manufacturing in the mid-1950s, plastics have become incredibly popular in business and daily life [Miranda, M.N et al.]. Plastics' chemical makeup makes it possible to produce goods that are both temperature- and chemical-resistant as well as durable building materials (like polyvinyl chloride [PVC] pipework). Polychlorinated biphenyls (PCBs) and persistent organic pollutants (POPs) are two hazardous chemicals that plastics may transport due to their hydrophobic nature. PVC, polypropylene (PP), low density polyethylene (LDPE), high density polyethylene (HDPE), and polyethylene terephthalate (PET) are a few of the most popular polymers. These polymers are utilized in many different goods (such as implants, electronics, apparel, furniture, and pipes).

Mostly through physical-chemical degradation, plastics break down into ever-tinier fragments as they weather in the environment. By microbial deterioration, plastics can also break apart. This finding, together with the chemical characteristics of plastic, such their hydrophobicity and capacity to draw in other hydrophobic particles, led to a surge in the study of microplastics, or plastic particles smaller than 5 mm, starting in 2015. Any length, breadth, or height of the plastics under study that is 5 mm or less is a regularly used measure for identifying plastics as microplastics [Jovanović et al., B, Stapleton, P.A]. The origin of microplastics can also be used to categorize them as main or secondary [Piao, M et al.]. Primary microplastics, which are often found in the textile and pharmaceutical sectors, are polymers that are produced with a dimension of 5 mm or less. Plastic trash, including plastic bags, weathers and fragments in the environment to generate secondary microplastics [Liu, H et al.]. Every year, about 14.5 million tons of plastic garbage, including clothing and packaging, are generated in the US [Xia, J et al.]. Plastics can be spread via a variety of operations and procedures, such as agricultural methods and the use of water and wastewater systems. From 2014, the field of microplastics research has exploded. The effects of microplastics on the environment across the world and the possible risks they may bring to plants and animals are being studied by interdisciplinary sectors ranging from engineering and exposure sciences to biology and chemistry. In order to improve our comprehension of the effects of microplastics on the environment and human health, we have devised a technique for classifying the microplastic literature and identifying knowledge gaps for this scoping study.

MATERIAL AND METHOD:

NCBI:

https://www.ncbi.nlm.nih.gov/.

National Center for Biotechnology Information (NCBI) is a service of the National Institutes of Health (NIH), which is home to the United States National Library of Medicine (NLM). The NCBI was established in 1988 and provides access to biological and genetic data to support these academic disciplines. It has a huge collection of databases, such as BLAST for sequence comparison, PubMed for biomedical literature, and GenBank for

DNA sequence collections. The resources and tools provided by NCBI enable research by providing extensive, integrated data and computational resources for the analysis of genetic, genomic, and biological data.

Fig.1. Welcome to the NCBI Home Page

Pubchem:

https://pubchem.ncbi.nlm.nih.gov/.

Chemical compounds and their actions on biological tests are included in the publicly available database PubChem. The National Center for Biotechnology Information (NCBI), a branch of the National Library of Medicine in the US, is in charge of maintaining it. For research and development in chemistry, biology, and medicine, PubChem is a valuable resource that offers details on the biological functions of tiny molecules.

By using PubChem, chemists may look up compounds with certain features and obtain comprehensive chemical information. Researchers studying biology can examine the interactions between various substances and biological systems. By examining the biological activity of substances, pharmacologists can utilize the database to find possible medication candidates.

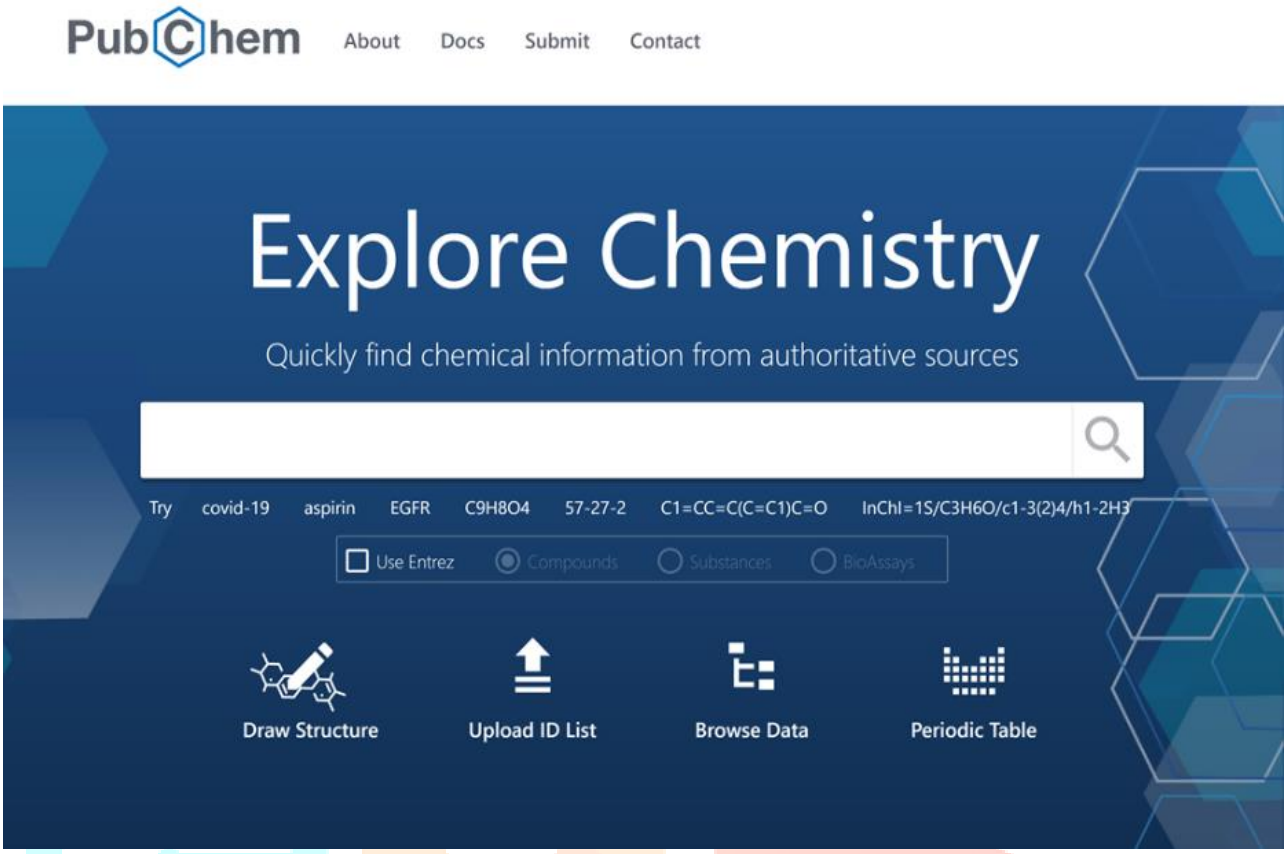


Fig.2. Welcome to the PubChem Home Page

ADMETLAB:

https://admet.scbdd.com/.

ADMETlab is a web-based platform for the in silico prediction of various properties of a compound with respect to its absorption, distribution, metabolism, excretion, and toxicity. It provides accurate, comprehensive ADMET predictions, thus helping in drug discovery and development research. Utilizing ADMETlab, Pharmaceutical Researchers can forecast the pharmacokinetic characteristics of novel drug candidates, assisting in the early detection of any problems throughout the drug development process. In order to help develop molecules with advantageous pharmacokinetic profiles, Chemists are able to assess the ADMET features of synthetic drugs.Assisting with safety evaluations, toxicologists are able to forecast the toxicity of chemical substances.

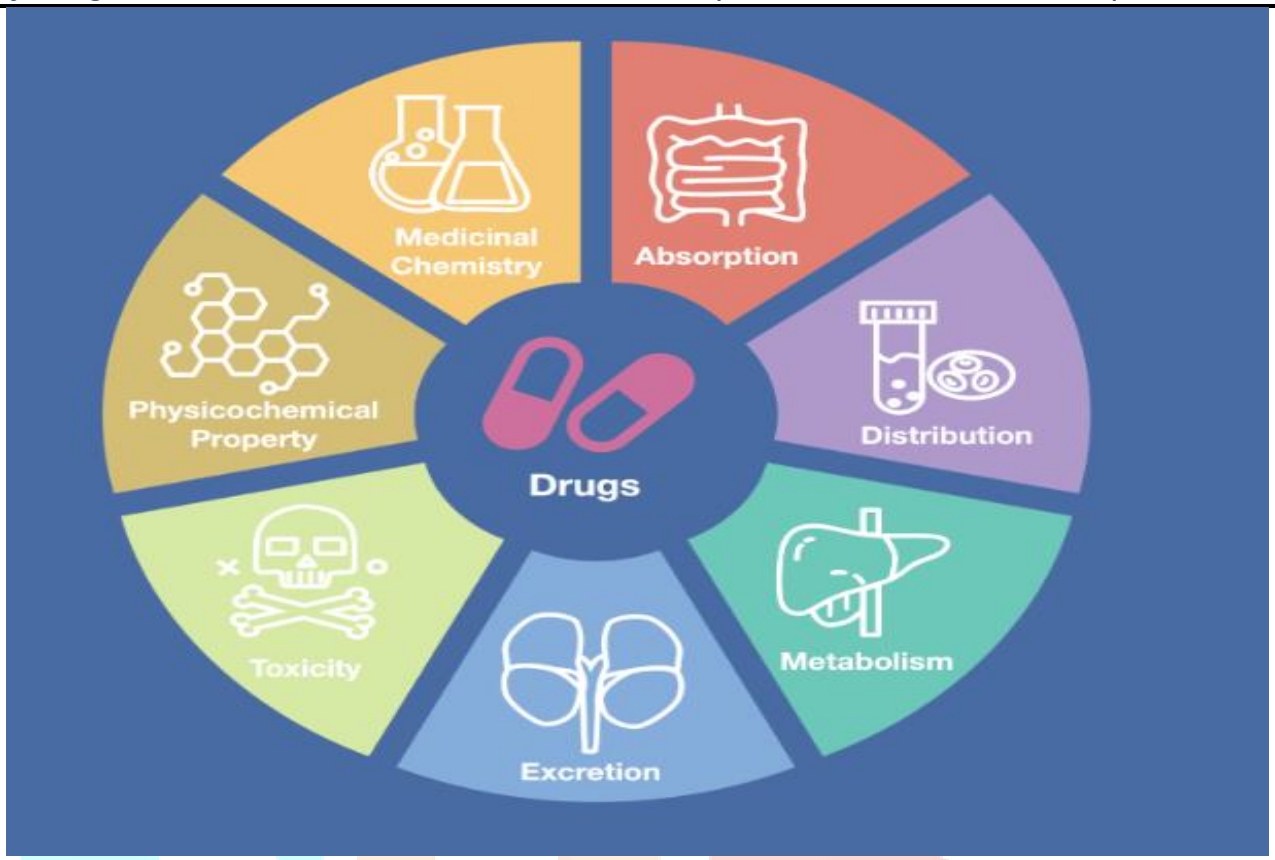


Fig.3. Welcome to the ADMETLab Home Page

CYTOSCAPE:

https://cytoscape.org/.

Intricate networks may be shown and combined with any type of attribute data using an open-source program called Cytoscape. It is extensively employed in systems biology, bioinformatics, and other disciplines that demand network analysis and visualization.

Bioinformaticians may assist in identifying important nodes and pathways by visualizing and analyzing molecular interaction networks using Cytoscape.

Systems biologists may investigate the intricate relationships found in biological systems by integrating several forms of omics data into networks.

Social scientists may comprehend linkages and impacts within a society by visualizing and analyzing social networks.

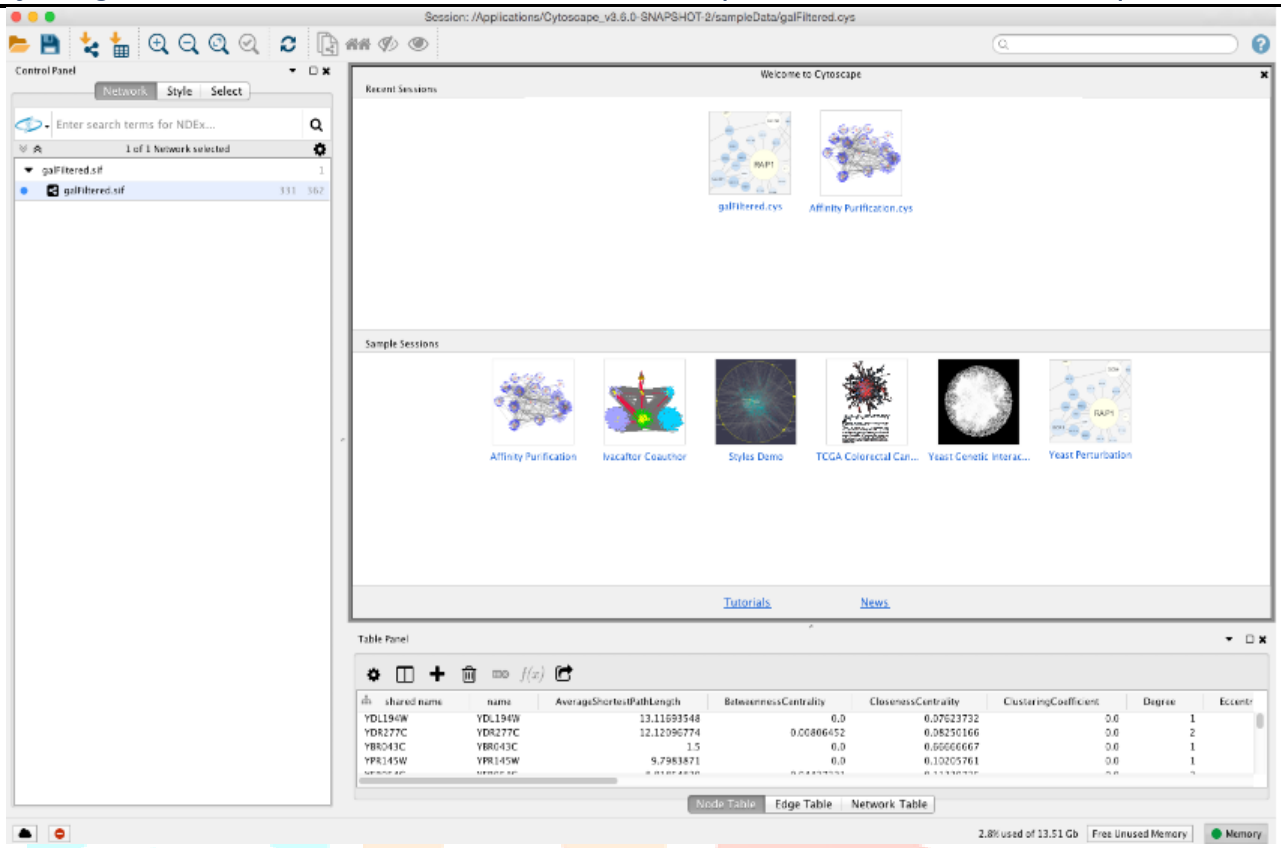


Fig.4. Welcome to the Cytoscape Home Page

SWISS MODEL:

https://swissmodel.expasy.org/](https://swissmodel.expasy.org/

An intuitive user interface for creating protein models from known templates is the goal of the automated structure of protein homology-modeling system SWISS-MODEL. Automating template selection, alignment, and model construction streamlines the process of predicting protein structures. The Template Library finds appropriate templates by searching through an extensive library of protein structures that have been identified via experimentation (found in PDB). Evaluation of Model Quality provides instruments for evaluating the quality of models, such as GMQE (Global Model Quality Estimation) and QMEAN (Qualitative Model Energy Analysis). Easy-to-use Interface Serves a broad spectrum of users, from novices to seasoned academics, and provides both programmatic and web-based use. Users can oversee several modeling projects and monitor their development with the help of project management. Analyses and Graphics incorporates visual aids for examining and assessing structural characteristics into the models.

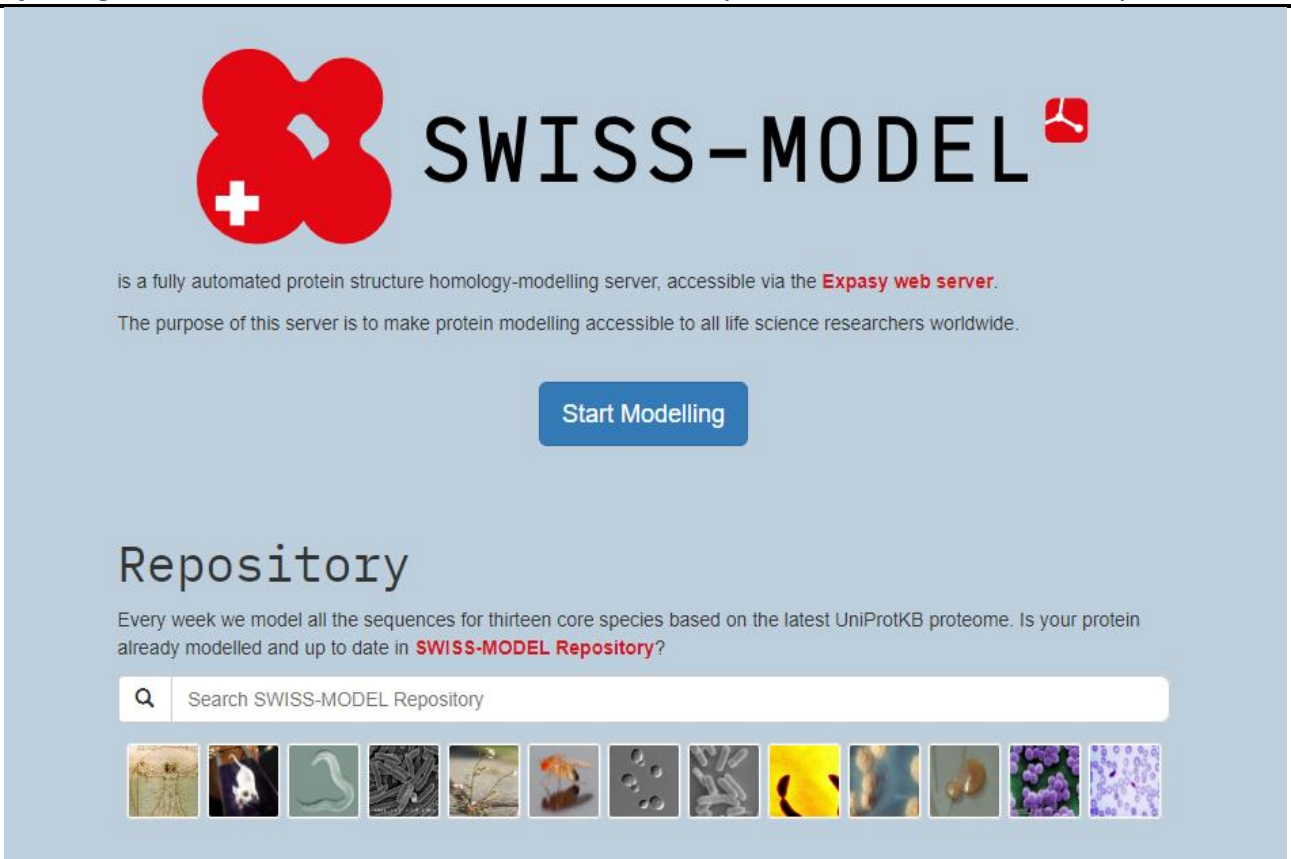


Fig.5. Welcome to the SWISS-MODEL Home Page

SEAMDOCK:

https://bioserv.rpbs.univ-paris-diderot.fr/services/SeamDock/

SeamDock is a molecular docking software used for predicting the binding affinity and interaction modes between small molecules and their protein targets**.** Incredibly Accurate Docking high accuracy ligand binding conformation most likely to occur using sophisticated algorithms. Easy-to-use Interface enables the setup of docking experiments, the visualization of data, and the analysis of interactions using a simple interface. Detailed Scoring Features optimizes docking findings by evaluating binding affinity through the use of several scoring systems. It is possible to mimic induced fit along with additional conformational changes with the support of flexible manipulation of ligands and protein structures. Combining Tools with One Another Allows for enhanced capability through seamless integration with existing cheminformatics and bioinformatics technologies. Combined Processing Suitable for virtual screening of huge chemical libraries, it enables high-throughput docking simulations.

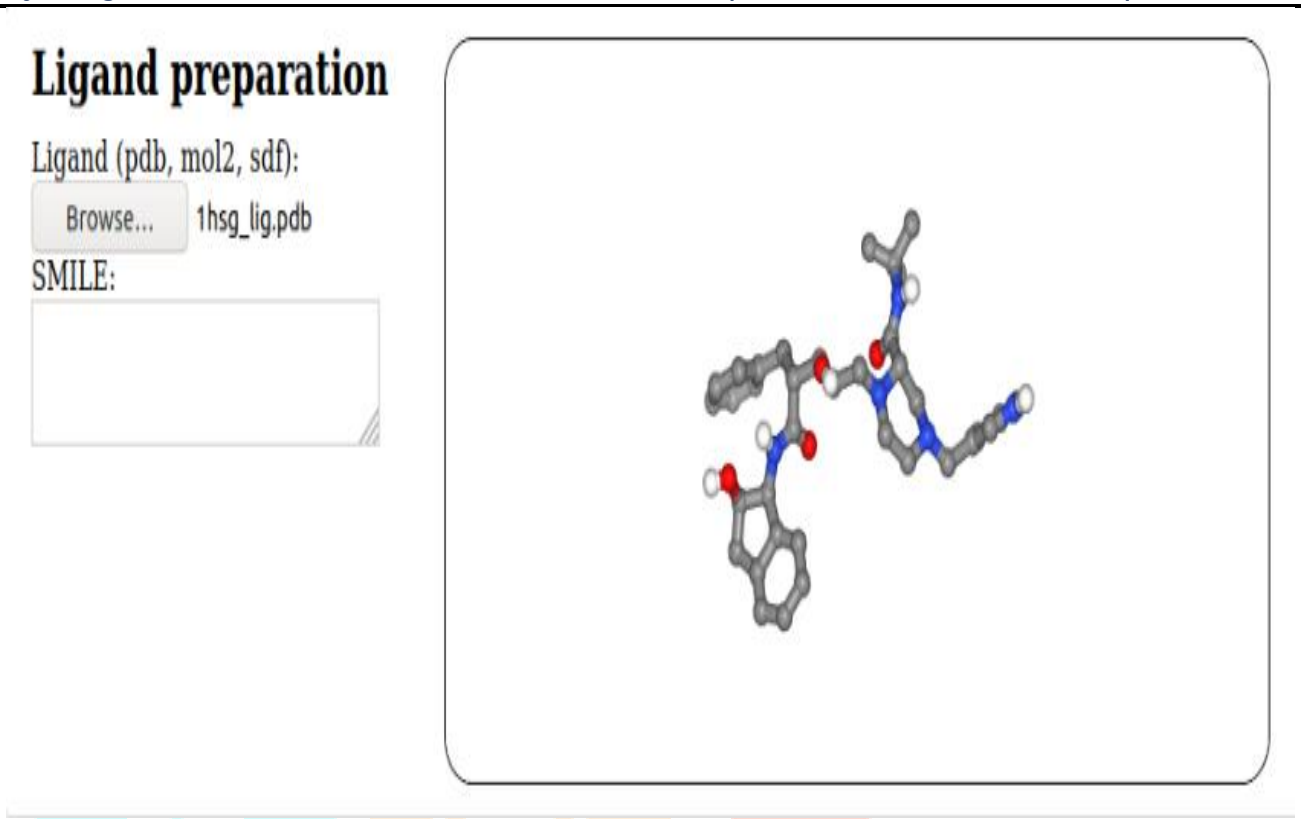
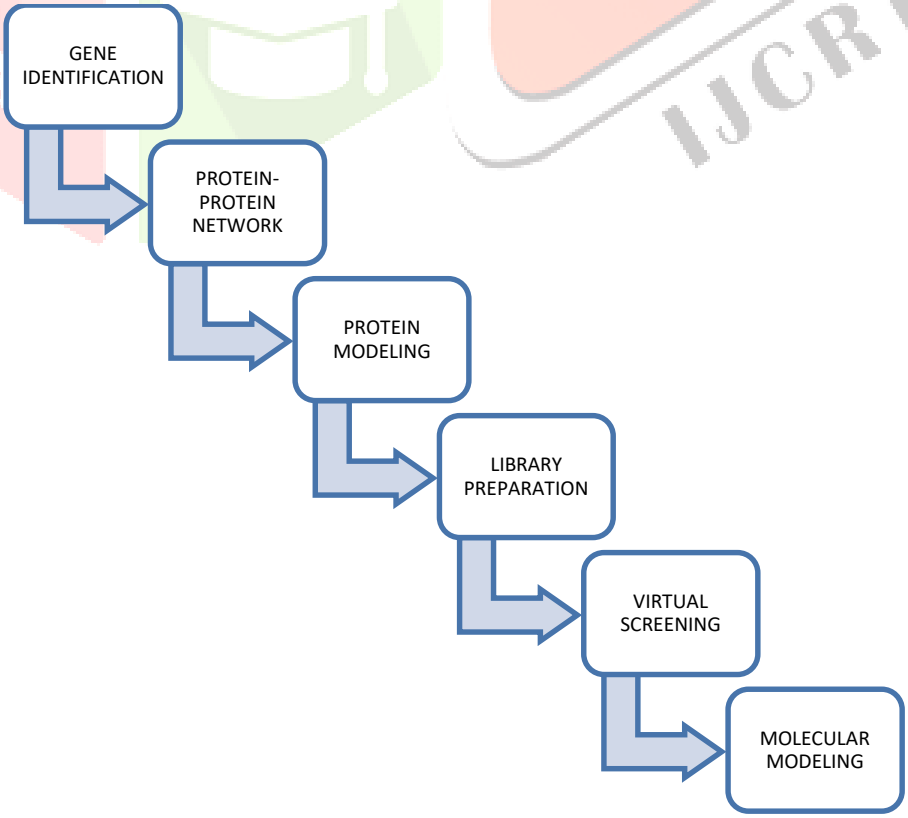


Fig.6. Welcome to the SeaDock Home Page

METHODOLOGY:



Gene Identification:

We used bioinformatics tools like MalaCard, GeneCard, and OMIM to identify genes affected by exposure to microplastics. These databases helped us pinpoint specific genes that are potentially impacted by microplastic pollution.

Protein-Protein Network:

To understand how these genes interact within biological systems, we constructed protein-protein interaction networks using 12 different cytohubba characteristics. This analysis identified TNF (Tumor Necrosis Factor) as a central hub gene, suggesting it plays a crucial role in the network affected by microplastic exposure.

Protein Modeling:

Using Swiss-Model, we generated a 3D structure model of TNF, the key hub gene identified in our protein-protein interaction network analysis. This modeling provided insights into the structural details of TNF, aiding in further computational studies.

Library Preparation:

From a thorough review of the literature, we compiled a list of phytochemicals known for their potential protective effects against microplastic exposure. These compounds were selected based on their documented bioactivity and safety profiles.

Virtual Screening:

We assessed the drug-like properties of the selected phytochemicals using ADMETLab 3.0. This step helped us evaluate their absorption, distribution, metabolism, excretion, and toxicity characteristics, crucial for identifying potential therapeutic agents.

Molecular Modeling:

The binding interactions between TNF and the chosen phytochemicals were investigated by molecular docking experiments. Ellagic Acid emerged as the most promising compound, showing strong binding affinity with TNF (binding energy of -9.36). This suggests Ellagic Acid's potential as a therapeutic agent against health risks associated with microplastic exposure.

RESULT:

Gene Identification and Network Analysis

We utilized bioinformatics tools, including MalaCard a detailed resource that compiles information on human diseases and their related genes, GeneCard a comprehensive database offering information on all documented and anticipated human genes and OMIM an extensive resource on human genes and their genetic traits, to identify genes potentially affected by microplastic exposure. This way we were able to gather a lot of information on genes influenced by exposure to microplastics.

Network Analysis

Our analysis revealed a set of genes whose expressions may be influenced by the presence of microplastics in the environment. The discovery of TNF crucial genes among others, involved a critical analysis that isolated a number of genes whose expressions could be influenced by microplastics in the environment. These findings underscore the genetic pathways through which microplastics could exert their biological effects.


MalaCard3.pdf


GeneCard.pdf


OMIM.pdf

Genes Compiled from MalaCard, GeneCard, and OMIM Databases

Protein-Protein Interaction Network

To elucidate the functional relationships among the identified genes, we constructed protein-protein interaction networks using 12 distinct cytohubba characteristics. Our analysis highlighted TNF (Tumor Necrosis Factor) as a central hub gene within this network. TNF emerged as a key regulator, suggesting its pivotal role in mediating cellular responses to microplastic-induced stress.

MCC	DMNC	MNC	Degree	EPC	Bottle Neck	EcCentricity	Closeness	Radiality	Betweeness	Stress	ClustringCoefficient
CCL2	CCL11	GAPDH	GAPDH	GAPDH	CXCL8	UBC	GAPDH	GAPDH	GAPDH	GAPDH	TM2D1
CD4	CCR6	ACTB	ACTB	ACTB	GAPDH	SNAP25	ACTB	ACTB	ACTB	ACTB	XYLT2
CXCL8	CD27	IL6	IL6	IL6	CD4	SOX2	IL6	IL6	APP	APP	COLGALT1
ICAM1	CXCR3	TP53	TP53	TP53	APP	RPSA	TP53	TP53	TP53	IL6	TMEM126B
IFNG	IL16	EGFR	EGFR	EGFR	IL2	TSC1	EGFR	EGFR	EGFR	TP53	TMEM230
IL10	IL33	AKT1	AKT1	AKT1	TP53	CALM1	AKT1	AKT1	AKT1	AKT1	REG1A

IL1A	IL7	IL1B	IL1B	IL1B	AKT1	HLA-B	IL1B	IL1B	ALB	ALB	NSMAF
IL1B	SELE	ALB	ALB	TNF	TNF	PSMA7	ALB	ALB	TNF	TNF	MST1
IL6	TLR5	TNF	TNF	INS	CCL2	HNRNPA2B1	TNF	TNF	CTNNB1	CTNNB1	TTBK1

Table.1. CytoHubba Parameters Overview: 12 Key Metrics for Network Analysis

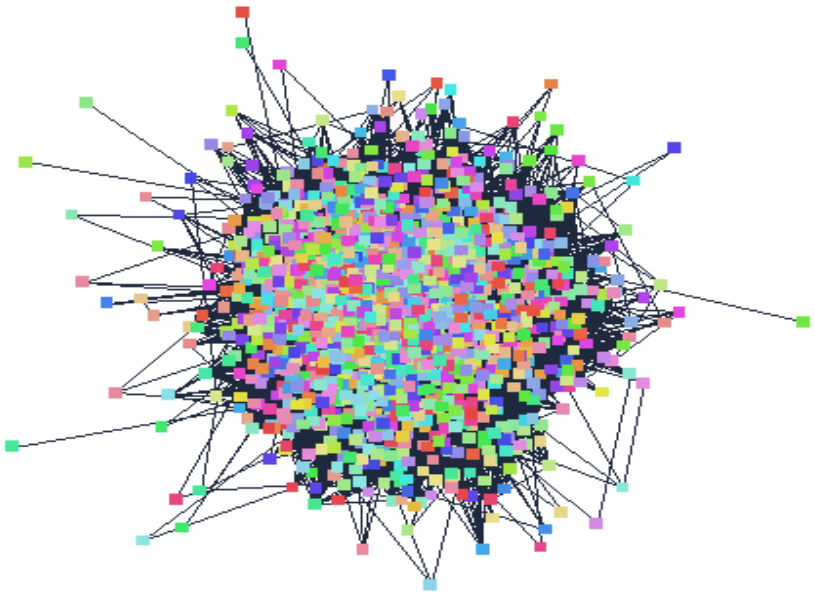


Fig.7. Visualization of Gene Network: Interactions and Connections

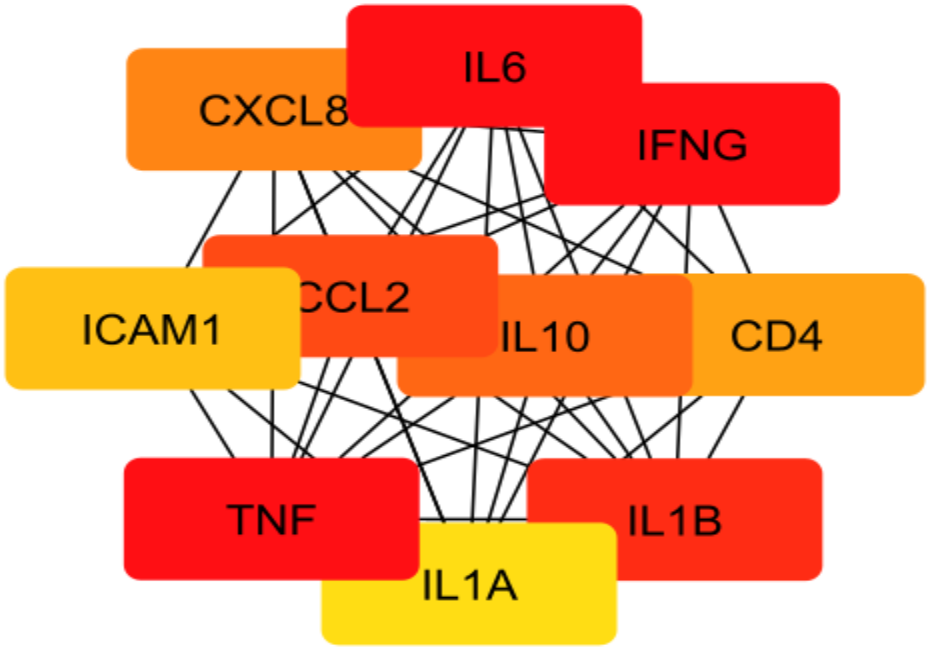


Fig.8. Gene Network Visualization Based on MCC Parameter: Identifying Key Interactions

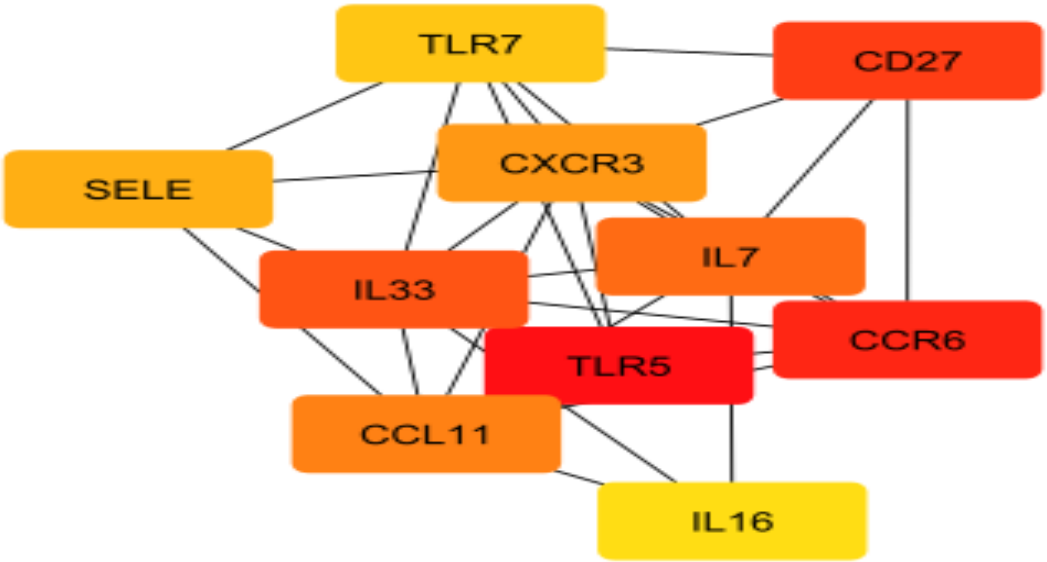


Fig.9. Gene Network Visualization Based on DMNC Parameter: Identifying Key Interactions

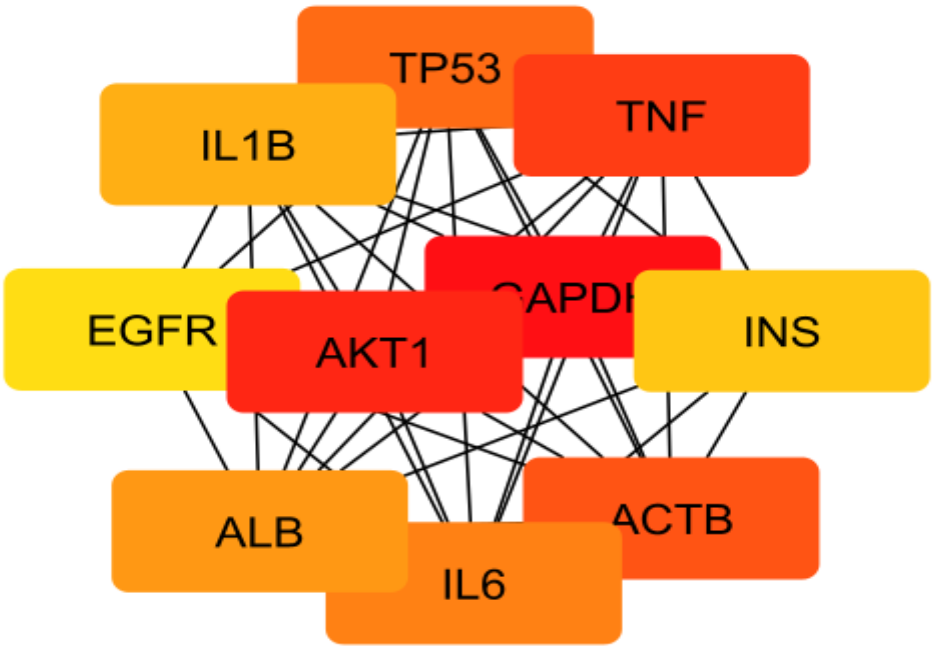


Fig.10. Gene Network Visualization Based on MNC Parameter: Identifying Key Interactions

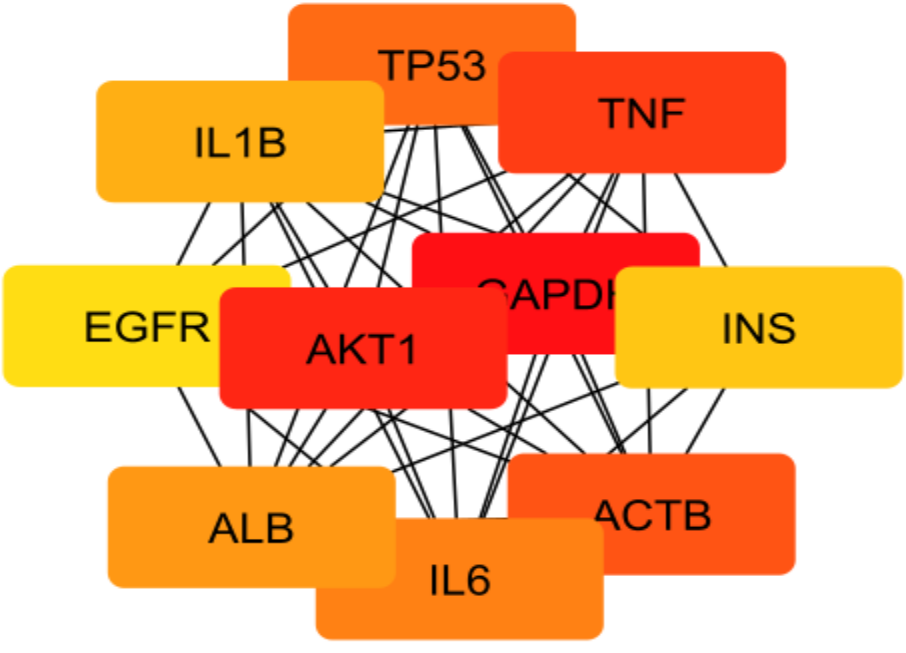


Fig.11. Gene Network Visualization Based on DEGREE Parameter: Identifying Key Interactions

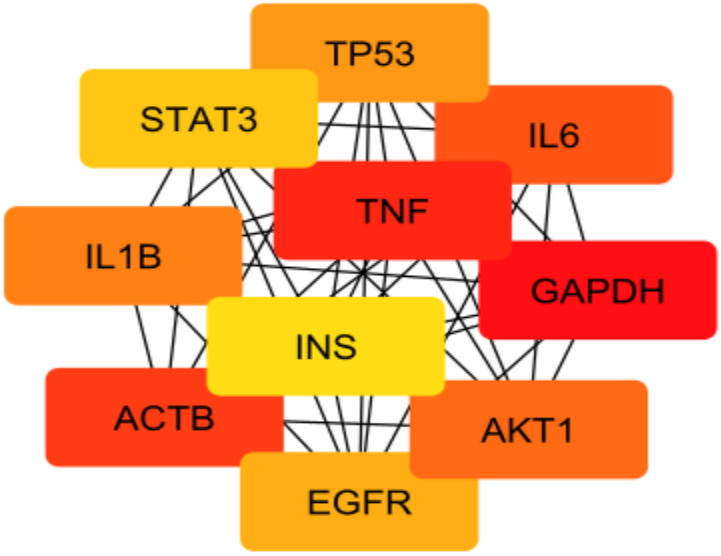


Fig.12. Gene Network Visualization Based on EPC Parameter: Identifying Key Interactions

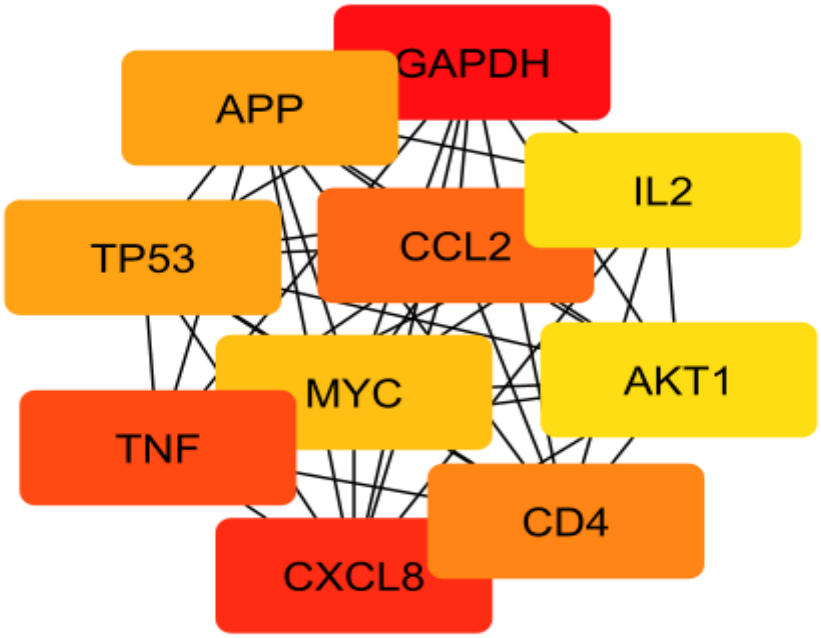


Fig.13. Gene Network Visualization Based on BottleNeck Parameter: Identifying Key Interactions

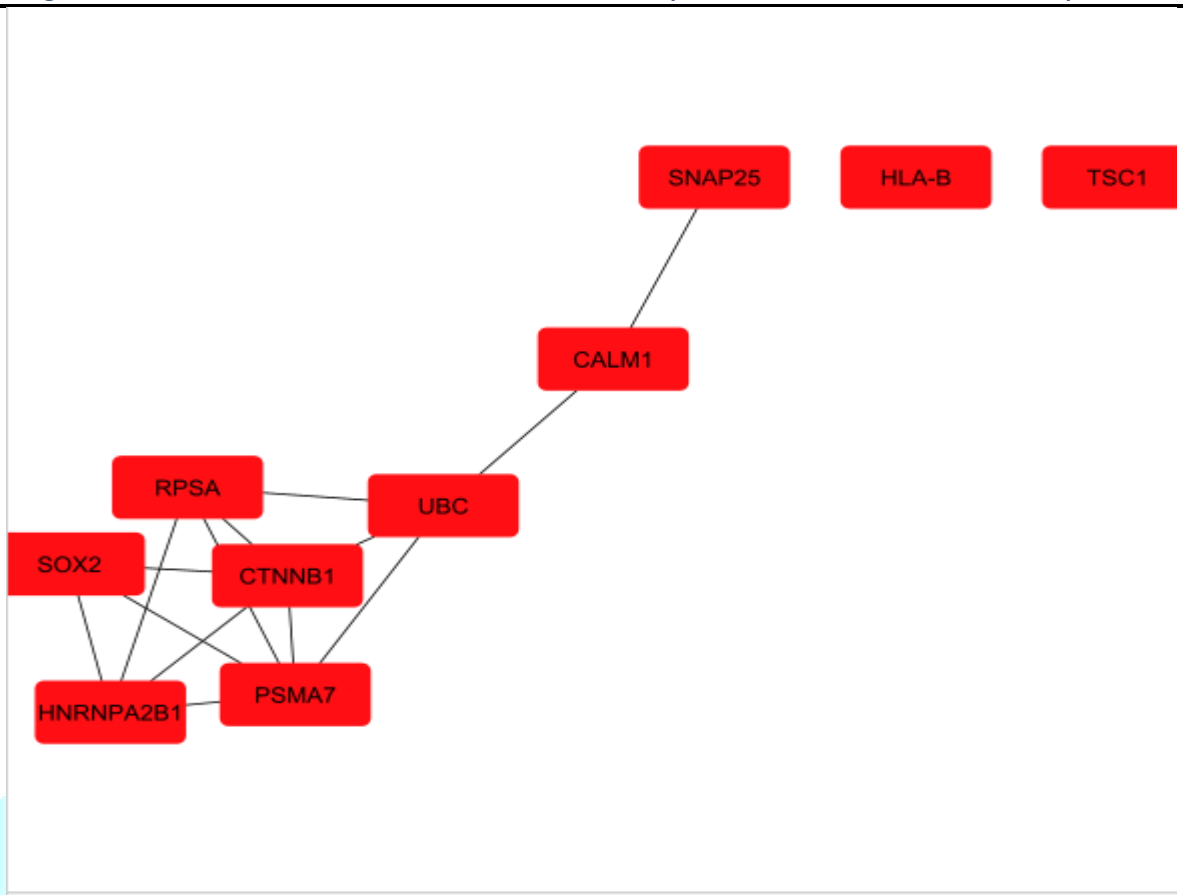


Fig.14. Gene Network Visualization Based on EcCENTRICITY Parameter: Identifying Key Interactions

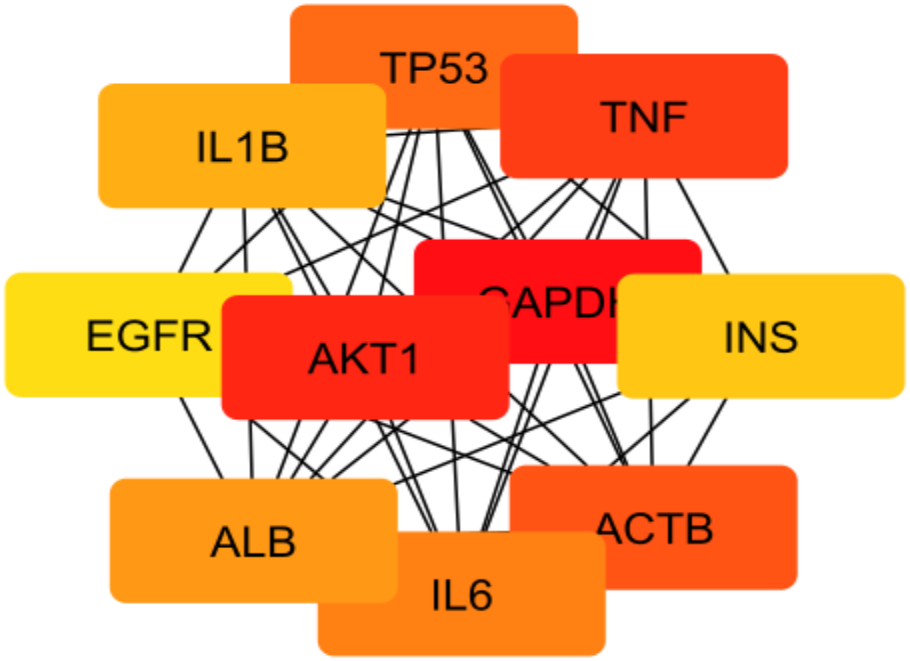


Fig.15. Gene Network Visualization Based on CLOSENESS Parameter: Identifying Key Interactions

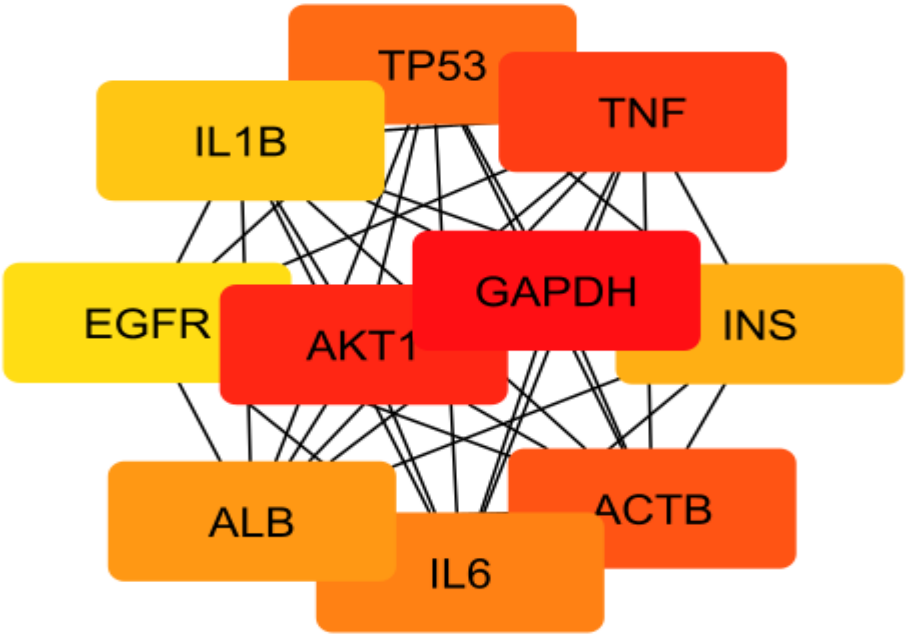


Fig.16. Gene Network Visualization Based on RADIALITY Parameter: Identifying Key Interactions

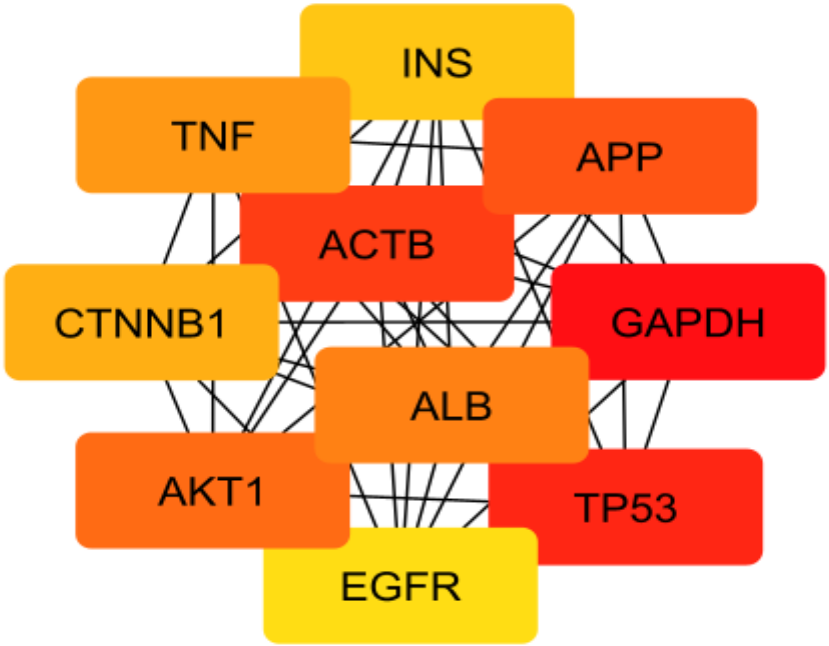


Fig.17. Gene Network Visualization Based on BETWEENESS Parameter: Identifying Key Interactions

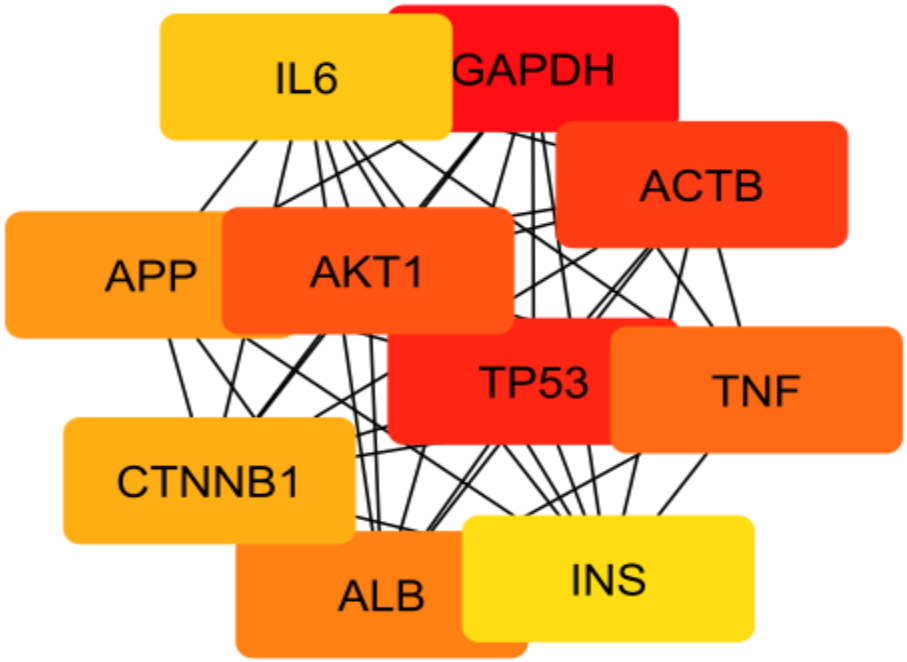


Fig.18. Gene Network Visualization Based on STRESS Parameter: Identifying Key Interactions

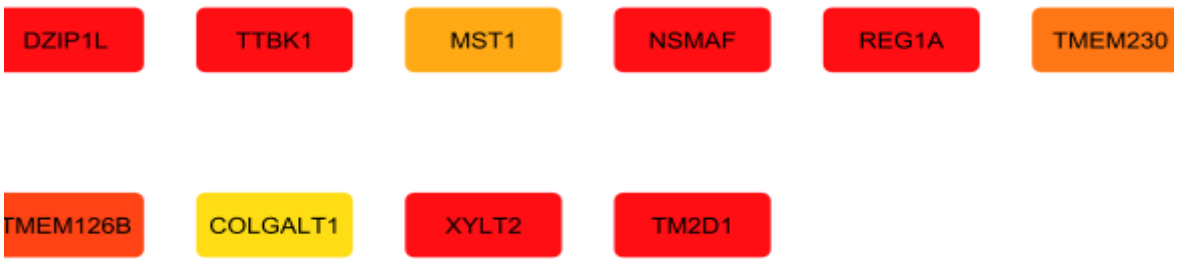


Fig.19. Gene Network Visualization Based on CLUSTERING CO-EFFICIENT Parameter: Identifying Key Interactions

Phytochemical Screening

To identify phytochemicals with potential protective effects against microplastic toxicity, we conducted a comprehensive literature review. This review centered on natural compounds renowned for their antioxidative, anti-inflammatory, and detoxifying qualities. We drew from scientific journals, databases, and previous studies on phytochemicals and their health benefits. From this literature review, we compiled a list of phytochemicals that showed promising effects against environmental toxins and stressors.

ADMET Analysis

Using ADMETLab 3.0, we evaluated the drug-like properties of these phytochemicals, focusing on their bioavailability and safety profiles. The screening process revealed several promising candidates with good pharmacokinetic properties that are worth further investigation.

Phyto compounds	Sources	Scientific Names	Canonical Smile	Lipinski Rule
Curcumin	Turmeric	Curcuma longa	COC1=C(C=CC(=C1)C=CC(=O)CC(=O)C=CC2=CC(=C(C=C2)O)OC)O	ACCEPTED
Resveratrol	Grapes	Vitis vinifera	C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O	ACCEPTED
Quercetin	Onions & Apple	Allium cepa & Malus domestica	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	ACCEPTED
Genistein	Soybeans	Glycine max	C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O)O	ACCEPTED
Luteolin	Celery & Green Peppers	Apium graveolens & Capsicum	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	ACCEPTED

		annuum		
Apigenin	Parsley & Chamomile	Petroselinum crispum & Matricaria chamomilla	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O	ACCEPTED
Kaempferol	Kale & Broccoli	Brassica oleracea & Brassica oleracea vsar.italica	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	ACCEPTED
Catechin	Green Tea & Cacao	Camellia sinesis & Theobroma cacao	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O	ACCEPTED
Naringenin	Grapefruits	Citrus paradisi	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O	ACCEPTED

Sulforaphane	Broccoli & Brussels Sprouts	Brassica oleracea var.italica & Brassica oleracea var.gemmifera	CS(=O)CCCCN=C=S	ACCEPTED
Berberine	Golden seal	Hydrastis canadenis	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC5=C(C=C4CC3)OCO5)OC	ACCEPTED
Ginsenoside	Ginseng	Panax ginseng	CC(=CCCC(C)(C1CCC2(C1CCC3C2(CCC4C3(CCC(C4(C)C)O)C)C)C)O)C	ACCEPTED
Thymoquinone	Black Cucumin	Nigella sativa	CC1=CC(=O)C(=CC1=O)C(C)C	ACCEPTED
Apigenin	Parsley	Petroselium crispum	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O	ACCEPTED
Gingerol	Ginger	Zingiber officinale	CCCCCC(CC(=O)CCC1=CC(=C(C=C1)O)OC)O	ACCEPTED

Ursolic Acid	Holy Basil	Ocimum sanctum	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1C)C)C(=O)O	ACCEPTED
Piperine	Black Pepper	Piper nigrum	C1CCN(CC1)C(=O)C=CC=CC2=CC3=C(C=C2)OCO3	ACCEPTED
Ellagic Acid	Pomegranates	Punica granatum	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	ACCEPTED
Rosmarinic Acid	Rosemary	Rosmarinus officinalis	C1=CC(=C(C=C1CC(C(=O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O	ACCEPTED
Curcumenol	Curcuma Species	Turmeric family	CC1CCC2C13CC(=C(C)C)C(O3)(C=C2C)O	ACCEPTED
Betulinic Acid	Birch Trees	Betulla species	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C(=O)O	ACCEPTED
Emodin	Rhubarb & Aloe vera	Rheum palmatum & Aloe barbadensis	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)O	ACCEPTED

Chlorogenic Acid	Coffee & Blueberries	Coffea species & Vaccinium corymbosum	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O	ACCEPTED
Apocynin	Picrorhiza Kurroa & Japanese Knotweed	Polygonum cuspidatum	CC(=O)C1=CC(=C(C=C1)O)OC	ACCEPTED
Gallocatechin	Green Tea	Camellia sinesis	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)O	ACCEPTED
Epigallocatechin gallate	Green Tea	Camellia sinesis	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O	**REJECTED**
Hesperidin	Oranges	Citrus sinesis	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O	REJECTED
Lycopene	Tomatoes	Solanum lycopersicum	CC(=CCCC(=CC=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC=C(C)CCC=C(C)C)C)C)C)C	**REJECTED**
Oleuropein	Olive Leaves	Olea europaea	CC=C1C(C(=COC1OC2C(C(C(C(O2)CO)O)O)O)C(=O)OC)CC(=O)OCCC3=CC(=C(C=C3)O)O	**REJECTED**

Baicalin	Chinese Skullcap	Scutellaria baicalensis	C1=CC=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC4C(C(C(C(O4)C(=O)O)O)O)O)O)O	**REJECTED**

Table.2. Screening of Phytochemicals with ADMET Analysis Results

Protein Modeling and Molecular Docking Studies

We generated a 3D structural model of TNF using Swiss-Model to gain insights into its molecular architecture. Subsequently, molecular docking studies were conducted to predict the binding affinities between TNF and selected phytochemicals. Among these compounds, Ellagic Acid exhibited the highest binding energy (-9.36 kcal/mol), suggesting strong potential as a therapeutic agent against microplastic-induced health risks.

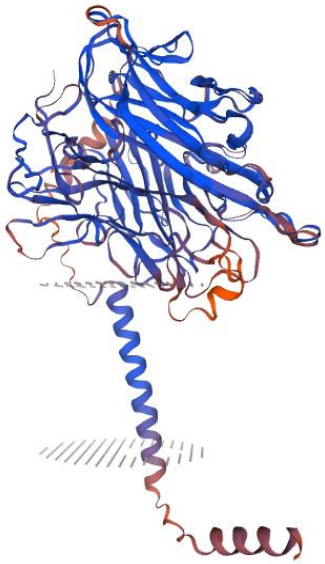


Fig.20. "Structural Model of TNF Gene Generated with Swiss Model: Insights and Analysis"

PHYTOCHEMICALS NAMAE	BINDING ENERGY	AMINO ACID RESIDUE
Curcumin	-6.13	L105, L119, N106, D121, R107, N122
Resveratrol	-7.35	L169, F200, V93, A94, P96, N110, F220, N168, H91, C11, C13
Quercetin	-6.44	Q201, L112 ,N106, R108, N110, L113, A111, A109
Genistein	-7.39	K188, Q178, R179, P176, T181, E186, E192, K174, S175, C177
Luteolin	-6.7	V93, A94, P96, F220, A109, A109, R108, S223, N110, G224
Apigenin	-7.03	V93,A94, P96, R108, A109, F220, V226, G224, G224
Kaempferol	-6.69	V93, A94, P96, R108, A109, F220,V226,G224, S223
Catechin	-7.32	K188, W190, Q178, R179, P176, T181, E186, C177, A187
Naringenin	-7.96	T181, K188, W190, Q178, R179, E180, E186, S175, P176, G144, C177, S175, P182
Sulforaphane	-5.62	P193, Y195, I194
Berberine	-7.25	K188, Q178, P176, T181, S175, E192
Ginsenoside	-6.52	K87, P88, A232, S85, S128, P84

Thymoquinone	-6.35	V93, F220, S223, V226, R108
Apigenin	-7.03	V93, A94, P96, R108, A109, F220, V226, G224, S223
Gingerol	-4.51	A185, K188, Q178, R179, P189, G144, W190
Ursolic Acid	-8.23	N95, Q103, L105, L119, N122
Piperine	-7.73	K188, W190, Q178, R179, T181, E186, S175
Ellagic Acid	**-9.36**	**V93, A94, A109, N110, F220, V226, R108, G224, S223**
Rosmarinic Acid	-7.02	K188, R179, T181, E180, E186, C145
Curcumenol	-7.92	K188, W190, Q178, G144
Betulinic Acid	-9.17	K141, E99, Y217, F220, A221, L218, Q143,G142, D219
Emodin	-8.15	V93, A94, P96, A109, N110, F220, V226, G224, R108, S223
Chlorogenic Acid	-5.26	R107, L113, E118, N106, L119, G116
Apocynin	-6.44	Y195, Q137, P193, I194

Gallocatechin	-7.41	V93, A94, P96, R108, F220,A109, V226, N168, S223, N110,

Table.3. Binding Energy and Amino Acid Residue Interactions of Phytochemicals

Top Docking Results Based on Highest Binding Energy

Fig.21. Ellagic Acid (-9.36)

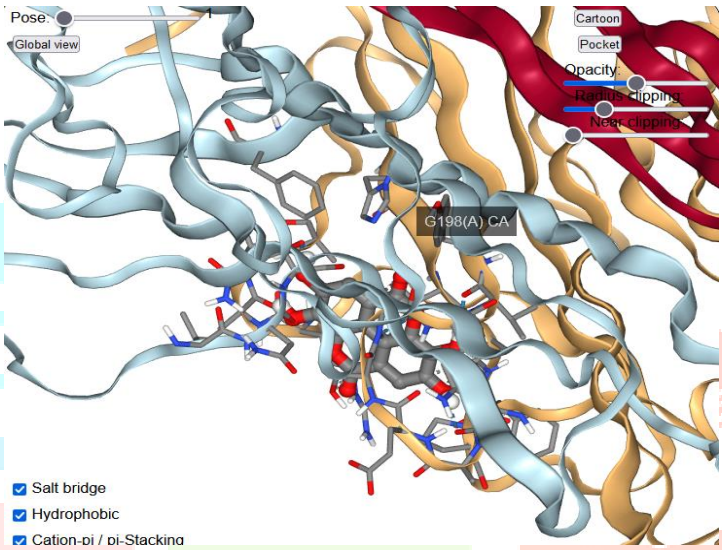
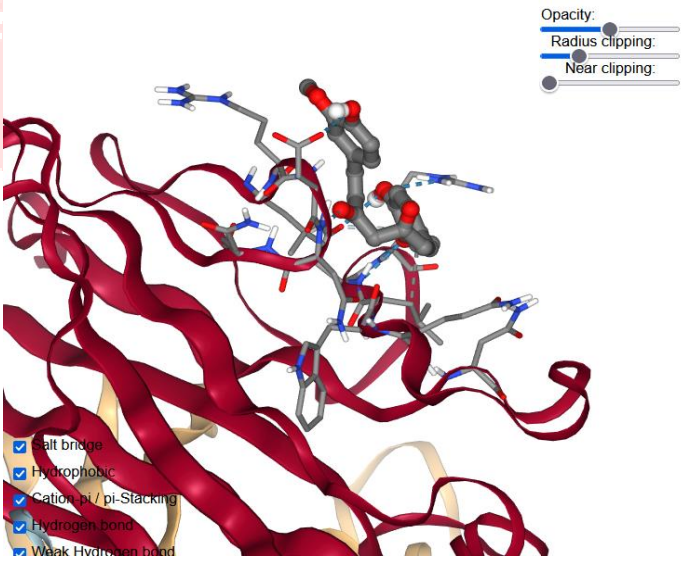


Fig.22. Curcumin (-6.13)



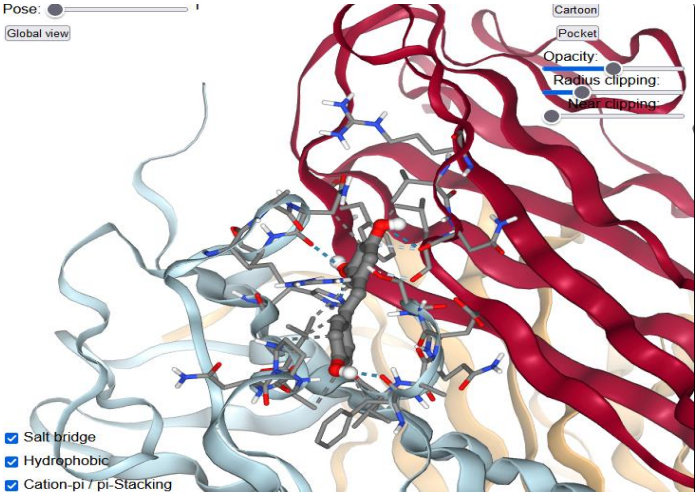


Fig.23. Resveratrol(-7.35)

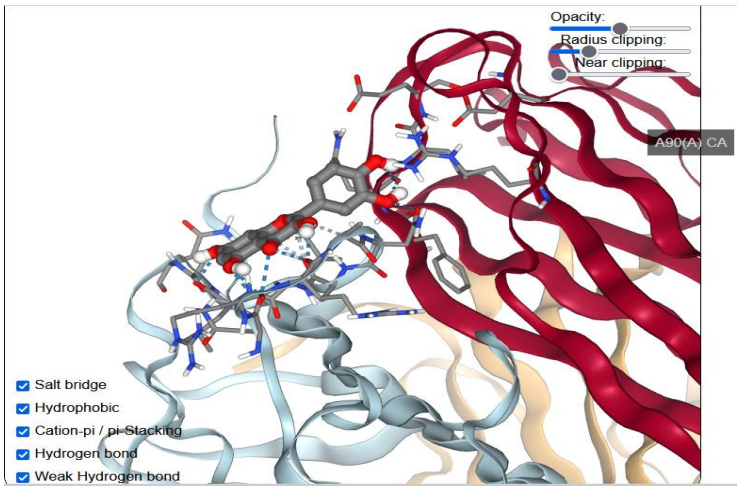


Fig.24. Quercetin(-6.44)

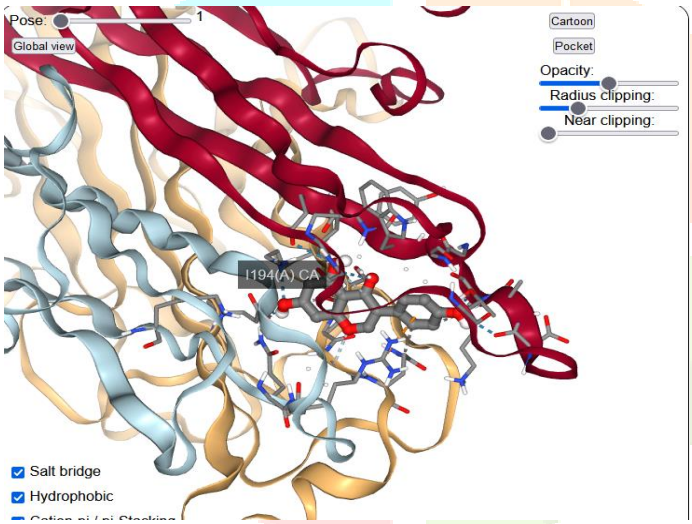


Fig.25. Genistein(-7.39)

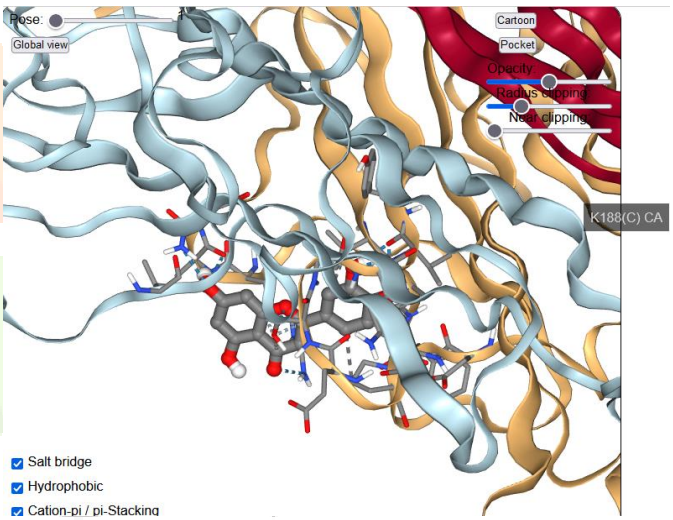


Fig.26. Luteolin(- 6.7)

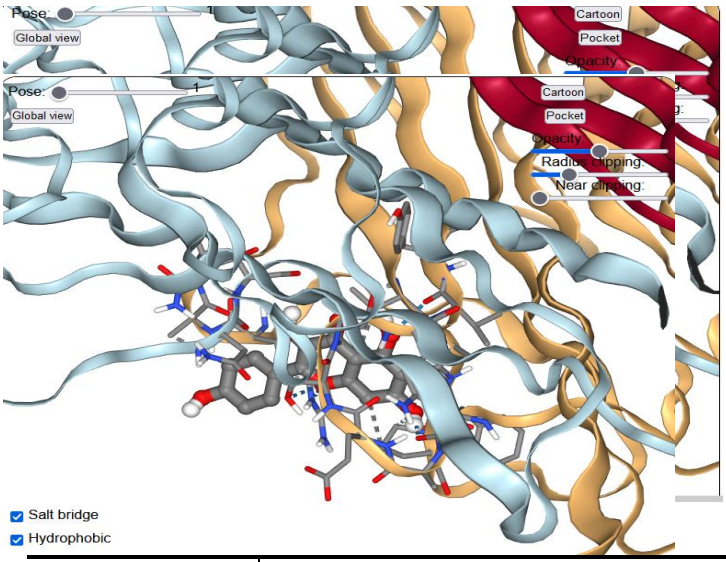


Fig.27.Apigenin (-7.03)

Fig.28.Kaempferol(-6.69).

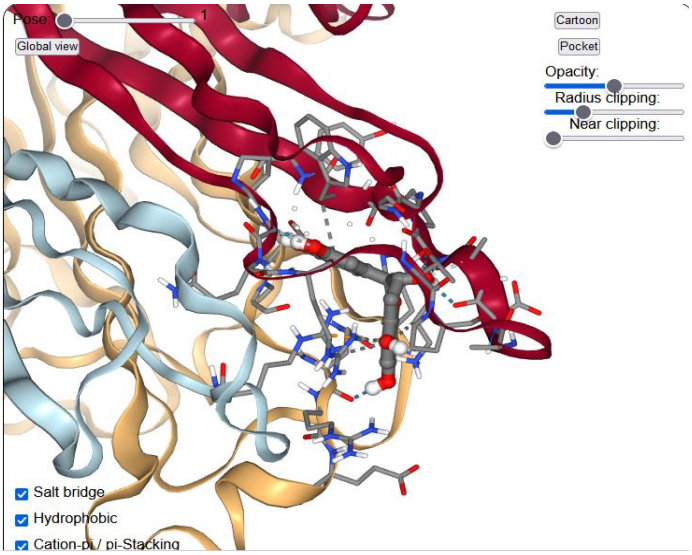


Fig.29. Catechin (-7.32)

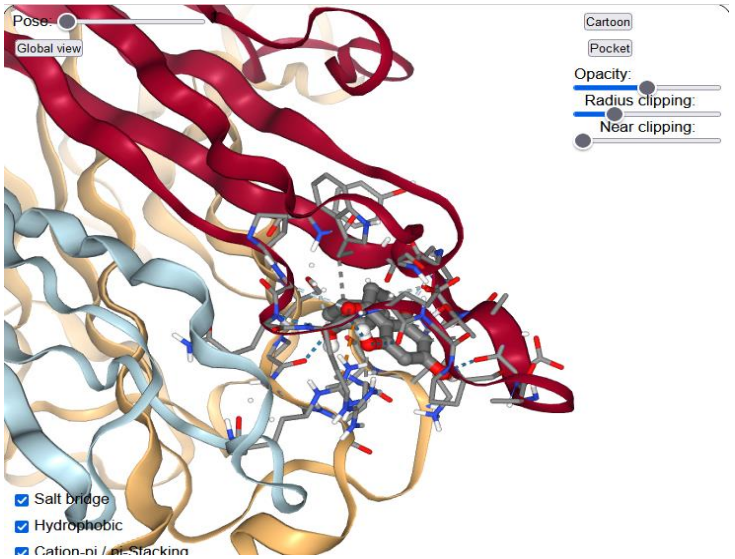


Fig.30. Naringenin (-7.96)

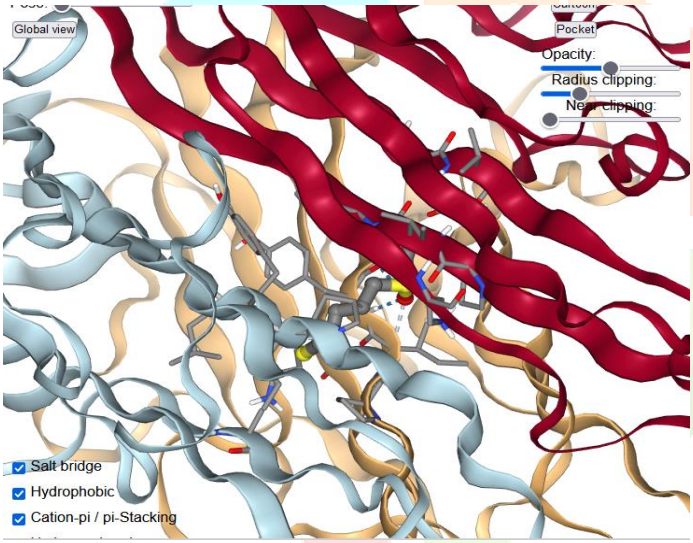


Fig.31. Sulforaphane (-5.62)

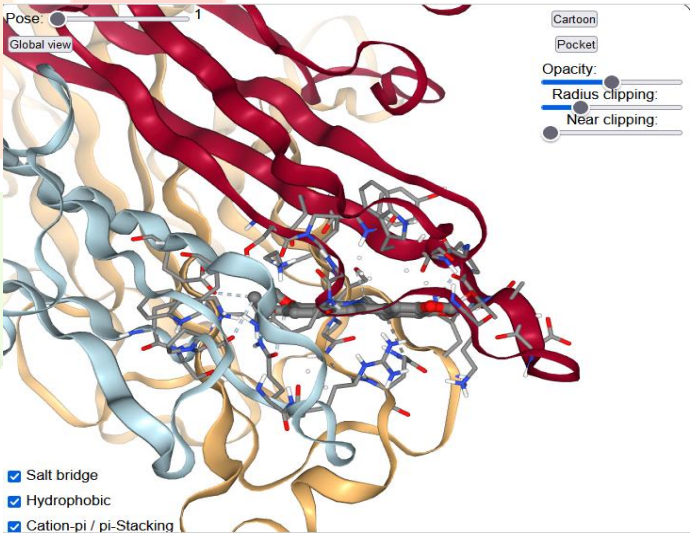


Fig.32. Berberine (-7.25)

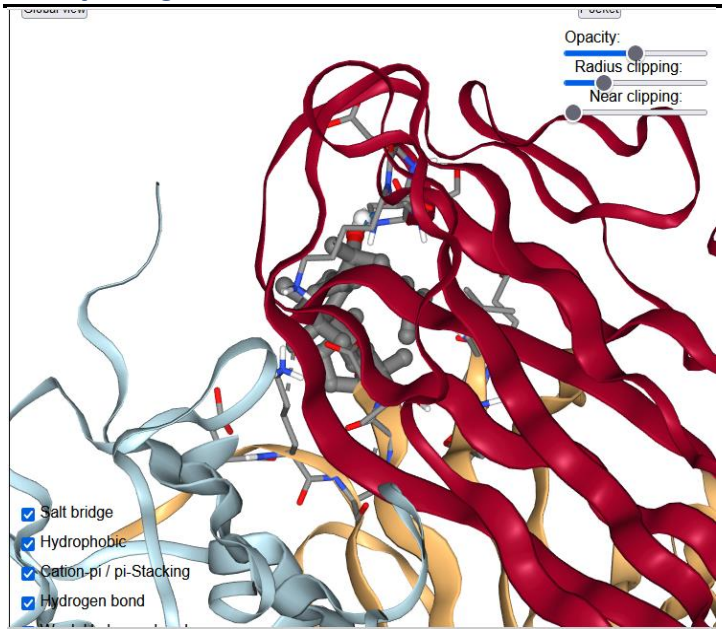


Fig.33. Ginsenoside (-6.52)

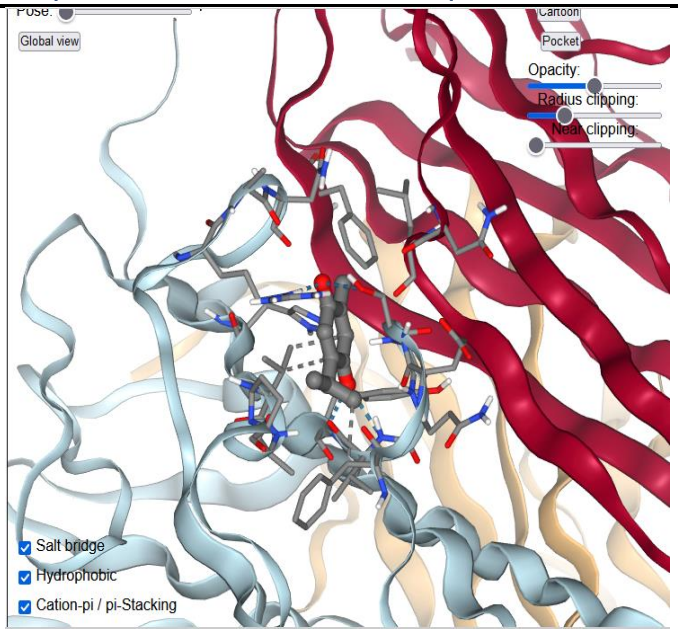


Fig.34.Thymoquinone(-6.35)

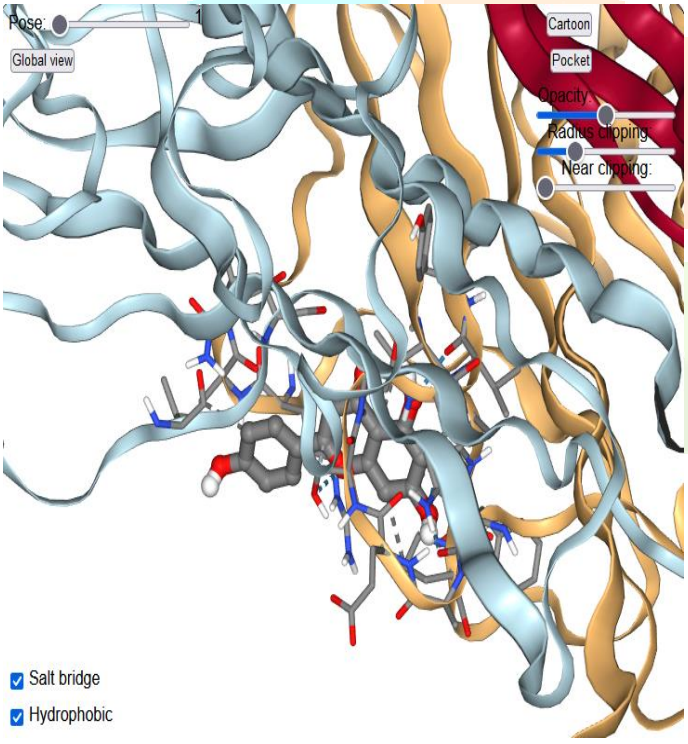


Fig.35. Apigenin (-7.03)

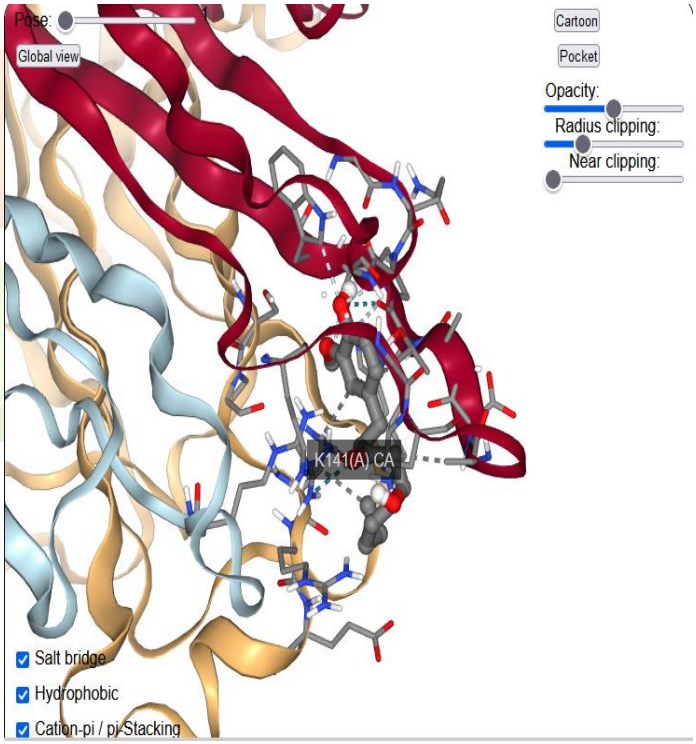


Fig.36.Gingerol(-4.51)

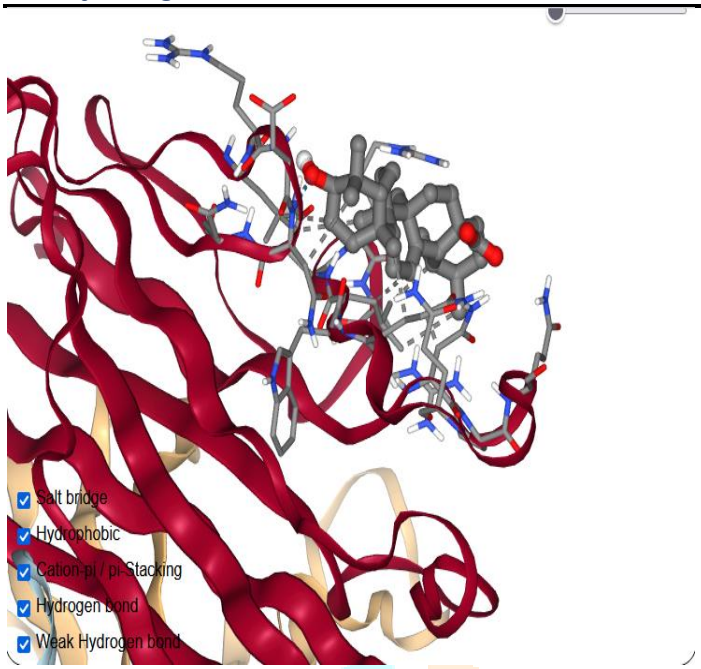


Fig.37. Ursolic Acid (-8.23)

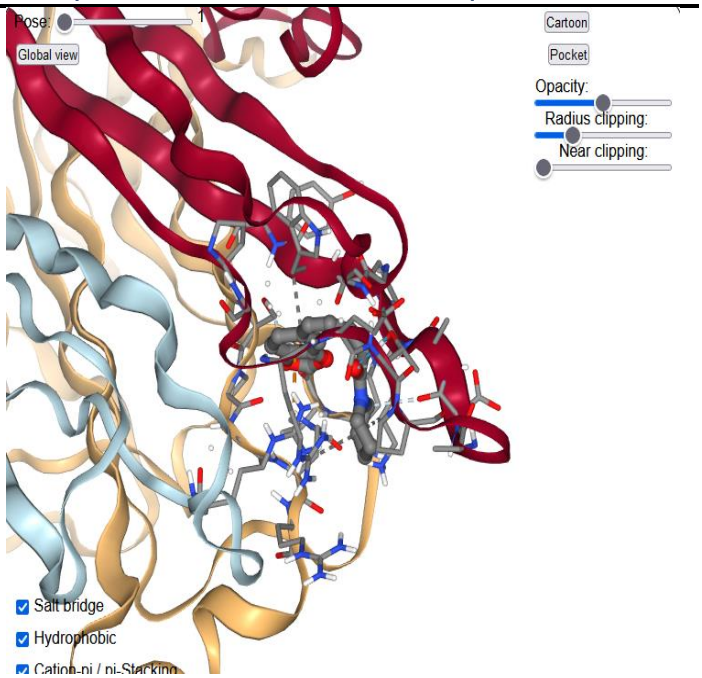


Fig.38.Piperine(-7.73)

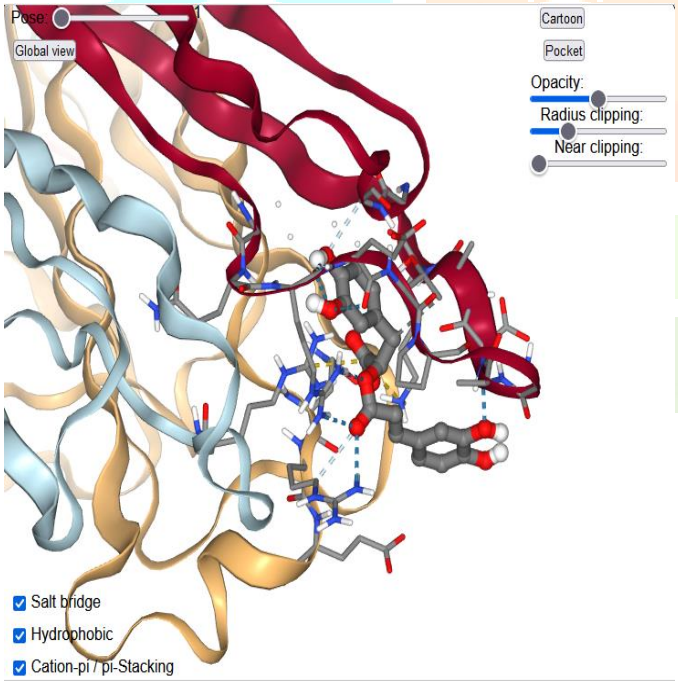


Fig.39.Rosmarinic Acid (-7.02)

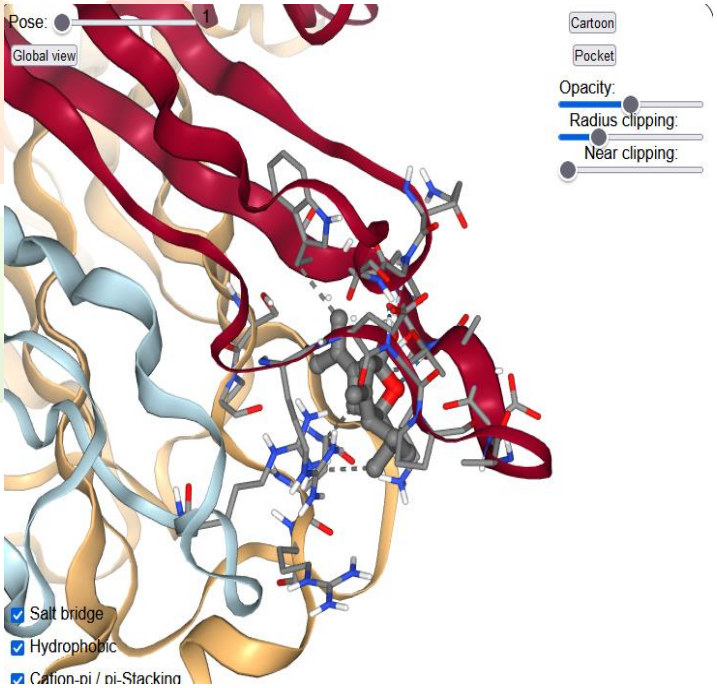


Fig.40.Curcumenol(-7.92)

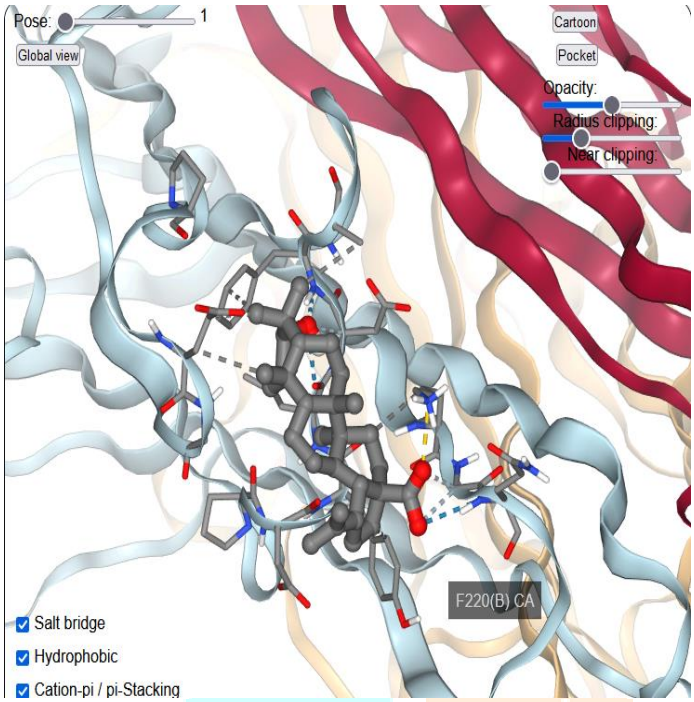


Fig.41. Betulinic Acid (-9.17)

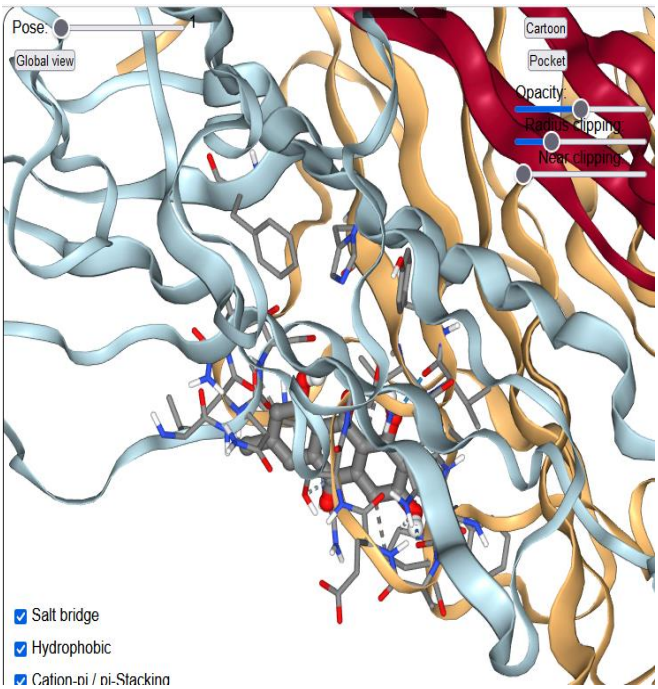


Fig.42.Emodin(-8.15)

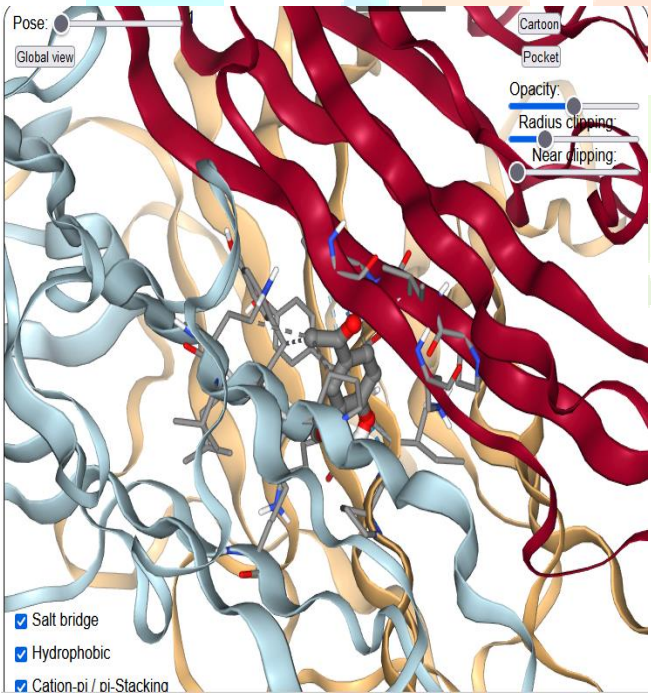


Fig.43. Chlorogenic Acid (-5.26)

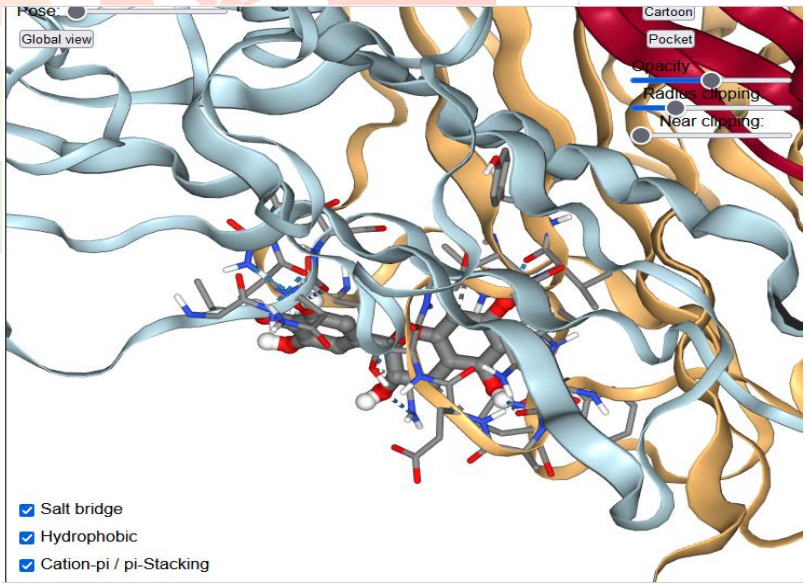


Fig.44. Apocynin (-6.44)

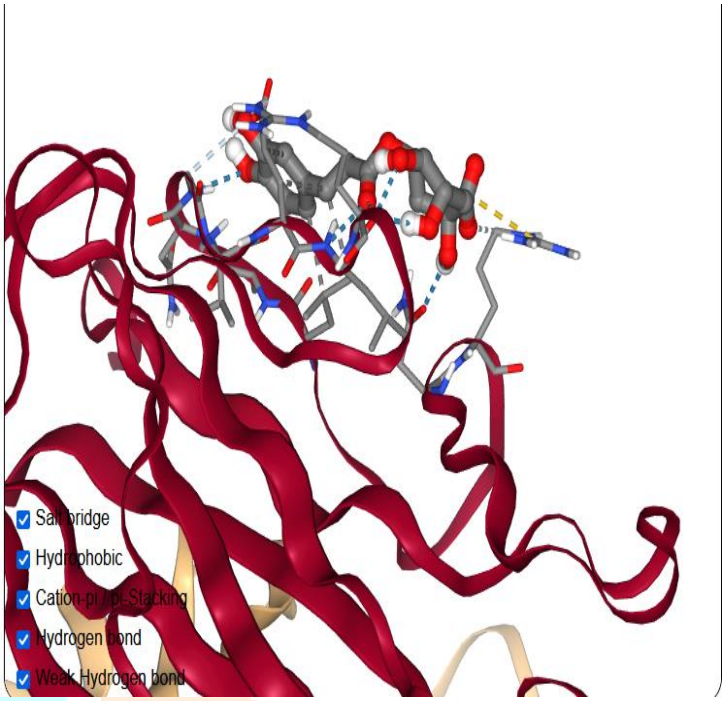


Fig.45. Gallocatechin (-7.41)

DISCUSSION:

Our study delves into the impact of microplastic exposure on gene expression, identifying TNF as a crucial hub gene within affected protein-protein interaction networks. By using bioinformatics tools like MalaCard, GeneCard, and OMIM, we pinpointed key genes influenced by microplastic pollution. TNF's central role in these networks underscores its significance in the biological response to microplastics. Through Swiss-Model, we visualized the 3D structure of TNF, enhancing our understanding of its functional mechanisms. We then curated a library of phytochemicals with potential protective effects and evaluated their ADMET properties using ADMETLab 3.0. Molecular docking studies revealed Ellagic Acid as a promising therapeutic candidate, showing a strong binding affinity with TNF. These findings highlight Ellagic Acid's potential to mitigate health risks posed by microplastic exposure, paving the way for further research into effective interventions.

CONCLUSION:

Microplastics pose a significant threat to human health and the environment, primarily through their ability to transport and absorb harmful substances. Our study employed computational biology techniques to investigate the impact of microplastic exposure at the molecular level.

Through gene identification and network analysis, we identified key genes, with TNF (Tumor Necrosis Factor) emerging as a critical regulator in protein-protein interaction networks affected by microplastics. This highlights TNF's potential role in mediating biological responses to microplastic-induced stress.

Furthermore, our screening of phytochemicals revealed Ellagic Acid as a promising candidate for mitigating microplastic toxicity. Molecular docking studies demonstrated Ellagic Acid's strong binding affinity to TNF, suggesting its potential as a therapeutic agent against microplastic-induced health risks.

Overall, our findings underscore the pervasive threat of microplastics and highlight the importance of computational biology in identifying potential interventions. Further research is warranted to validate these findings and explore the broader implications for environmental and human health.

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