A DISSERTATION ON

Understanding the molecular linkage of commonly exposed toxins withprimary molecular targets in human body

SUBMITTED TO THE
DEPARTMENT OF BIOENGINEERING
FACULTY OF ENGINEERING INTEGRAL UNIVERSITY, LUCKNOW

IN PARTIAL FULFILMENT
FOR THE DEGREE
M.TECH
IN BIOTECHNOLOGYBY

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M. Tech Biotechnology (IV Semester)
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UNDER THE SUPERVISION OF

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CSIR- INDIAN INSTITUTE OF TOXICOLOGY RESEARCH, LUCKNOW

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DECLARATION FORM

I, **Shikha Sharma,** a student **M. Tech Biotechnology (II Year / IV Semester)**, Integral University have completed my six months dissertation work entitled **"Understanding the molecular linkage of commonly exposed toxins with primary molecular targets in human body"** successfully from the **CSIR- Indian Institute of Toxicology Research, Lucknow** under the able guidance of **Dr Ramakrishnan Parthasarathi.**

I, hereby affirm that the work has been done by me in all aspects. I have sincerely prepared this project report and the results reputed in this study are genuine and authentic.

Shikha Sharma
Signature:

Dr. Salman Akhtar
(Course Coordinator)
Signature:

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यह प्रमाणित किया जाता है कि **सुश्री सिखा शर्मा** [Enrollment No: 2000101215] **M.Tech (बायोटेक्नालॉजी)**, इंटीग्रल यूनिवर्सिटी, कुर्सी रोड, लखनऊ, उत्तर प्रदेश 226026 लखनऊ में अध्ययन कर रही है । इन्होने विषय **Understanding the Molecular Linkage of Commonly Exposed Toxins with Primary Molecular Targets in Human Body** विषय पर दिनांक **10/02/2022 से 09/08/2022** तक शोधकार्य का प्रशिक्षण **डॉ रामकृष्णन पार्थसारथी,** प्रधान वैज्ञानिक,, सीएसआईआर-आईआईटीआर लखनऊ, उत्तर प्रदेश के पर्यवेक्षण में प्राप्त किया है।

हम सभी **सुश्री सिखा शर्मा** के उज्जवल भविष्य की कामना करते है।

To Whomsoever it May Concern

This is to certify that **Ms Sikha Sharma** [Enrollment No: 2000101215] student of **M.Tech (Biotechnology)**, Integral University, Kursi Road, Lucknow, 226026 Uttar Pradesh, has undergone dissertation training on **Understanding the Molecular Linkage of Commonly Exposed Toxins with Primary Molecular Targets in Human Body** during **10/02/2022 to 09/08/2022** under **Ramakrishnan Parthasarathi,** Principal Scientist CSIR - Indian Institute of Toxicology Research, Lucknow. Uttar Pradesh

We wish **Ms Sikha Sharma** succes in her future endeavours.

Professor V P Sharma
Head,
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CERTIFICATE BY INTERNAL ADVISOR

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I wish her good luck and bright future.

Dr. Reena Vishvakarma
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I wish her good luck and bright future.

Dr. Alvina Farooqui
Head of the Department
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Date **Shikha Sharma**

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LIST OF ABBREVEATIONS

ALDH	Aldehyde Dehydrogenase
NRF2	Nuclear Factor-erythroid Factor 2-Related Factor 2
PPAR	Peroxisome Proliferator-Activated Receptors
DNA	Deoxyribonucleic Acid
RIPs	Ribosome-Inactivating Proteins
KEAP1	Kelch-like ECH-associated protein 1
ROS	reactive oxygen species
BNL	Brookhaven National Laboratories
PDB	Protein Data Bank
RCSB PDB	Research Collaboratory for Structural Bioinformatics PDB
WHO	World Health Organization
IUGR	Intra-Uterine Growth Restriction
PAH	Polycyclic Aromatic Hydrocarbons
T3DB	Toxin and Toxin Target Database
ToxRefDB	Toxicity Reference Database (ToxRefDB*)*
NTP	National Toxicology Program

ECOTOX	Ecotoxicology Knowledgebase
FAO	Food and Agriculture Organization
MT	Metallothionein
RBP	Retinol-binding protein
IPCS	International Programme on Chemical Safety
CAS	Chemicals Abstract Service
SMILES	Simplified Molecular Input Line Entry System
CastP	Computed Atlas of Surface Topography of Proteins

ABSTRACT

Toxins are extremely damaging to our bodies, and they can be found in our environment, food, and cosmetics. They cause cell destruction. Herbivores and plant pathogens, as well as other species such as viruses, bacteria, and fungus, including humans, can be poisoned by many plant and food components. Toxic substances enter the nervous system through ingestion, trans-cutaneous absorption, and mucous membrane absorption via aerosols.

This study's goal is to comprehend the mechanism of toxicity induced by plant and food- related toxins and to knowledgeably aware mankind to the consequences of toxic exposure. We curated nearly a hundred toxins from T3db to which humans are exposed either directly or indirectly and categorized them into plant and food toxin categories. Post categorization, we identified the molecular targets present in the human body to which these toxins interact by performing the in-depth study of available literature and taking aid from online tools such as TargetHunter. These interacting toxins lead to ramification at the genotypic and hence phenotypic level. We then studied the target and identified their roles in various metabolic pathways along with understanding the consequence of target-toxin interactions which deciphers whether it up or down-regulates the expression of the target. We selected the top three targets forfurther investigation based on the fact that the majority of toxins are targeting them. These include Aldehyde Dehydrogenase (ALDH), Nuclear Factor-erythroid Factor 2-Related Factor 2 (NRF2), and Peroxisome Proliferator-activated Receptors (PPAR).

Molecular docking is excellent in silico approach for understanding the molecular level interaction and binding of receptor and ligand molecules. Thus, ninety-six toxins were docked within the active site of each of the three aforementioned targets. The results were compared andminimum binding energy and binding interaction residues in the targets' active sites were reported. The reported results deciphered where and how efficiently the commonly exposed toxins interact in the human body and how these interactions affect the metabolism.

AIMS AND OBJECTIVES

- To comprehend the consequences of exposure to common toxins
- Identification of human molecular receptors that bind with toxins
- Molecular docking studies of toxins against identified molecular targets
- Evaluation of the binding affinity and interactive active residues of toxin and molecular targets

1. INTRODUCTION

Toxicology is the study of a chemical or physical agent's "adverse" effect on a live organism.Some toxins can be utilized as a cancer-killing. Doses, duration of exposure, routes of exposure, species, gender, and environment are all factors that influence chemical toxicity. Toxicity tests can be performed *in vivo* (on the entire animal), *in vitro* (on isolated cells or tissues), or *in silico* (on computer models, in a computer simulation)[4].

Toxicity is a measure of the concentration of a substance required to harm a living organism[1]. When a drug reaches a hazardous dose, it begins to harm an organism. The metabolic processes that occur in an organism when a potential toxin is introduced determine the toxin's effects substantially. Some toxins damage ion channels within cells, while others can destroy the cell membrane or cause DNA mutations[2]. If the toxin is not removed, all of these factors will eventually cause the creature to end up dying.

Toxins are abundant in the environment, and individuals are exposed to them in a variety of ways, both direct and indirect. Pollutants, heavy metals, pesticides, dietary sources, air, water, and other ways of contact can all be contributing factors to susceptibility[3,4]. Toxins can be classified as natural, created by living cells, or chemical[5]. They have negative human repercussions. Toxin exposure can occur in a variety of ways, including inhalation, ingestion, and skin and ocular contact [6]. The lungs are the primary interface for hazardous products, yet they are also the most vulnerable. Inhaled airborne contaminants can be deposited in the lungs and absorbed if they are soluble. Coughing and macrophage cleansing are two protective systemsfor the lungs[7]. Heavy metal poisoning can be caused by industrial exposure[8], air or water pollution[9], foods, pharmaceuticals[10], inadequately insulated food containers[11], or absorption of lead-based paints[12]. Heavy metal toxicity covers a wide spectrum of heavy metals, such as cadmium, mercury, and lead, all of which are on the World Health Organization's list of ten compounds of serious public concern [13].

The plant often produces toxins spontaneously, however, can be more allelopathic under stress, such as improper cultivation, harvesting, storage, and transportation circumstances [21]. Toxic levels of plant toxins, such as tomatine or glycoalkaloids, can be dramatically increased by fungal pathogenic infections. In a soy-rich diet, some plant toxins, such as phytate can induce

vitamin and mineral deficiencies[22]. Food toxins are natural substances made up of a variety of molecules produced by the metabolism of fungi, algae, plants, or bacteria that can affect humans and other vertebrates even at extremely low doses. Food poisoning is caused by food toxins, which are most commonly caused by salmonella bacteria present in meat, eggs, and dairy products [23]. Claviceps generate ergotamine, which is one of the ergot alkaloids and grows on cereal kernels and grass seeds[24]. Acute ergotamine ingestion of 12 milligrams has been associated with mortality.

Toxins target various molecular receptors present in the cellular makeup of humans. For instance, the Gb3 receptor, which is mostly expressed on the cell surface of endothelial cells of the intestine, kidney, and brain in humans, is the principal molecular target for Shiga toxins activation. It belongs to the group of type 2 ribosome-inactivating proteins (RIPs) bacterial toxins[30]. These receptors are engaged in one or the other metabolic pathways necessary to maintain the proper functioning of the body and their interaction with toxic chemicals will manifest an unwanted response. This will lead to cytotoxicity which is often lethal in various ways.

The development of methods to identify and overcome these toxic side effects of the toxins to which are exposed in our day-to-day life can be done with the aid of in silico tools including PDB, CastP and others.The Protein Data Bank (PDB) was founded in 1971 with less than 10 X- ray crystallographic structures of proteins, making it the first open-access digital data repository in biology [1]. The structural biology community 628 began debating how best to archive protein crystallographic results and make them widely available soon after the X-ray structures of myoglobin [2, 3] and hemoglobin were published. In 1971, Brookhaven National Laboratories (BNL) (1) developed the Protein Data Bank (PDB) as a repository for biological macromolecular crystal structures18. The deposition rate has increased over the last year, with 2693 structures added to the PDB between June 1999 and July 2000.The PDB considers all data gathered from depositors to be primary data. The RCSB takes an average of fewer than two weeks to complete all entries, including author amendments. Structures have also become significantly more sophisticated. In August 2000, the structure of the major subunit of the ribosome, which contains 2833 RNA nucleotides and 27 proteins, was published [19].

Swiss Model is a web server for programmed comparative protein modeling. Three-dimensional protein structures are used to guide a number of applications in life science research and provide essential information about their molecular activity. Many biological processes usually revolve around protein complexes. A thorough description of the interactions between protein complexes and networks as well as the overall quaternary structure is necessary for a complete understanding of biological systems, how they function, and how we could affect them [20,21].

The CASTp service intends to provide a quantitative characterization of topographic aspects of proteins in a complete and detailed manner [22,23]. The CASTp server has received 45 000 visitors and satisfies 33 000 calculation requests annually since its deployment 15 years ago. It has become a very useful tool for a variety of studies & researches which includes signaling receptor research [1], cancer drug discovery [24], drug mechanism of action understanding [25], immune disease research [26], protein-nanoparticle interactions [27], protein function inference [28], and the development of high-throughput computational tools [29,30].

Discovery Studio® is a graphical interface with a single, easy-to-use interface for advanced drug design and protein modeling research. It includes both tried-and-true applications (such asCatalyst, MODELER, CHARMm, and others) with years of published results, as well as cutting- edge science to solve today's drug discovery challenges. The SciTegic Pipeline PilotScitegic Enterprise Server platform TM is the foundation of Discovery Studio. A platform that allows for the seamless integration of protein modeling, pharmacophore analysis, and structure-based drug design third-party Programmes, as well as design [40].

Four categories of current methods for predicting targets of tiny molecules can be made: According to Bender et al., the pioneers in target prediction, "chemical similarity searching, data mining/machine learning, panel docking, and the evaluation of bioactivity spectra [41]. A crucial area of research is the identification of known bioactive compounds' targets as well as new synthetic analogues. The Targets Associated with its Most Similar Counterparts, a ground-breaking in silico target prediction method, was created by TargetHunter by examining the largest chemo genomic databases, ChEMBL. It also includes Bioassay Geo Map, an embedded geography tool thatallows users to quickly find possible collaborators who can experimentally validate the anticipated biological target(s) or off-target(s). TargetHunter thus offers a viable strategy to

overcome the research gaps between biology and chemistry, allowing chemogenomics researchers to dramatically increase their productivity in the *in silico* drug design and discovery.

AutoDock Vina (referred to as Vina in the following) was released in 2010, by the same company that released AutoDock, to improve accuracy and performance. It's also released under the GNU General Public License [42]. A scoring function is employed to determine the free energy of the modeled system, and an exploration approach is utilized to sample the positional and conformational space in most docking programmes43. One of the various protein-ligand docking programmes available is AutoDock. It was first released in 1990, and it has since been updated [43-52].

2. REVIEW OF LITERATURE

2.1.Toxicology

Toxicology is a branch of science that studies the negative consequences of chemicals, substances, and conditions on humans, animals, and the environment. Toxicology uses science to foretell which compounds will be dangerous and in what ways, then disseminates this knowledge to protect the public's health. According to the World Health Organization (WHO), there are 10 chemicals of serious public health concern which include Arsenic, asbestos, benzene, cadmium, dioxin-like substances, mercury, inadequate or excess fluoride, and lead. Computer toxicology is a burgeoning field of study that combines improvements in molecular biology and chemistry with modeling and computational science to improve the subject's prediction potential (U.S. EPA, 2003). Toxicology has only recently gained prominence, and in a society where the safe use of chemicalsubstances is valued more than their toxicity.The prediction of potential (eco) toxicological effects and chemical destiny qualities is one of the most common applications of computational approaches. A variety of commercial and non-commercial software tools are available for this general purpose.This has proven to be more challenging than toxicity prediction in general, but a variety of software methods have been created and utilized, particularly in the pharmaceutical industry[53].

Toxins interact with molecular targets in the human body which results in adverse outcomes. These targets could be any of the macromolecules including DNA, RNA or proteins. Some of these are discussed below.

2.2.Aldehyde Dehydrogenase

Aldehyde Dehydrogenase is a type of protein *(figure 1a)*, the second enzyme in alcohol metabolism's primary oxidative pathway. The electrophoretic mobilities, kinetic characteristics, and subcellular localization of two primary liver isoforms of this enzyme, cytosolic and mitochondrial, can be separated; this gene encodes the main cytosolic isoform, which has a lower affinity for aldehydes than the mitochondrial enzyme [5]. ALDH1 is a retinoic acid enzyme that catalyzes the transformation of vitamin A (retinol) to retinoic acid. ALDH1A1 and ALDH2 are involved in the metabolism of alcohol [6]. The elevated expression of ALDH1A1 in cancers has

been discovered to provide a pathway for malignancies to resist treatment, especially cyclophosphamide [7,8,9].

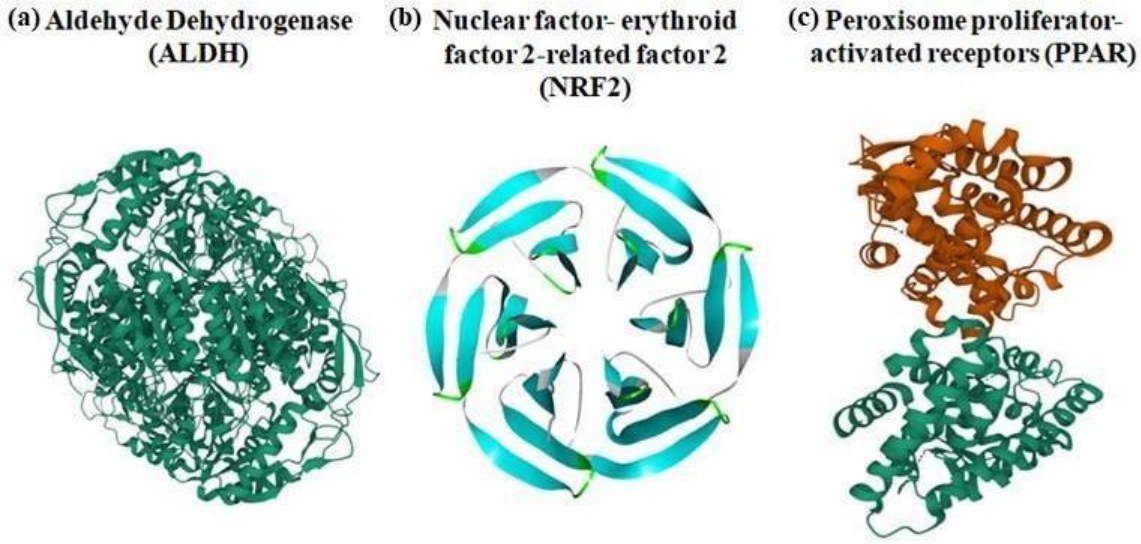


Figure 1: Molecular targets of some common toxins

2.3.Nuclear factor erythroid 2-related factor 2 (NRF2)

In the cellular cytoprotective responses, nuclear factor erythroid 2–related factor 2 (Nrf2) *(figure 1b)* regulates redox equilibrium like a master [10]. Keap1 (Kelch-like ECH-associated protein 1), a cytosolic repressor, keeps Nrf2 sequestered in the cytoplasm, where it is constantly destroyed [11]. However, in response to oxidative stress, Nrf2 is uncoupled from Keap1 repression, translocates to the nucleus, forms heterodimers with tiny musculoaponeurotic fibrosarcoma proteins, binds to antioxidant response elements, and activates a number of genes. [12]. The interaction of nrf2 with the toxic compounds leads to deficient levels of nrf2 in the humanbody. Lack of Nrf2 resulted in a rise in intracellular ROS levels, an increase in the ratio of oxidisedto reduced glutathione, a shortage in the production of numerous antioxidant enzymes, and more [121].

2.4.Peroxisome proliferator-activated receptor delta (PPAR)

PPAR *(figure 1c)* is essential for lipid metabolism and glucose homeostasis, according to various studies. Its activation is particularly beneficial in the prevention of metabolic diseases like

obesity, type 2 diabetes, and dyslipidemia [13,14,15,16]. PPAR activation inhibits the signal transducer and activator of the transcription 3 (STAT3) pathway in adipocytes and hepatocytes, which prevents IL-6-induced insulin resistance [17]. PPARs are ligand-activated transcription factors that regulate target gene expression in response to both intrinsic and extrinsic ligands. PPAR ligands have been designed to cure a variety of disorders, including dyslipidemia and diabetes. As a result of their interactions with toxic compounds, they might be unable to bind to specific ligands 122.

Toxicology emerged as a major multidisciplinary science as a result of major events in the development and application of chemistry and biology. Specific hazardous chemicals could not be recognized and described in terms of exposure, dose, mechanism of action, and toxicity until the late 18th century [53]. Some of the lethal toxins are discussed below.

2.5.Fenvalerate

For a long time, fenvalerate*(figure 2a)*, a type II synthetic pyrethroid, has been utilized in agriculture and household contexts to control a range of insects (Tang et al., 2018). The broad insecticidal range, great efficiency at low concentrations, and low acute toxicity to animals are the key benefits of fenvalerate. The general public is exposed to fenvalerate mostly through food,and drinking water (Cui et al., 2018) According to reports, even though it has been found in the aquatic environment and soil (Zhang et al., 2019), metabolites were discovered in bovine milk, fruit (Del, 2015), and urine even breast milk and urine from humans. Increasing data reveals that fenvalerate is a toxicant with the potential to cause harm to numerous toxicity pathways in non- target organisms. As per the laboratory's animal model, the exposure to fenvalerate at Fetal intrauterine growth restriction (IUGR) was produced by a late gestational stage [54].

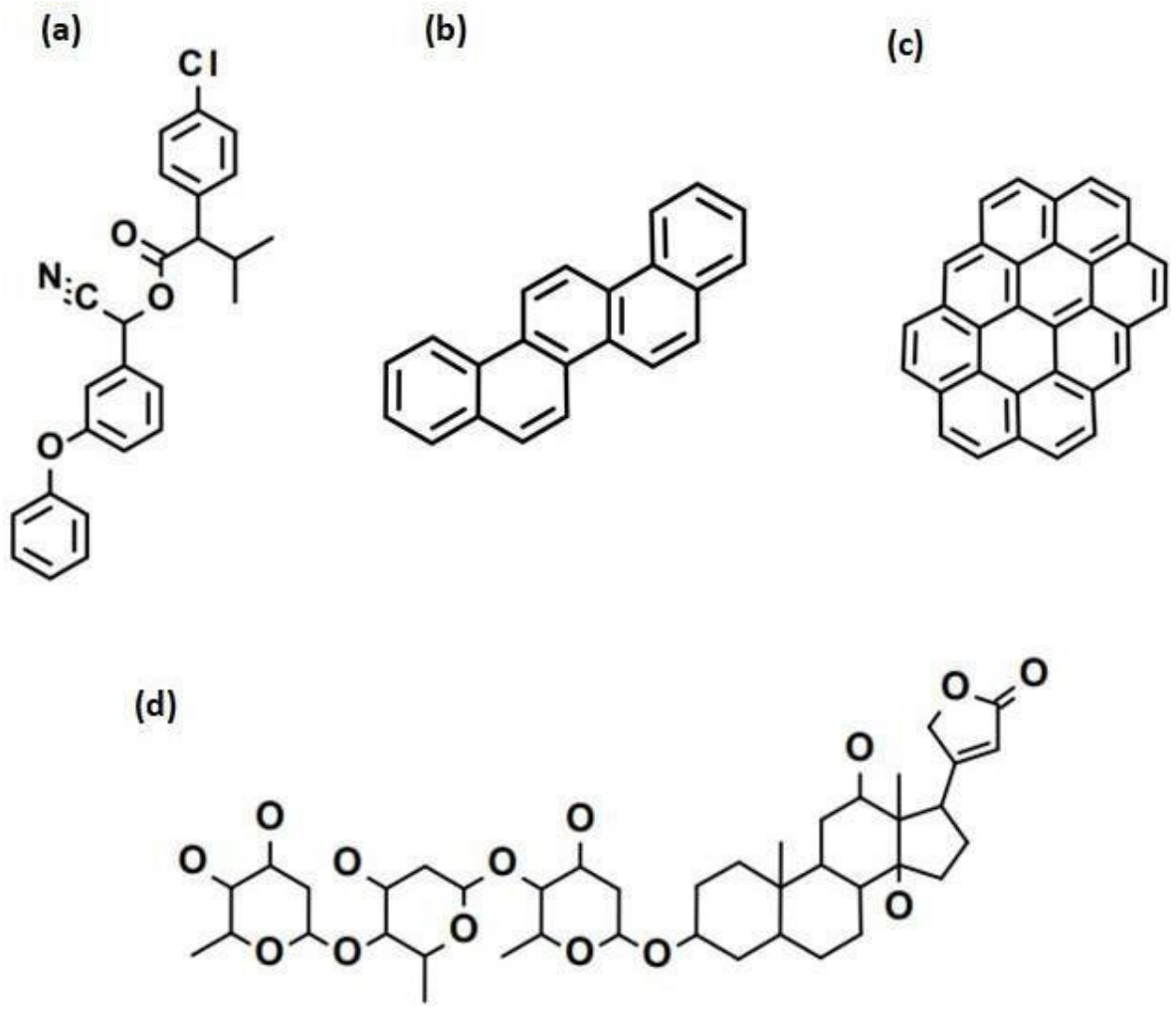


Figure 2: Structures of some commonly exposed toxins: (a) Fenvalerate, (b) Picene, (c) Ovalene, and (d) Digoxin

2.6.Picene

Picene (benzo [a]chrysene) *(figure 2b)*, like other polycyclic aromatic hydrocarbons (PAH), is widely disseminated in the environment as a result of incomplete organic matter combustion [55, 58]. Picene was found to be inactive as a full carcinogen in various studies [59, 64] although it was reported to operate as a weak tumor promoter in large doses[66]; however, this conclusion could not be validated. Picene is poorly soluble in water-miscible organic solvents, such as 120

pg/ml acetone, although the number of organic solvents used in microsomal incubation should be kept as low as possible to avoid interactions with microsomal enzymes [67].

2.7.Ovalene

Ovalene *(figure 2c)* is a ten-membered polycyclic aromatic hydrocarbon with the formula C32H14. Coronene is a close relative. It is a chemical with a reddish-orange hue. Solvents including benzene, toluene, and dichloromethane are only marginally soluble in them. When exposed to UV light, its solutions glow green [68]. Deep-sea hydrothermal vent regions and the hydrocracking process of petroleum refining have both been demonstrated to produce ovalene.

2.8.Digoxin

Digitalis lanata produces digoxin *(figure 2d)*, a cardiac glycoside (Hollman, 1996). It's been used extensively to treat a variety of heart conditions, including congestive heart failure, atrial fibrillation or flutter, and some cardiac arrhythmias. Digoxin is one of the oldest cardiac medications. It works by increasing the myocardial contractility, increasing the blood pressure and stroke volume, lowering the heart rate, and extending the duration between contractions. It may improve cardiac function and hemodynamics while also increasing tissue perfusion. The poisonous plant
D. lanata (foxglove) has long been known for its harmful effects.

Herbalists classified the plant as deadly nearly four centuries ago, and it was a favorite poisoning technique of many mystery writers, including Mary Webb, Agatha Christie, and others. Around 70% of the gastrointestinal tract is absorbed after digoxin is taken orally (Hausner et al., 2017). Digoxin is linked to serum albumin to the tune of 25%. Due to digoxin's significant binding to muscle tissue, its distribution volume is considerable; fat tissue is almost unbound. Digoxin passes past the placental barrier and into the mother milk after penetrating the cerebrospinal fluid (Saunders et al., 2019). Dialysis is unable to eliminate digoxin from the body [68].

2.9.Toxic Compound Databases

2.9.1. Toxin and Toxin Target Database (T3DB)

T3DB not only has the most comprehensive list of toxin targets, but it also has thoroughdescriptions of how the toxins interact with their targets under the 'Mechanism of Toxicity' data area. In terms of general content, layout, and goal, the most recent edition of T3DB is fairly similar to the original version. The basic objective of T3DB is still the same: to give in-depth knowledge on harmful compounds (i.e., the toxic exposome) and their targets at the molecular level. In-depth explanations of the mechanism of toxicity, metabolism, lethal or toxic dose levels, potential carcinogenicity, exposure sources, symptoms or health effects, suggested therapeutic options, references, and targets are all included in this database along with broad descriptions, structural information, nomenclature, physicochemical information, external links, and targets.. The initial version of T3DB attempted to gather information on common toxins, poisons, and toxic substances such pollutants, pesticides, preservatives, drugs, cosmetic toxins, colours, and cleaning compounds. Many of these substances are xenobiotics, and the majority of them are acutely poisonous. To better capture the toxic exposome for this year's T3DB release, we opted to collect additional information on relativelybenign, naturally occurring, or chronically hazardous substances. T3DB is still under creation. T3DBmpounds will develop together with the fields of toxicology, toxico-metabolomics, exposomics,biochemistry, and epidemiology [69].

2.9.2. Toxicity Reference Database (ToxRefDB)

ToxRefDB contains data from conventional in vivo animal toxicity studies, the majority of which came from information submitted to support the registration of pesticide active compounds in the United States and covering "almost 30 years and $2 billion in animal testing outcomes". We've listed some of the difficulties we've run into when utilisingToxRefDB below.ToxRefDB is a freely accessible database that includes thorough study and effect information on over 400 substances[70]. In line with NTP's findings, ToxRefDB's endpoint vocabulary distinguished between non-neoplastic and neoplastic lesions. Because the terminology found in OCSPP guidelines or NTP study specifications may not always match the reported pathology, clinical chemistry, and toxicology study results, where terminology is sometimes more specific, improving the controlled endpoint vocabulary for ToxRefDB was a particular challenge [71]. The data from OPP for pesticide active chemicals and the results of OPP experts' analysis of these studies are being used to construct ToxRefDB, a key component of ToxCast. [72].

2.9.3 ECOTOXicology Knowledgebase

To find and offer ecological toxicity data with consistency and transparency, the ECOTOX team established a literature search, review, and data curation process. present a high-level overview of the systematic methodologies and procedures, from chemical verification to search term development to literature evaluation and data extraction.

2.9.4 SuperToxic

Toxic compounds are used by animals and plants in nature to protect themselves from predators. Toxins are used by deadly mushrooms and plants to protect themselves from herbivores. To protect themselves from other animals, many snakes, scorpions, and spiders create poison. Many of these toxins, which were formerly used by animals or plants to kill their foes, have been shown to be beneficial in medicine. A huge number of hazardous compounds are compiled by SuperToxic from publically accessible sources and scientific publications. Currently, the database contains approximately 60 000 structures with matching characteristics. The database also contains features such as the number of hydrogen bond (H-bond) donors and acceptors, molecular weight, and the octanol–water partition coefficient logP, which can be used to evaluate Lipinski's Rule of Five can be found in the database[73].

2.9.5 RISCTOX

A method for analysing and assessing substitutes is available in RISCTOX's database of hazardous compounds with substitution case studies (ALTERNATIVAS).It is only offered in Spanish and is managed by ISTAS. [74]. The RISCTOX database contains data on over 100,000 chemical agents in files that include:

- Substance classification according to Regulation 1272/2008 (CLP)
- Particular health risks Environmental hazards in particular Regulations concerning the environment and health

RISCTOX does not include information on all health and environmental dangers posed by a material, but just on those that have been discovered[75].

2.10. Consequences related to commonly exposed toxins curated from published literatures-

2.10.1 Cadmium

Cadmium is a pollutant found in most human consumables due to its high rates of soil-to-plant transfer, making nutrition difficult. A major source of exposure in non-smokers and non-occupationally exposed people[76]. Itai-itai illness is caused by long-term high-dose cadmium exposure. This condition primarily affects women and is marked by significant pain.tubular and glomerular dysfunction, as well asosteomalacia and osteoporosis that is widespread numerous bone fractures as a result.Long-term low-dose cadmium exposure has been linked to tubular impairment, including nutrient, vitamin, and mineral reabsorptive capacity reduction. Zinc and copper bound to the metal binding protein metallothionein (MT), glucose, amino acids, phosphate, calcium, 2-MG, and retinol-binding protein are among the substances lost (RBP) [International Programme on Chemical Safety (IPCS) In general, urine cadmium levels reflect long-term exposure before kidney impairment develops, whereas blood cadmium levels are considered an indicator of recent exposure (IPCS 1992). Blood cadmium, rather than urine cadmium, is regarded a superior indicator of body load in people over 60 years old [122].

2.10.2 Colchicine

Colchicine binds to beta-tubulin heterodimers, which make up microtubules, altering the cytoskeleton and activating a variety of signalling pathways and cellular processes, which leadsto its anti-inflammatory mechanism of action in the treatment of gout [18,19]. Colchicine inhibits the inflammasome complex in neutrophils and monocytes, preventing the proinflammatory cytokine interleukin-1beta from being activated, albeit the specific mechanism is unknown [124]·In mice and rabbits, but not in monkeys, colchicine or its derivative demecolcine was teratogenic. 4 A handful of reports of its safe use in human pregnancy have been recorded. as well as studies· Three of the trials are encouraging, albeit tiny. Ehrenfeld et al [14] studied 16 healthy children whose mothers had taken colchicine. BenChetrit and Levy [15] focused on the efficacy and safety of colchicine treatment, reporting on 11 pregnant women who took colchicineand had 15 healthy babies at term.The current prospective study backs up the safety of colchicinein pregnant women and finds no evidence of an increased cytogenetic risk[77, 81].Colchicine is routinely prescribed for the treatment of gout flares and is considered standard of therapy. In the United States, the medicine is now licensed for the treatment and prevention of gout flares in adults [82,88].

2.10.3. Caffeine

Many individuals link caffeine in beverages with a variety of health benefits, including increased alertness, improved mental and physical performance, and an overall feeling of well-being. Caffeine habituation, on the other hand, causes physical dependency in at least 30% of users, but some writers contradict this result [86,88].Chronic high caffeine exposure is unpleasant and anxiogenic, whereas chronic low caffeine exposure is reinforcing [89, 91]. The urge to avoid substance withdrawal symptoms appears to be the reinforcing factor in habitual caffeine usage, rather than the desire to boost mood and psychomotor performance (in particular, headache). As a result, one can argue that the global passion for coffee and tea stems mostly from a desire to avoid headaches.Chronic coffee administration causes upregulation of adenosine receptors, facilitated agonist binding to adenosine receptors, and significant tonic effects in humans and animals. Adenosine plasma concentrations have increased [92, 94]. Chronic caffeine intake can have physiologic effects that are very different from those that come from a single dose.resulting from acute exposures [95].

2.10.4. Picene

Picene (benzo[a]chrysene) is widely diffused in the environment, as are other polycyclic aromatic hydrocarbons (PAH) [96, 99]. Picene is weakly soluble in water-miscible organic solvents, such as 120 pg/ml acetone; on the other hand, the number of organic solvents used in microsomal incubation should be kept as low as possible to avoid interactions with microsomal enzymes [100. 102].

2.10.5. Quinone

Quinones and quinone imines are extremely reactive organic compounds that belong to the quinone family. In biological systems, toxicological intermediates16 interact alone or by producing ROS to stimulate inflammatory reactions, reawaken immune cells, oxidize DNA, and in this way, toxicity induction. Chemical Research in Toxicology says they can cause in vivo effects including immunotoxicity [103].Quinones and quinone imines also influence cell signalling pathways that protect cells from inflammatory responses and cell damage. These effects differ based on the quinone in question and its concentration [104].

2.10.6. Ricin

Ricin is one of the most dangerous plant poisons yet discovered It is significantly easier to make than other biological agents like anthrax or botulinum toxin [105, 107] as it simply takes fundamental chemistry procedures taught in undergraduate chemistry classes [108, 109].Ricin is a ribosome-inactivating protein of Type II consisting of two polypeptide chains connected by a disulfide link. To generate toxicity, these chains must be connected [110, 113]. The lectin B- chain features galactose-binding sites on both ends to make hydrogen bonding with cell surface glycoproteins and glycolipids easier [114, 115]. The N-glycosidase A-chain [116, 117] removes adenine from the 28 S ribosomal RNA subunit [118]. This prevents elongation factors from binding, resulting in protein synthesis failure [119, 121].

2.10.7. Vanadium

Despite the fact that most meals have low quantities of vanadium (,1 ng V/g), [17] food remains the most common source of vanadium exposure for the general public. Vanadium is found in black pepper, dill seed, mushrooms (0.05–2 g/g), parsley (1.8 g/g), shellfish, spinach (0.5–0.8 g/g), and some prepared foods, with the highest source of vanadium being black pepper, dill seed, mushrooms (0.05–2 g/g), parsley (1.8 g/g), shellfish, spinach (0.5–0.8 g/g), and some prepared foods [18]. When compared to terrestrial animal sources of food, seafood has higher vanadium contents. Smaller levels (,1– 10 ng V/g) can be found in beverages, fresh fruits and vegetables, cereals, liver, fats, and oil[123]. The amounts of vanadium in food tend to rise as it is processed.9 Tobacco has high levels of vanadium, and tobacco smoke contains 1–8 ppm V. 17 The mushroom Amanita muscaria has a concentration of around 100 times that of other plants and mushrooms (100 ppm V) [124].

2. MATERIAL AND METHOD

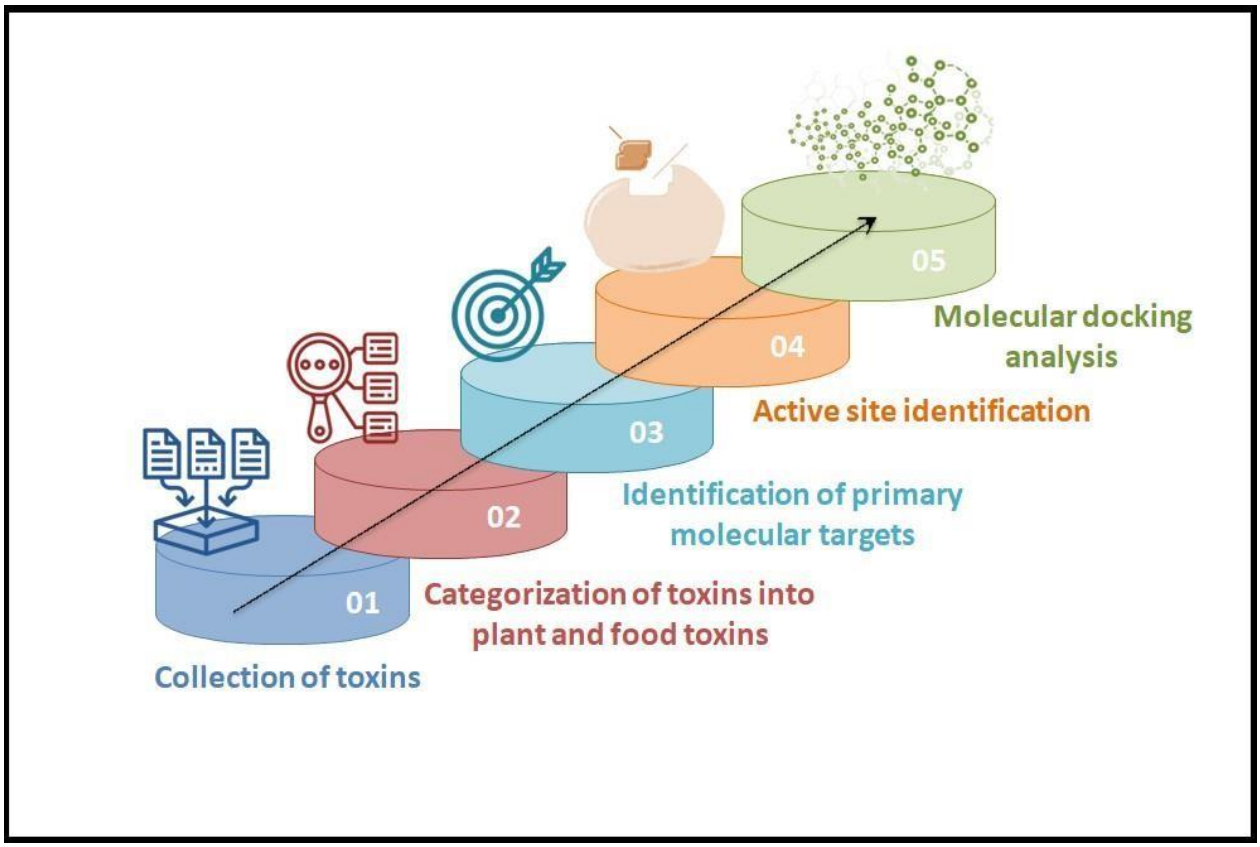


Figure 3: Schematic representation of workflow

3.1. Collection and categorization of toxins

Toxic compounds are abundant in present era. Others are extremely toxic and can harm the exposed organism instantly upon contact or ingestion, while some are just moderately toxic and only cause disease or harm after years of exposure. By performing intense literature analysis regarding the data availability of toxic substancesas a result of our research, we discovered the Toxin-Toxin -Target Database (T3DB), which details all human environmental exposures from birth to death. T3DB's first version, released in 2010, included chemical characteristics, descriptions, targets, toxic effects, toxicity thresholds, sequences, processes, and references for over 2900 common toxic compounds. Its homepage is shown in *figure 4.* Then by curated a list of ninety-six toxins from the database and enlist their identifiers including CAS Number, PubChem CID, SMILES and other related attributes.

With the ideology of focusing on commonly exposed toxins, we categorized the set of collected chemicals toxins between the plant-based and the food-based toxins. Humans are exposed to these toxins either through direct eating or by contact; therefore public welfare and medical agendas have recently been more vigorous in widely exposed areas of toxicology. Some of food toxin like tomato contains Tomatin toxin so its fruit is not toxic but root, stem, leaves are toxic. Phytate is also a plant -based food toxins which is present in soy, grains, legumes in which necessary minerals is not absorbed in our body.

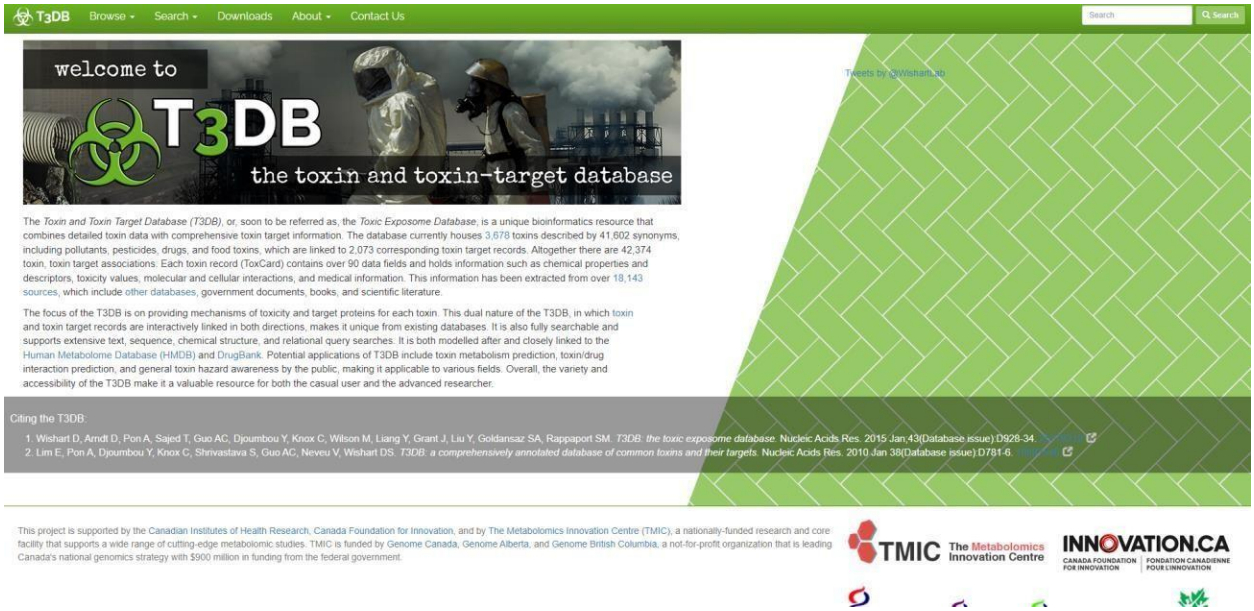


Figure 4: The toxin and toxin target database

3.2. Identification and analysis of targets

We performed literature analysis to identify the molecular receptors of the curated toxins. Molecular targets play an important role by being the underlying cause of phenotypic toxic effects. We explored the possible options to identify targets and found TargetHunter that is an online tool for predicting biological targets of various compounds. It is based on biologically annotated chemogenomic databases that contain millions of bioactivity records, such as the ChEMBL database. For target prediction automation, the tool uses the TAMOSIC algorithm. Weidentified the targets by providing SMILES (simplified molecular input line entry system) of toxins as input data and the tool outputs a list of target for each of the 98 toxins. We analyzed theoutputs with the aim to select the most repetitive targets. The maximum occurrence was suggestive of maximum interactions.

3.3.Active Site Prediction

Post the identification and selection of top three targets for further analysis, we predicted their active sites to better comprehend their interactions with the toxins. This was performed using CastP (The Computed Atlas of Surface Topography of Proteins) web server as shown in *figure 5*,the server aids the user to identify, properly define and quantify the cavities or regions on the three-dimensional structures of proteins which serve as the binding sites. Proteins perform their functions through interacting with other molecules such as substrates, ligands, DNA, and other protein domains. The goal of the web server is quantification of protein topographic characteristics. The CASTp server accepts protein structures in PDB format and a probe radius as input for topographic computing.

Figure 5: Snapshot of CastP web server

3.4. Molecular docking

The goal of molecular docking is to use computer methods to anticipate the structure of the ligand-receptor complex. Docking is accomplished in two steps: first, sampling ligand conformations in the active site of the protein, and then ranking these conformations using a scoring function.The molecular docking approach can be used to represent the atomic level

interaction between a small molecule and a protein, allowing us to characterize small molecule behavior in target protein binding sites as well as elucidate key biochemical processes. The latest version of AutoDock Vina for molecular docking and virtual screening was recently published.

The binding energies and interactions analyses between the commonly exposed toxins and the selected receptor molecules were quantified and analyzed using AutoDock Vina. The docking process began with the target and ligand files being converted to.pdbqt format. The grid box is then produced to define a 3D binding space.The grid values are set up so that the grid box encloses the active sites of the protein. The grid box dimensions for ALDH (110 x 110 x 116, with centers of x = 45.534, y = -14.777, z = 19.727), NRF2 (110 x 110 x 110, with centers of x =14.575, y = 16.726, z = 7.092) and PPAR (100 x 100 x 100, with centers of x = 23.238, y = 4.725, z = 70.483) were defined in the configuration file for further processing. The Autodock Vina run was finally started with a specified line of commands to generate the output files. The most effective toxins with the lowest binding energy upon interaction with the targets were chosen and examined from the generated outputs to comprehend the binding pattern.

Docking has been performed in a stepwise manner, the first step of molecular docking is to read the molecule in pdb format then edit and add the polar hydrogen andrequired including Gastgier andKollman. Next, the macromoleculeis saved in .pdbqt format. Preparation of ligand is the next step in the process; we input the ligand and refined it by choosing and detecting the root. It is then saved in .pdbqt format. Then we set the grid box to define the aforementioned dimensions. We put the required Vina extension files in and prepared molecules in a folder and saved it in ‘C’drive. The last step is to give command lines to run the docking under Autodock Vina. We opened the command prompt and gave the commands as shown in *figure 6*.

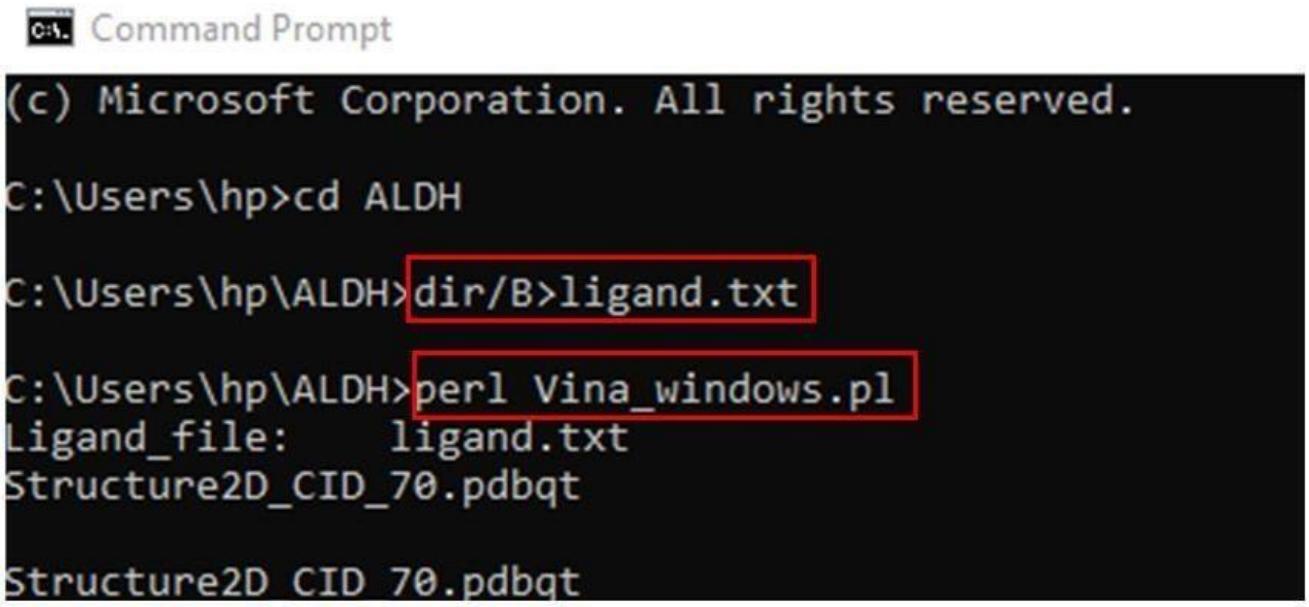


Figure 6: Autodock Vina command lines for Molecular Docking

3. RESULT AND DISCUSSION

We collected 96 toxins out of which 62 were food toxins, 8 were plant toxins and remaining were found in both the sources.Some of them lay in other categories of toxins which were not considered for the current *in silico* study. *Table 1* enlists the collected toxins along with their identifiers including PubChem CID, CAS Number and SMILES. Categorization of the toxins is illustrated in the Venn diagram shown in *figure 7*.

Table 1:Collected toxins along with their identifiers including PubChem CID, CAS Number and SMILES

S. No.	Chemical Name	CAS Number	PubChem CID/ SID	SMILES
1	Cadmium	7440-43-9	23973	Cd
2	Clofenotane	50-29-3	3036	C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)(Cl)Cl)Cl
3	Trichloroethylene	28861	6575	C(=C(Cl)Cl)Cl
4	Acrolein	107-02-8	7847	C=CC=O
5	Endosulfan sulfate	1031-07-8	13940	C1C2C(COS(=O)(=O)O1)C3(C(=C(C2(C3(Cl)Cl)Cl)Cl)Cl)Cl
6	Toluene	108-88-3	1140	CC1=CC=CC=C1
7	2-Oxohexane	591-78-6	11583	CCCCC(=O)C
8	Zinc	7440-66-6	23994	
9	Naphthalene	91-20-3	931	C1=CC=C2C=CC=CC2=C1
10	Thiocyanate	302-04-5	9322	C(#N)[S-]
11	Selenium	7782-49-2	6326970	[Se]
12	p-Cresol	106-44-5	2879	CC1=CC=C(C=C1)O
13	Vanadium	7440-62-2	23990	[V]

14	Dibromochloromethane	124-48-1	31296	C(Cl)(Br)Br
15	Phosphine	7803-51-2	24404	
16	Styrene	100-42-5	7501	C=CC1=CC=CC=C1
17	Arsenous acid	13464-58-9	545	O[As](O)O
18	Methylarsine	593-52-2	6335627	C[As]
19	Lead tetroxide	1314-41-6	16685188	O1[Pb]O[Pb]12O[Pb]O2
20	Tetracene	92-24-0	7080	C1=CC=C2C=C3C=C4C=CC=CC4=CC3=CC2=C1
21	Pentacene	135-48-8	8671	C1=CC=C2C=C3C=C4C=C5C=CC=CC5=CC4=CC3=CC2=C1
22	Quinoline	91-22-5	7047	C1=CC=C2C(=C1)C=CC=N2
23	Picene	213-46-7	9162	C1=CC=C2C(=C1)C=CC3=C2C=CC4=C3C=CC5=CC=CC=C54
24	Adenosylcobalamin	13870-90-1	70678541	CC1=CC2=C(C=C1C)N(C=N2)C3C(C(C(O3)CO)OP(=O)([O-])OC(C)CNC(=O)CCC4(C(C5C6(C(C(C(=N6)C(=C7C(C(C(=N7)C=C8C(C(C(=N8)C(=C4[N-]5)C)CCC(=O)N)(C)C)CCC(=O)N)(C)CC(=O)N)C)CCC(=O)N)(C)CC(=O)N)C)CC(=O)N)C)O.[CH2-]C1C(C(C(O1)N2C=NC3=C(N=CN=C32)N)O)O.[Co]
25	Antimony	7440-36-0	5354495	[Sb]
26	Roxarsone	121-19-7	5104	C1=CC(=C(C=C1[As](=O)(O)O)[N+](=O)[O-])O
27	Pentacene	135-48-8	8671	C1=CC=C2C=C3C=C4C=C5C=CC

				=CC5=CC4=CC3=CC2=C1
28	Ovalene	190-26-1	67446	C1=CC2=C3C4=C1C=CC5=CC6=C7C8=C(C=CC9=C8C1=C(C=C9)C=C(C3=C1C7=C54)C=C2)C=C6
29	Rotenone	83-79-4	6758	CC(=C)C1CC2=C(O1)C=CC3=C2OC4COC5=CC(=C(C=C5C4C3=O)OC)OC
30	Paraquat dichloride	1910-42-5	15938	C[N+]1=CC=C(C=C1)C2=CC=[N+](C=C2)C.[Cl-].[Cl-]
31	Sodium ferrocyanide	13601-19-9	26129	[C-]#N.[C-]#N.[C-]#N.[C-]#N.[C-]#N.[C-]#N.[Na+].[Na+].[Na+].[Na+].[Fe+2]
32	Isobergapten	482-48-4	68082	COC1=C2C=CC(=O)OC2=C3C=COC3=C1
33	Heratomin	61265-06-3	181312	CC(=CCOC1=C2C(=C3C(=C1)C=CC(=O)O3)C=CO2)C
34	Pimpinellin	131-12-4	4825	COC1=C(C2=C(C=CO2)C3=C1C=CC(=O)O3)OC
35	Fenvalerate	51630-58-1	3347	CC(C)C(C1=CC=C(C=C1)Cl)C(=O)OC(C#N)C2=CC(=CC=C2)OC3=CC=CC=C3
36	Orellanine	37338-80-0	89579	C1=CN(C(=C(C1=O)O)C2=C(C(=O)C=CN2O)O)O
37	Gyromitrin	16568-02-8	9548611	CC=NN(C)C=O
38	Psilocin	520-53-6	4980	CN(C)CCC1=CNC2=C1C(=CC=C2)O
39	Ergotamine	113-15-5	8223	CC1(C(=O)N2C(C(=O)N3CCCC3C2(O1)O)CC4=CC=CC=C4)NC(=O)

				C5CN(C6CC7=CNC8=CC=CC(=C78)C6=C5)C
40	Phalloidin	17466-45-4	4752	CC1C(=O)NC2CC3=C(NC4=CC=CC=C34)SCC(C(=O)N5CC(CC5C(=O)N1)O)NC(=O)C(NC(=O)C(NC(=O)C(NC2=O)CC(C)(CO)O)C)C(C)O
41	Ricin	9009-86-3	349938942	
42	Bufotenin	487-93-4	10257	CN(C)CCC1=CNC2=C1C=C(C=C2)O
43	Cinobufagin	470-37-1	11969542	CC(=O)OC1C(C2(CCC3C(C24C1O4)CCC5C3(CCC(C5)O)C)C)C6=COC(=O)C=C6
44	Digoxin	20830-75-5	2724385	CC1C(C(CC(O1)OC2C(OC(CC2O)OC3C(OC(CC3O)OC4CCC5(C(C4)CCC6C5CC(C7(C6(CCC7C8=CC(=O)OC8)O)C)O)C)C)C)O)O
45	Caffeine	58-08-2	2519	CN1C=NC2=C1C(=O)N(C(=O)N2C)C
46	Boric acid	10043-35-3	7628	B(O)(O)O
47	Fenamiphos	22224-92-6	31070	CCOP(=O)(NC(C)C)OC1=CC(=C(C=C1)SC)C
48	Flumioxazin	103361-09-7	92425	C#CCN1C(=O)COC2=CC(=C(C=C21)N3C(=O)C4=C(C3=O)CCCC4)F
49	Flusilazole	85509-19-9	73675	C[Si](CN1C=NC=N1)(C2=CC=C(C=C2)F)C3=CC=C(C=C3)F
50	Folpet	133-07-3	8607	C1=CC=C2C(=C1)C(=O)N(C2=O)SC(Cl)(Cl)Cl
51	Iprodione	36734-19-	37517	CC(C)NC(=O)N1CC(=O)N(C1=O)

		7		C2=CC(=CC(=C2)Cl)Cl
52	Oxytetracycline	79-57-2	54675779	CC1(C2C(C3C(C(=O)C(=C(C3(C(=O)C2=C(C4=C1C=CC=C4O)O)O)O)C(=O)N)N(C)C)O)O
53	Molybdenum	7439-98-7	23932	[Mo]
54	Dicumarol	66-76-2	54676038	C1=CC=C2C(=C1)C(=C(C(=O)O2)CC3=C(C4=CC=CC=C4OC3=O)O)O
55	Citreoviridin A	25425-12-1	6436023	CC1C(C(C(O1)(C)C=C(C)C=CC=CC=CC2=C(C(=CC(=O)O2)OC)C)O)(C)O
56	Fusaric Acid	536-69-6	3442	CCCCC1=CN=C(C=C1)C(=O)O
57	Nonanal	124-19-6	31289	CCCCCCCCC=O
58	Testosterone	58-22-0	6013	CC12CCC3C(C1CCC2O)CCC4=CC(=O)CCC34C
59	Creatine	57-00-1	586	CN(CC(=O)O)C(=N)N
60	Glyceric acid	473-81-4	752	C(C(C(=O)O)O)O
61	L-Isoleucine	73-32-5	6306	CCC(C)C(C(=O)O)N
62	L-Leucine	61-90-5	6106	CC(C)CC(C(=O)O)N
63	L-Serine	56-45-1	5951	C(C(C(=O)O)N)O
64	L-Threonine	72-19-5	6288	CC(C(C(=O)O)N)O
65	L-Proline	147-85-3	145742	C1CC(NC1)C(=O)O
66	Ketoleucine	816-66-0	70	CC(C)CC(=O)C(=O)O
67	S-Sulfocysteine	1637-71-4	115015	C(C(C(=O)O)N)SS(=O)(=O)O
68	Tyramine	51-67-2	5610	C1=CC(=CC=C1CCN)O
69	Propionic	79-09-4	1032	CCC(=O)O

	acid			
70	Phytanic acid	14721-66-5	26840	CC(C)CCCC(C)CCCC(C)CCCC(C)CC(=O)O
71	Ethylmalonic acid	601-75-2	11756	CCC(C(=O)O)C(=O)O
72	Sulfite	14265-45-3	1099	[O-]S(=O)[O-]
73	Diazoxon	962-58-3	13754	CCOP(=O)(OCC)OC1=NC(=NC(=C1)C)C(C)C
74	Diphenylamine	122-39-4	11487	C1=CC=C(C=C1)NC2=CC=CC=C2
75	Malaoxon	1634-78-2	15415	CCOC(=O)CC(C(=O)OCC)SP(=O)(OC)OC
76	Maneb	12427-38-2	3032581	C(CNC(=S)[S-])NC(=S)[S-].[Mn+2]
77	Quinone	106-51-4	4650	C1=CC(=O)C=CC1=O
78	Butanone	78-93-3	6569	CCC(=O)C
79	Caprylic acid	124-07-2	379	CCCCCCCC(=O)O
80	Dodecanoic acid	143-07-7	3893	CCCCCCCCCCCC(=O)O
81	Heptanoic acid	111-14-8	8094	CCCCCCC(=O)O
82	Prunasin	99-18-3	119033	C1=CC=C(C=C1)C(C#N)OC2C(C(C(C(O2)CO)O)O)O
83	Estradiol	50-28-2	5757	CC12CCC3C(C1CCC2O)CCC4=C3C=CC(=C4)O
84	Iron	7439-89-6	23925	[Fe]
85	Ozone	10028-15-6	24823	[O-][O+]=O

86	Aminopterin	54-62-6	169371	C1=CC(=CC=C1C(=O)NC(CCC(=O)O)C(=O)O)NCC2=CN=C3C(=N2)C(=NC(=N3)N)N
87	Estrone	53-16-7	5870	CC12CCC3C(C1CCC2=O)CCC4=C3C=CC(=C4)O
88	Benzoic acid	65-85-0	243	C1=CC=C(C=C1)C(=O)O
89	Estriol	50-27-1	5756	CC12CCC3C(C1CC(C2O)O)CCC4=C3C=CC(=C4)O
90	Palmitic acid	57-10-3	985	CCCCCCCCCCCCCCCC(=O)O
91	Forskolin	64657-11-0 and 66575-29-9	47936	CC(=O)OC1C(C2C(CCC(C2(C3(C1(OC(CC3=O)(C)C=C)C)O)C)O)(C)C)O
92	Retronecine	480-85-3	10198	C1CN2CC=C(C2C1O)CO
93	Colchicine	64-86-8	6167	CC(=O)NC1CCC2=CC(=C(C(=C2C3=CC=C(C(=O)C=C13)OC)OC)OC)OC
94	Alcuronium	23214-96-2	21158560	C=CC[N+]12CCC34C1CC(C(=CCO)C2)C5=CN6C7C(=CN(C53)C8=CC=CC=C48)C9CC1C7(CC[N+]1(CC9=CCO)CC=C)C1=CC=CC=C16
95	Grayanotoxin I	1030234	9548612	CC(=O)OC1C2CCC3C1(CC(C4(C(C3(C)O)CC(C4(C)C)O)O)O)CC2(C)O
96	Tutin	2571-22-4	75729	CC(=C)C1C2C(C3(C4(CO4)C5C(C3(C1C(=O)O2)O)O5)C)O

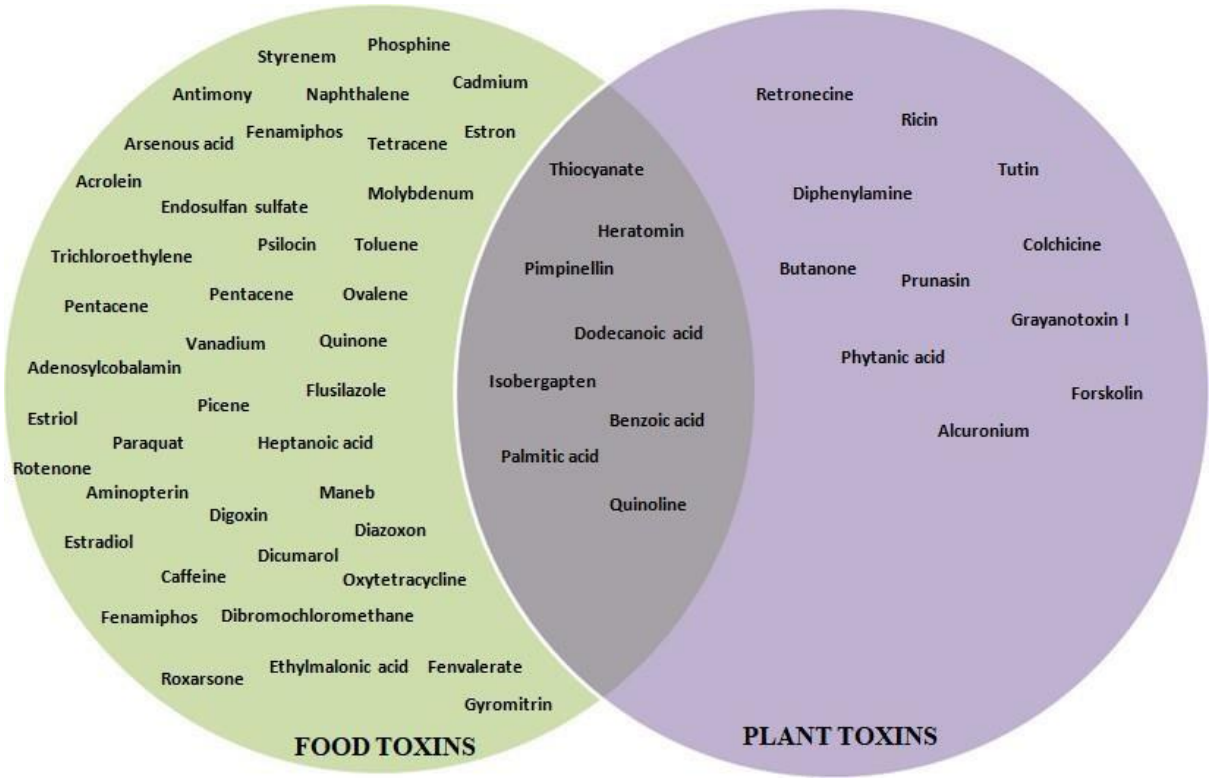
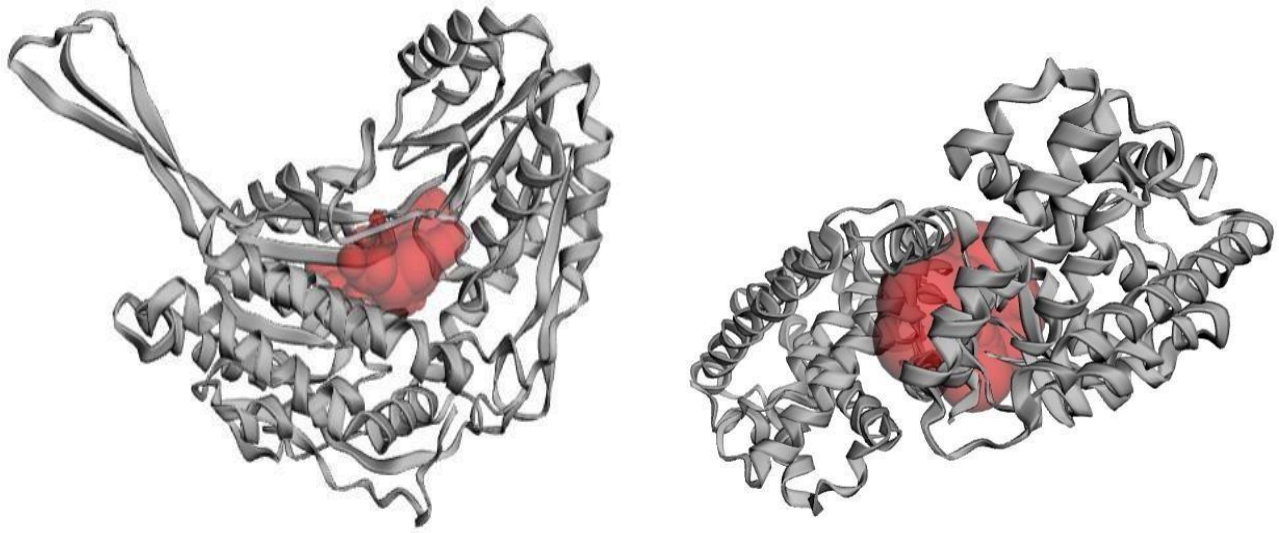


Figure 7: Categorization of Toxins

3-dimensional structure of the targets were downloaded from RCSB Protein Data Bank inPDB format. The PDB IDs of targets, Aldehyde Dehydrogenase 1A1 and Peroxisome proliferator-activated receptor delta were 4WJ9 and 3D5F respectively. The model for analysis of Nuclear factor erythroid 2-related factor 2 was developed by using SwissModel web server. Further, we predicted the active sites of the targets using CASTp online reserve and validated thebinding cavities with the aid of Discovery Studio software. The active site positions are shown in*figure 7* highlighted in red color.



(a) 4WJ9 **(b) 3D5F**

Fig 8: Active site prediction of targets using CASTp web server, (a) 4WJ9 and (b) 3D5F

Molecular docking was performed of all the three receptors, Aldehyde Dehydrogenase, Peroxisome proliferator-activated receptor deltaand Nuclear factor erythroid 2-related factor 2 with the classified groups of toxins. It has been deciphered that toxin, fenvalerate, ovalene, picene, and digoxin interact with targets with minimum binding energy and the results were expressed in Kcal/mole. These ligands show plausible binding with targets, for instance, with Aldehyde Dehydrogenase the toxins, fenvalerate, ovalene, picene, and digoxin show binding energy -12.2 Kcal/mole, -12.8Kcal/mole, -11.7Kcal/mole and -13.1 Kcal/mole, respectively. Similarly, the other two targets and their binding energy with top four commonly exposed toxins on the basis of molecular interaction is shown in *figure 9* and *table 1*.

Table 1:*Binding energy of standard fenvalerate, ovalene, picene, and digoxin with the targets (ALDH, NRF2 and PPAR)*

	Fenvelerate	**Ovalene**	**Digoxin**	**Picene**
Aldehyde Dehydrogenase (ALDH)	-12.2 Kcal/mole	-12.8 Kcal/mole	-13.1 Kcal/mole	-11.7 Kcal/mole

Nuclear factor-erythroid factor 2-related factor 2 (NRF2)	-13.1 Kcal/mole	-10.7 Kcal/mole	-14.7 Kcal/mole	-10.63 Kcal/mole
Peroxisome proliferator-activated receptors (PPAR)	-10.3 Kcal/mole	-10.6 Kcal/mole	-11.8 Kcal/mole	-10.9 Kcal/mole

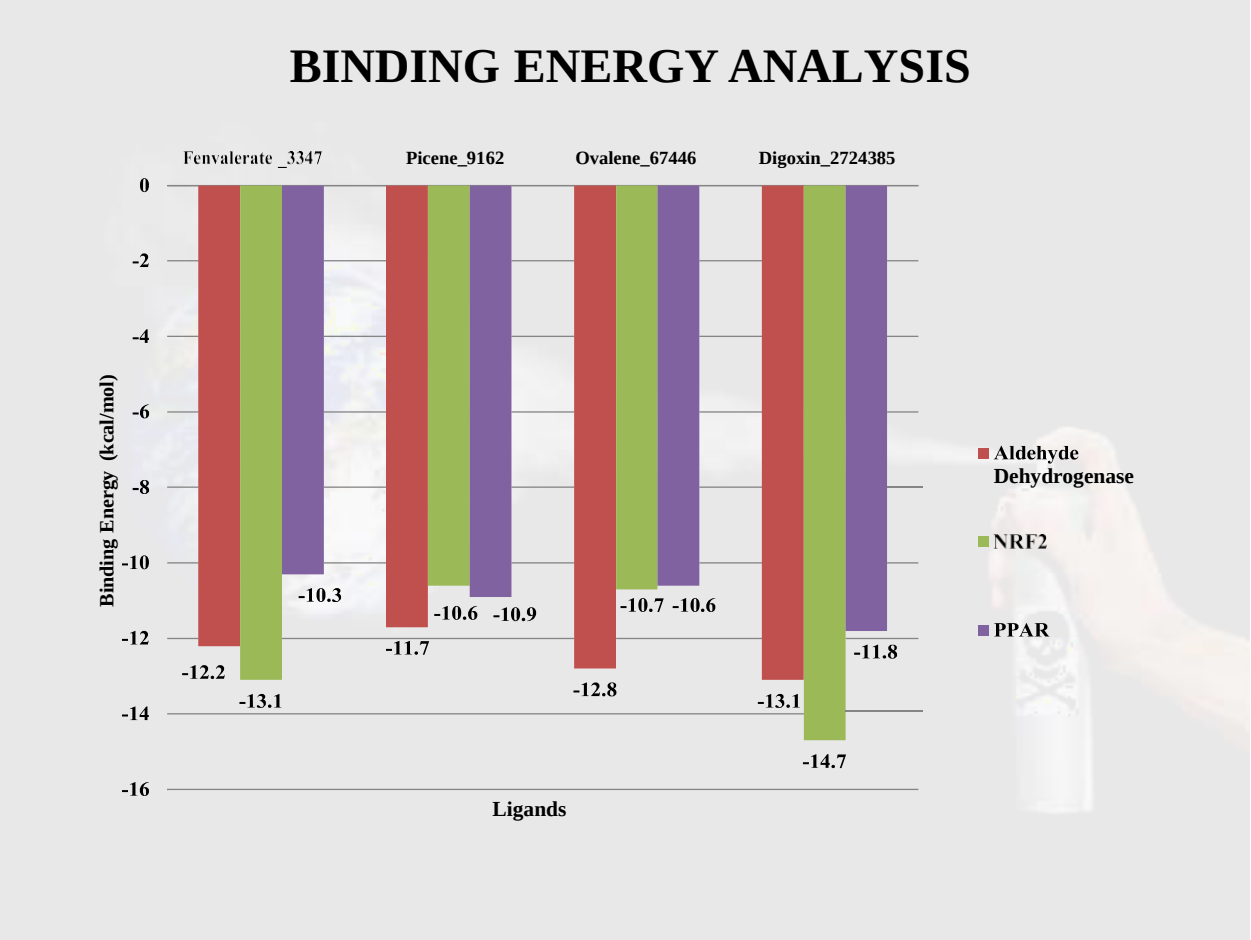
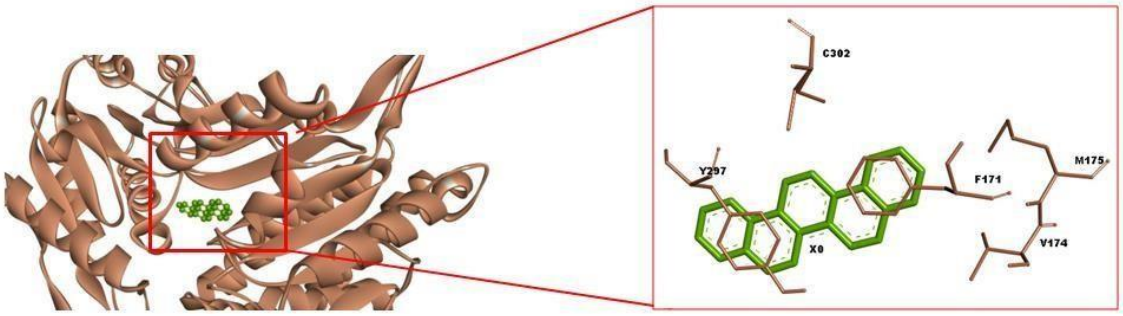
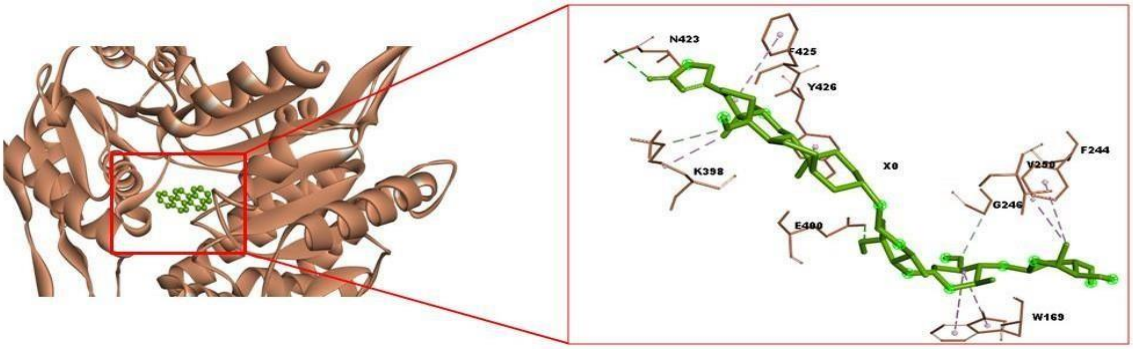


Figure 9: Graph showing binding energy of standard fenvalerate, ovalene, picene, and digoxinwith the targets (ALDH, NRF2 and PPAR)

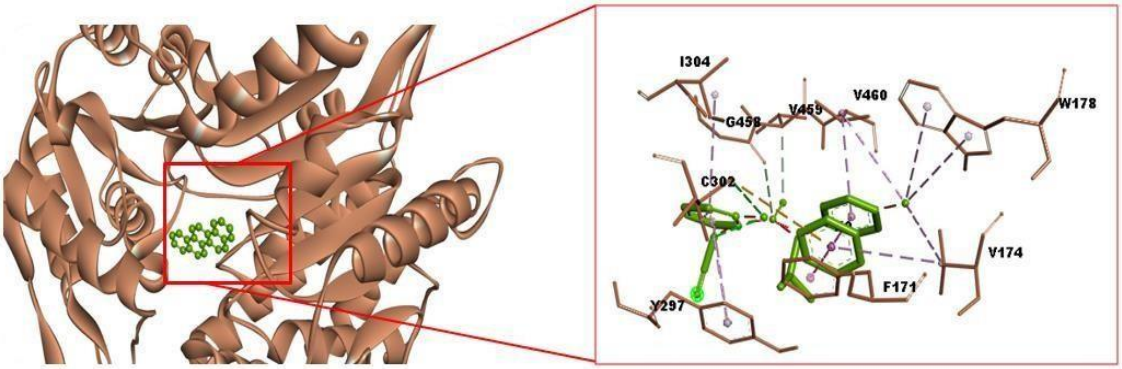
(a)


C302
Y297
F171
M175
V174
X0

(b)


N423
T425
Y426
K398
X0
V288
F244
G246
E400
W169

(c)


I304
V460
W178
G458
V459
C302
V174
F171
Y297

(d)

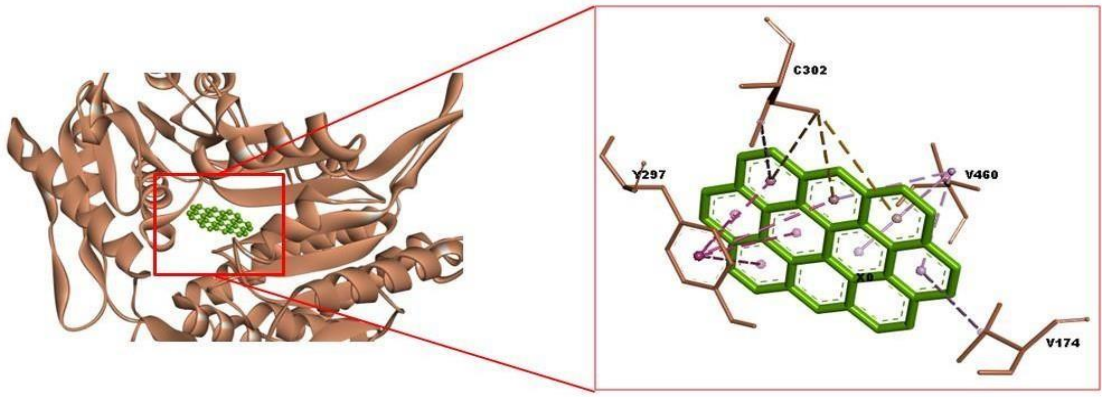


Fig 10: Pictorial representation of toxin-target interaction (a)Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with ALDH

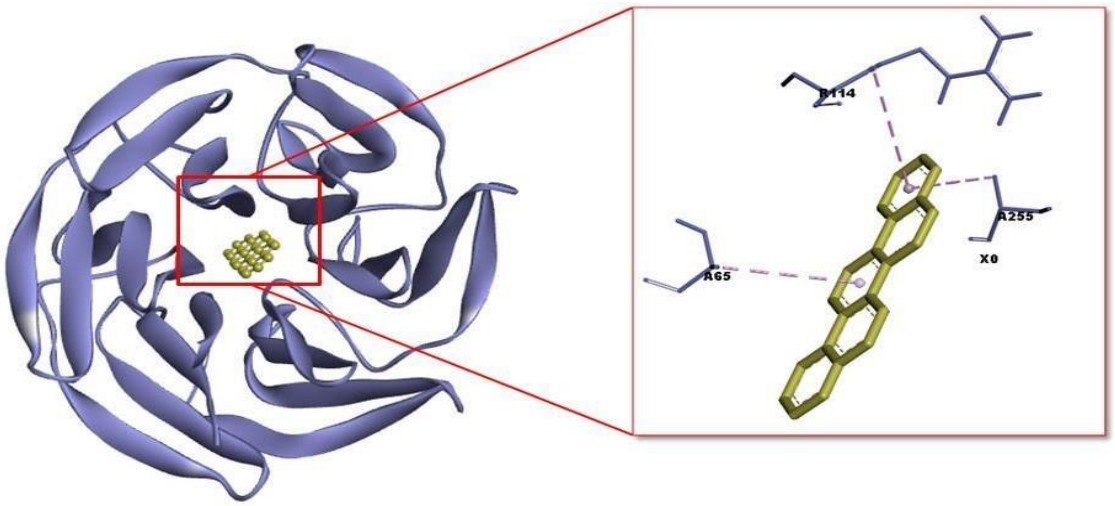
The docking result also revealed the amino acid residues involved in the binding of toxins with targets. For instance, residues C302, Y295, F171, M175, and V174 are involved in binding of Picene with ALDH. The interactions are shown in *figure 10* and details of interaction are given in *table 2*.

Table 2: Details of minimum binding energy and residues involved in bonding revealed through molecular docking of the toxins, Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with the target,Aldehyde Dehydrogenase

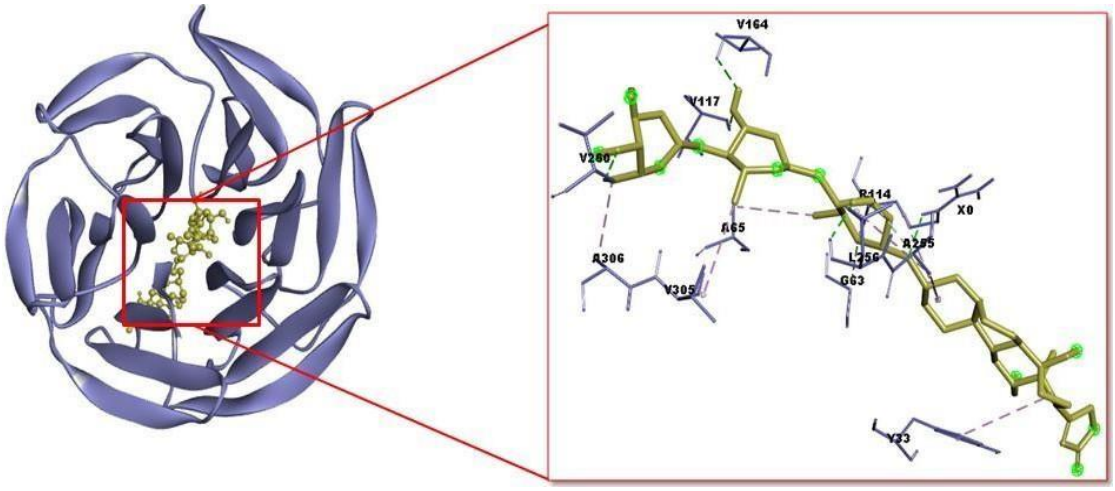
Ligand	**Minimum binding energy (kcal/mole)**	**Residue involve in bonding**
Picene (9162)	**-11.7**	**C302,Y295,F171,M175,V174**
Digoxin (2724385)	**-13.1**	**N423,F425,V426,K398,E400,G246,V250,F244,W169**
Fenvalerate (3347)	**-12.2**	**I304,G458,V459,C302,Y297,F171,V460,W178,V174**
Ovalene (67446)	**-12.8**	**Y297,C302,V460,V174**

Similarly, residues V164, V117, V260, A306, VE05, A65, R114, L256, G63, A295, and Y33 are involved in binding of Digoxin with NRF2. The interactions are shown in *figure 11* and details of interaction are given in *table 3.*

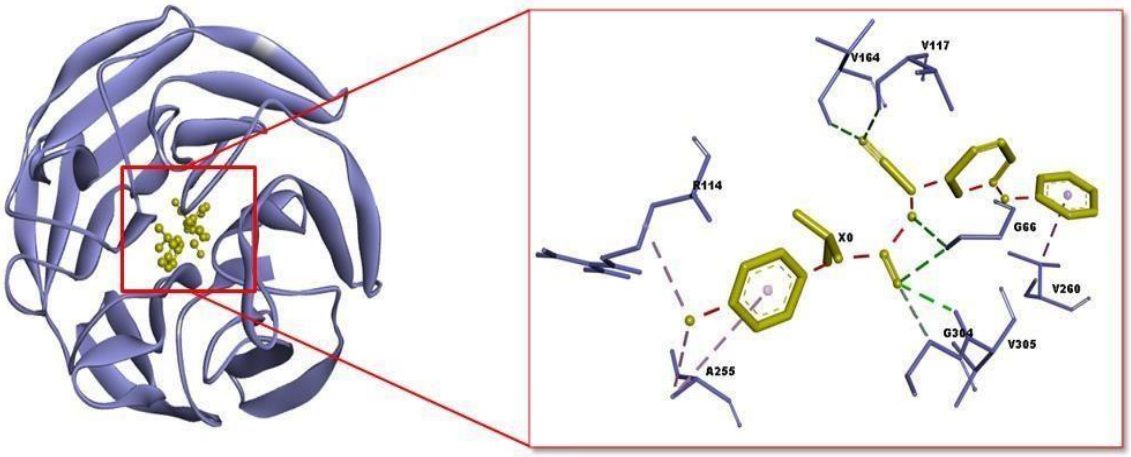
(a)



(b)



(c)



(d)

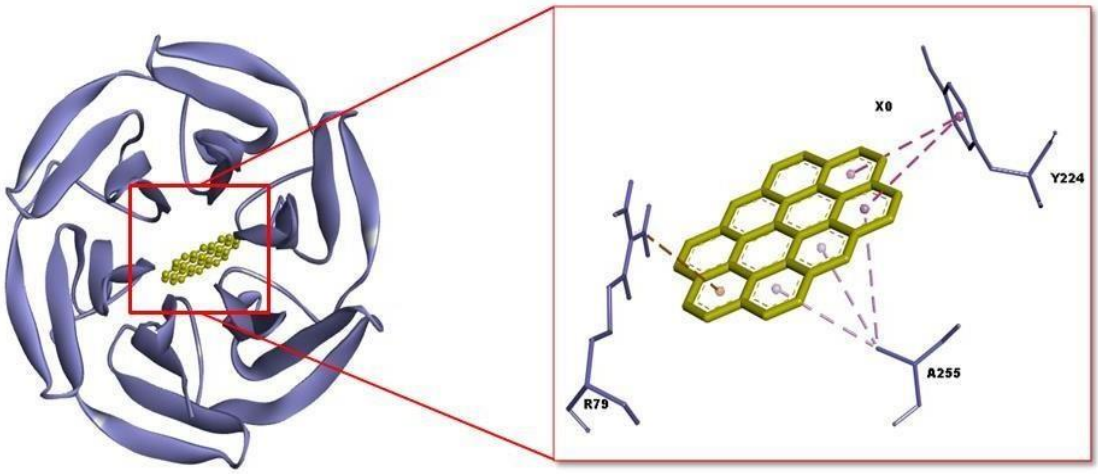


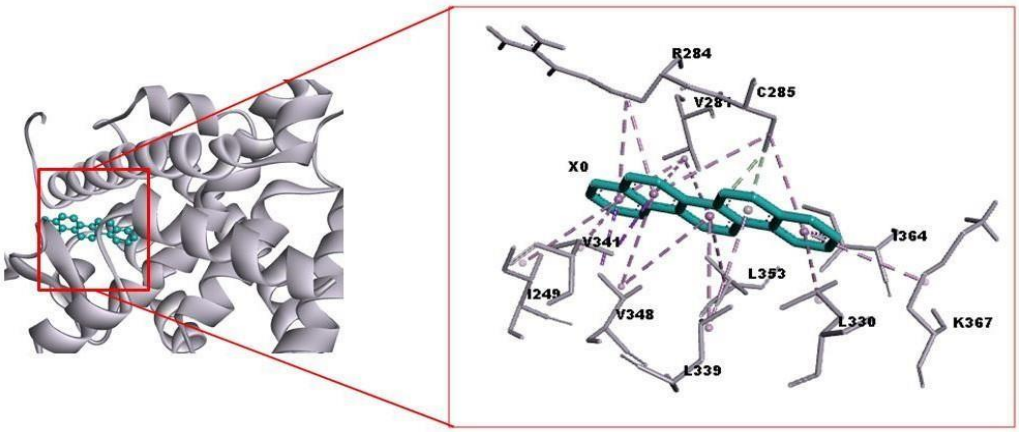
Fig 12: Pictorial representation of toxin-target interaction (a)Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with NRF-2

Table 3: **Details of minimum binding energy and residues involved in bonding revealed through molecular docking of the toxins, Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with the target,Nuclear factor-erythroid factor 2-related factor 2**

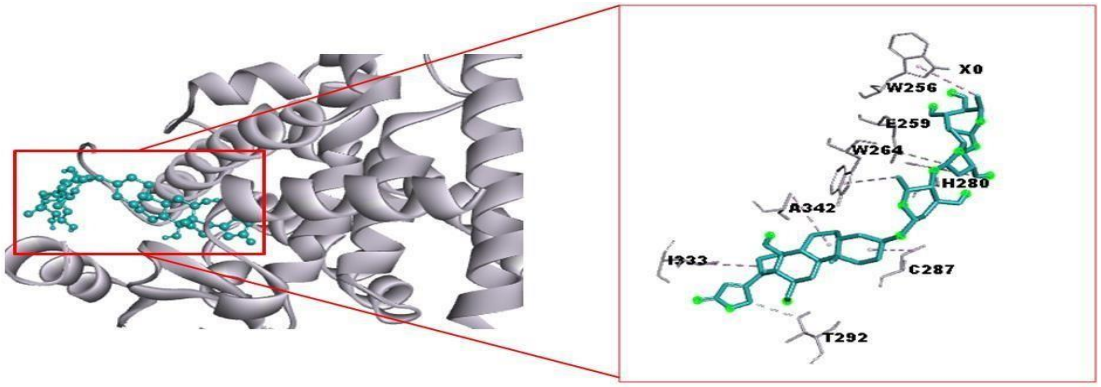
Ligand	**Minimum binding energy**	**Residue involved in hydrogen binding**
	(kcal/mole)	
Picene (9162)	**-10.6**	**R114,A255,A65**
Digoxin (2724385)	**-14.7**	**V164,V117,V260A306,VE05,A65,R114,L256,G63,A295,Y33**
Fenvalerate (3347)	**-13.1**	**V117,V164,G66,V260,V305,GE04,R114,A255,**
Ovalene (67446)	**-10.7**	**Y224,A255,R70**

Further, residues W256, E259, W264, H280, A342, 1333, C287, T292 are involved in binding of Fenvalerate with PPAR. The interactions are shown in *figure 12* and details of interaction are given in *table 4*.

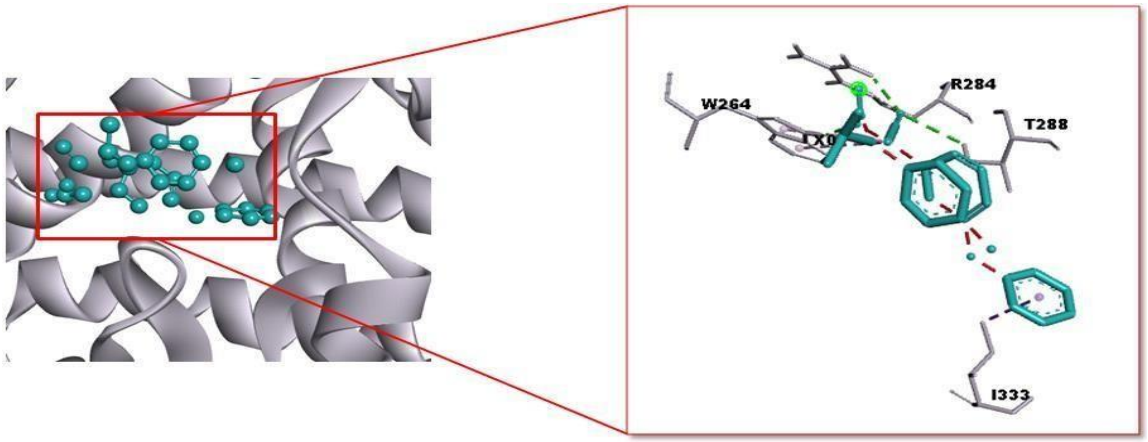
(a)



(b)



(c)



(d)

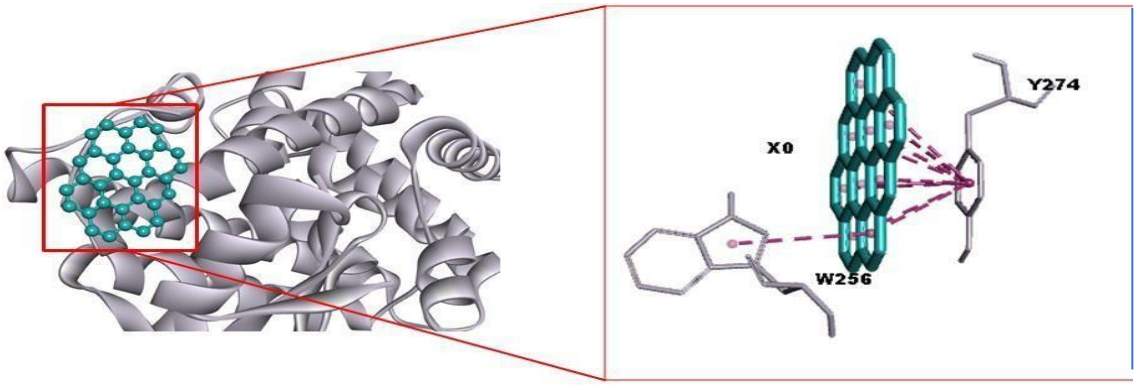


Fig 11: Pictorial representation of toxin-target interaction (a)Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with PPAR

Table 4: *Details of minimum binding energy and residues involved in bonding revealed through molecular docking of the toxins, Picene, (b) Digoxin, (c) Fenvalerate, (d) Ovalene with the target, Peroxisome proliferator-activated receptors*

Ligand	**Minimum binding energy (kcal/mole)**	**Residue involved in hydrogen binding**
Picene (9162)	**-10.9**	**R284V287,C285,1249,V348,L353,L330,K367**
Digoxin (2724385)	**-11.8**	**W256,E259,W264,H280,A342,1333,C287,T292,XO**
Fenvalerate (3347)	**-10.3**	**W264,R284,T288,1333,XO**
Ovalene (67446)	**-10.6**	**W256,Y274,XO**

3. CONCLUSION

Toxicity is the capacity of a substance to cause an adverse reaction when the chemical has sufficiently accumulated at a precise area inside the body. The very little of a substance must be absorbed before it has detrimental ramifications if it is more toxic. Hazard is the likelihood that this concentration will occur in the body.

Some diseases are exacerbated by toxic substances, while others are brought on by exposure to chemicals. Smog-related illnesses like asthma, asbestos-related illnesses like mesothelioma, and lead-related illnesses like learning difficulties are a few instances of illnesses brought on by exposure.

This work will pave a way to identify compounds that could potentially replace or substitute for toxic substances present in the commonly used products. To properly grasp how a substance mayaffect a diverse, real-world population, future toxicologyresearch will require an understanding of how toxicants interact with the targets .in current in silico study Digoxin was predicted best target for Nuclear factor erythroid2-related factor 2 as shown by binding energies.Digoxin belongs to a class of medication called cardiac glycosides. This relieves stress on the heart and aids inthe maintenance of a regular, steady, and powerful heartbeat. Despite the fact that this medication isused to treat a specific form of irregular heartbeat, it might occasionallycause other irregular heartbeats.

Natural substances have recently gained popularity as superior possible medicines due to their usefulness in boosting health while having fewer negative effects. Given the costly and time-consuming nature of new medication development, pharmaceutical companies face a pressing needto explore new avenues for drug research and development. We have deciphered the human molecular targets of some of the commonly exposed toxins and comprehensively studied the consequences of toxin exposures. Consumption of relatively small amounts of food toxins is unavoidable since some food toxins cannot be eliminated from foods and others can be generatedduring processing or cooking. It paved the way for consumers to be protected from situations thatwere reasonably predictable.

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