IN SILICO ANALYSIS OF MICROBIAL ENZYMES FOR DEGRADATION OF BISPHENOL A (BPA) AND ITS DERIVATIVES

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Submitted by

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CANDIDATE'S DECLARATION

I **Surbhi** hereby certify that the work which is being presented as the Major Project in the thesis entitled **'In silico analysis of microbial enzymes for degradation of Bisphenol A (BPA) and its derivative'** in partial fulfillment of the requirements for the award of the Degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own work, carried out during the period from January 20224 to May 2024 under the supervision of Prof. Jai Gopal Sharma.

I have not submitted the matter presented in the report for the award of any other degree of this or any other institute/University.

Surbhi

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CERTIFICATE BY THE SUPERVISOR

Certified that **Surbhi (2K22/MSCBIO/65)** has carried out their search work presented in this thesis entitled **'In silico analysis of microbial enzymes for degradation of Bisphenol A (BPA) and its derivative'** for the award of Degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi under my supervision. This thesis embodies results of original work, and studies are carried out by the student herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

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IN SILICO ANALYSIS OF MICROBIAL ENZYMES FOR DEGRADATION OF BISPHENOL A (BPA) AND ITS DERIVATIVES

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ABSTRACT

Current industrial and human activities, whereby EDCs-like compounds such as BPA have become more prevalent in the environment (an environmental contaminant) over decades. This synthetic chemical of polycarbonate and epoxy resins used in plastics disrupts endocrine functions with major health, and environmental risks known as BPA. The present study, with the most comprehensive analyses by looking at multiple health outcomes of BPA exposure should warn us about its serious effects on health leading to various endocrine diseases such as perturbation in thyroid function, metabolic disturbances, reproductive health issues, and hormone-dependent cancers. In practice, replacing BPA by analogs such as Bisphenol B, S, F, Z, and AF does not necessarily solve the problem because these substitutes have an equivalent or greater toxicity than BPA raising new health problems such as autism spectrum disorder (ASD), breast cancer, diabetes and polycystic ovary syndrome. This study reveals how current methods for degradation of this nature are ineffective, and often lead to pollution of soil and water. Microbial degradation is an assuring method to degrade these compounds. This study utilizes molecular docking to explore the interaction between BPA and microbial enzymes. This study aims to pick out effectual bioremediation by grasping the binding mechanism of three enzymes with BPA. This study contributes to developing a safe ecosystem by understanding the binding mechanism of BPA, mitigating the risk to health concentrating on the necessity for safer options, and spreading awareness to the public.

LIST OF PUBLICATIONS

1. Surbhi and Prof. Jai Gopal Sharma “Bisphenol A Polycarbonate Remediation: A Molecular Docking Approach to Understanding Microbial Enzyme Activity” has been accepted for Publication in the International Conference on Intelligent Computing and Communication Techniques at JNU New Delhi, India.

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BPA	Bisphenol A
BPF	Bisphenol F
BPB	Bisphenol B
BPS	Bisphenol S
BPZ	Bisphenol Z
BPAF	Bisphenol AF
LiP	Lignin Peroxidase

CHAPTER 1
INTRODUCTION

Endocrine-disrupting compounds/chemicals (EDCs)/ xenoestrogens have been widely released in the surroundings in recent decades. One of those chemicals is Bisphenol A, a synthetic chemical utilized for manufacturing polycarbonate types of plastic and also epoxy resins [1]. The two hydroxyphenyl functional groups that make up the structure of bisphenol are joined by a bridging carbon, while other functional groups divide it into analogs. As a main monomer, bisphenol A is a widespread endocrine-disruptive chemical in most everyday goods [2].

The public is exposed to this chemical through their meal, skin contact, as well as inhalation of household dust as it is present in the environment [3]. BPA can indirectly enter through landfill garbage containing plastic, paper, and metal debris and through chemical producers, recycling firms, and foundries. Fish are the most vulnerable species regarding BPA's effect on well-being, procreation, and progression in marine organisms. Around lower exposure levels, endocrine effects have been documented in amphibians, reptiles, and aquatic invertebrates. In addition to its wide range of uses, BPA is obtained in sewage, soil, groundwater, surface water, and sediments, among other environmental compartments.

India has the greatest yearly increase in BPA manufacturing, which is correlated with a 19% rise in the demand for polycarbonate and high BPA concentrations. Endocrine disruptors are chemicals that function by binding to receptors and can interfere with hormone synthesis, clearance, and tissue metabolism. They can also be hormone mimics or antagonists. High temperatures and harsh environments can lead to the colorless chemical BPA, leak out of plastic goods and into food and beverages. The pace at which BPA enters the human body is accelerated by high temperature, exposure to acidic or basic substances, and high concentrations of vegetable oils or salt chloride. This substance is present in packages and infant bottles as colorless crystals

or powder [4]. BPA can cross across the placenta and into the tissues and fluids of the human womb by being detected inthe serum of both the mother and the fetus as well as the human placenta. Urine contains the byproduct of liver breakdown of the phenolic chemical BPA, which is bisphenol A glucuronide. Through ER-dependent signaling pathways, it interacts with estrogen receptors, it interconnects with estrogen receptors, functioning like an agonist/ antagonist. Endocrine diseases such as premature puberty, metabolic abnormalities, infertility, and hormone-dependent tumors like breast and prostate cancer are caused by this.

To overcome difficulties, BPB, BPZ, BPF, BPAF, and BPS have been added to the production of food-contacting materials. It has been discovered that bisphenol analogs, such as bisphenol AF, have harmful effects on both individuals and the environment. These consequences include genotoxicity, neurotoxicity, cytotoxicity, endocrine disruption, and toxicity similar to that of dioxin. Certain bisphenol analogs, including BPB, BPF, BPS, and BPAF have more genotoxicity and estrogenic activity than BPA, and BPF and BPS are not safe substitute for bisphenol A. These adverse consequences emphasize the necessity of raising public awareness of bisphenol analog safety issues. Since BPA's strong chemical stability and poor solubility in water, natural breakdown is difficult, and conventional technology frequently has trouble fully degrading and eliminating BPA from the environment. Numerous drawbacks cause bisphenol A degradation techniques to frequently fail. Physical processes like burning and adsorption need a lot of energy and might not completely break down BPA, which could result in pollution. Chemical degradation, on the other hand, can lead to incomplete breakdown and hazardous intermediates. Plant-based biodegradation is sluggish, reliant on particular environmental factors, and frequently requires expensive operating expenses and sophisticated equipment. In the mild conditions, microbial degradation is more competent, least expensive and ecologically safe in comparison to the supplementary methods. This can break down BPA into harmless compounds.

That appreciation is required to design bioremediation strategies that will result in the efficient elimination of BPA contamination. Our molecular study could help us understand how bisphenol A binds to enzymes of microbes. The molecular docking, a computational approach for studying the enzyme-ligand interactions molecule-wise

has been one of the most widely used approaches[5]. In this study, we tried to explore the interaction of 3 microbial enzymes: Carboxylesterase, lignin peroxidase, and IsPETase with BPA and its derivatives. It utilizes algorithms to predict the binding as well as the degradation in terms of lock and key theory involving ligand-molecule binding mechanism [6]. Further investigation on microbial enzymes and bisphenol A interaction also has a great research interest to understand a mechanism needed for future BPA removal in the ecosystem.

OBJECTIVE – The aims of the present study is to predict the molecular interactions responsible for biodegradation of BPA from the environment mediated through microbial enzymes, through computational tool such as molecular docking.

CHAPTER 2

REVIEW OF LITERATURE

2.1 BISPHENOL A

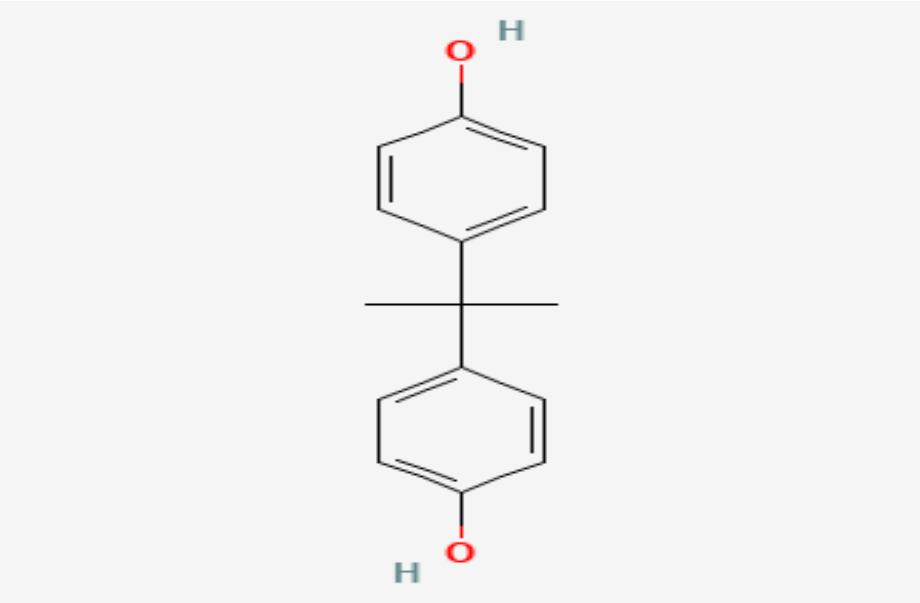


Fig. 2.1 Structure of Bisphenol A

Bisphenol A (BPA) is a man-made chemical used in the synthesis of plastics-polycarbonate. It is a man-made compound formed by adding phenol to acetone. BPA is a high-volume chemical used in the fabrication of epoxy resins and polycarbonate plastics that line the insides of many food and beverage containers. A natural endocrine disruptor, it is dangerous and even over 90% of urine levels tested confirm that it is a serious environmental health threat. The substance's ability to leak has sparked environmental and public health issues. Endocrine disruptor BPA can attach to estrogen receptors and alter gene expression to produce anti-androgenic properties. Research indicates that elevated amounts of BPA in kids might cause health problems like asthma, behavioral issues, and obesity.

2.1.1 Synthesis of Bisphenol A

Aleksandr P. Dianin, a Russian chemist, originally synthesized BPA in 1891 by mixing phenol to acetone in the company of an acid catalyst. Scientists found in the 1950s, that BPA and phosgene react to create polycarbonate, a transparent, rigid material used in the production of plastics. An acid catalyst (HCl or H2SO4) is added to a mixture of phenol (2): and acetone (1) in a stoichiometric ratio. Acetone's carbonyl group is protonated by the catalyst, increasing its electrophilicity and vulnerability to phenol nucleophilic attack. Next, BPA, unreacted phenol, water, and the catalyst are added to the mixture. Distillation is used to extract water, and unreacted phenol is recovered and recycled. By dissolving the crude BPA in a solvent and cooling the mixture to create crystalline crystals, BPA is refined by the process of crystallization. Filtration or centrifugation is frequently used to remove the crystals from the solution.

2.1.2 Utilization of BPA

BPA is largely utilized in Polycarbonate (PC) raw material due to its excellent impact resistance and visual clarity, typically achieved by the phosgene reaction. A modern,

environmentally friendly PC production plant uses transesterification [7]. This substance is used in numerous types of industries, including water pipe liners, food, and beverages can coatings, paints, adhesives, circuit packaging materials, printed circuit boards, thermal paper coated with BPA, tetrabromobisphenol A, and polyvinyl chloride antioxidants in products such as billboards, signs, building materials, and furniture [8].

2.2 DERIVATIVES OF BPA

BPA's detrimental impact on public health has led to restrictions or outright bans on its use in several nations. Although BPA derivatives are intended to take the place of BPA in the manufacturing sector, they have already been found in human body fluids and tissue samples, the ecosystem, and the food chain. The derivatives of BPA are Bisphenol F (BPF), Bisphenol B (BPB), Bisphenol Z (BPZ), Bisphenol AF (BPAF), and Bisphenol S (BPS) [9]. The structural resemblance and shared qualities of BPA derivatives, along with their greater detection in humans and the environment, offer major health problems. However, the extent of their possible harmful effects on the human neurological system is still unknown.

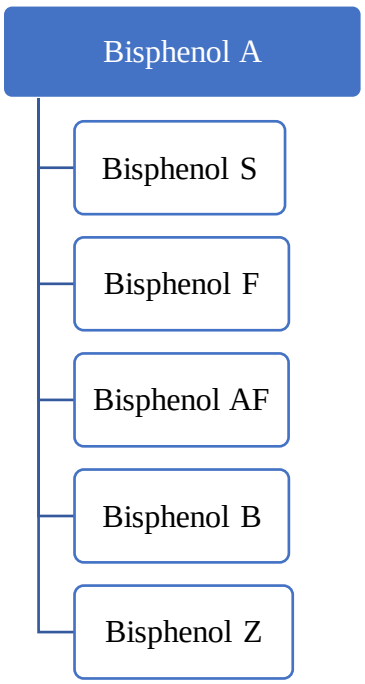


Fig. 2.2 Bisphenol A derivatives

2.2.1 Bisphenol F (BPF)

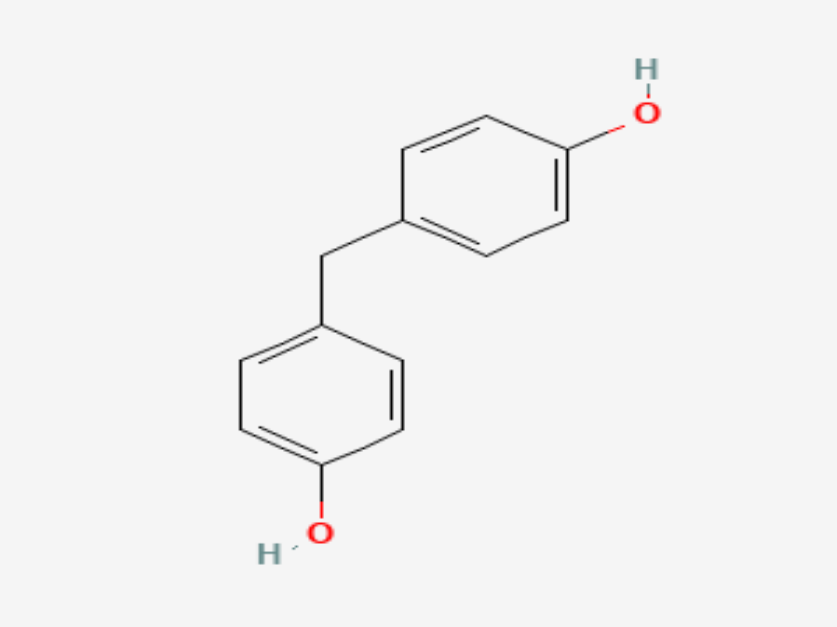


Fig. 2.3 Structure of Bisphenol F

Popular BPA substitute bisphenol F (BPF) is present in soft drinks, thermal paper receipts, and canned goods. It exhibits genotoxic effects, endocrine-modulating qualities, carcinogenic potential, reproductive complacencies, and oxidative stress. Fifty-five of the 100 urine samples tested positive for BPF, a BPA analog used in plastics industries. The less potent alternative, BPF, can act like estrogen and disrupt hormones, which problems with development, reproduction, and metabolism. The immunological system and neurological systems can have an impact.

2.2.2 Bisphenol S (BPS)

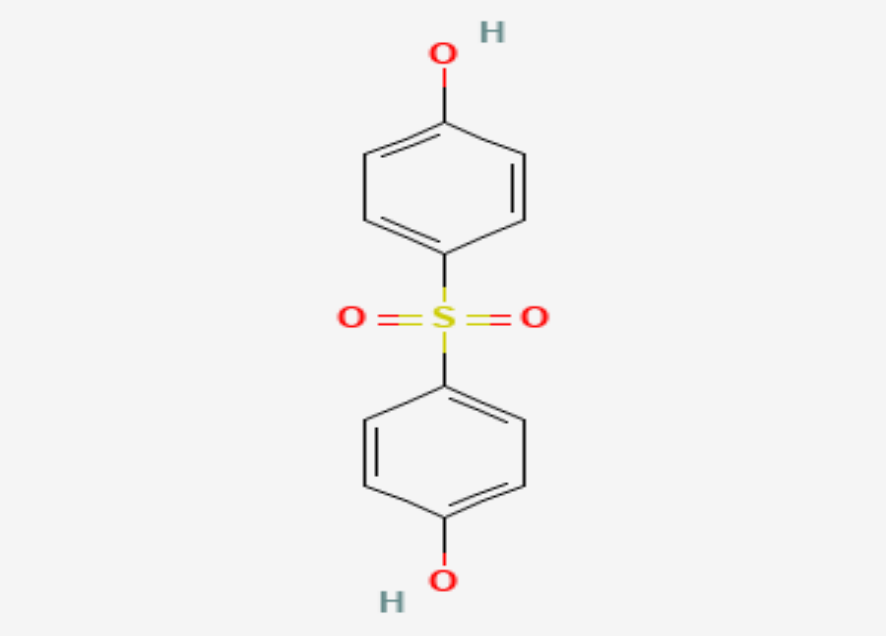


Fig. 2.4 Structure of Bisphenol S

BPS is a molecule which consists of 2 hydroxyphenyl groups connected via a sulfone (SO_2) bridge. BPS is often used as an alternative to BPA in a wide array of consumer products including thermal paper and paper products with food contact, such as cartons, as well as plastic products and epoxy resins. BH4 is often used in the manufacture of calcium NH4HPB1 to replace bethesa system foundry services co. as discovered due to the heat and photo-resilient nature of BPA. As the contamination has spread persky olers to encompass up to 81 percent of people in the US and in Asia, test of urine sampled have indicated that the disease is a result of BPS exposure. As a result, there has been a lot more scientific research done to determine the safety of

BPS, as it is mostly taken in via food. The results highlight the importance of further exploration and understanding of health implications of BPS.

2.2.3 Bisphenol AF (BPAF)

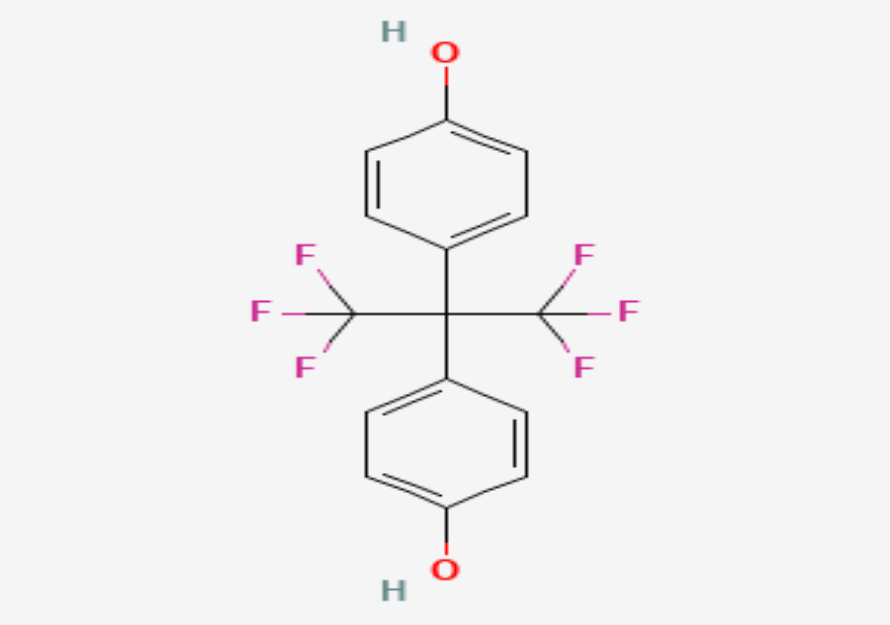


Fig. 2.5 Structure of Bisphenol AF

Bisphenol AF (Chemical analog of BPA)- used in resins for high-performance applications required heat stability and chemical resistance. The Environment Protection Agency is concerned because it has an unusual structure: two phenol groups joined by a hexafluoro propane bridge. The result of hormone disruption due to BPAF may lead to metabolic, developmental and reproductive issues bioaccumulation and long-term ecosystem impacts come into question as it remains continuously on the ecosystem. BPAF is scrutinized by environmental and health organizations, which have demanded a comprehensive assessment and regulation to reduce the effect of this chemical.

2.2.4 Bisphenol B (BPB)

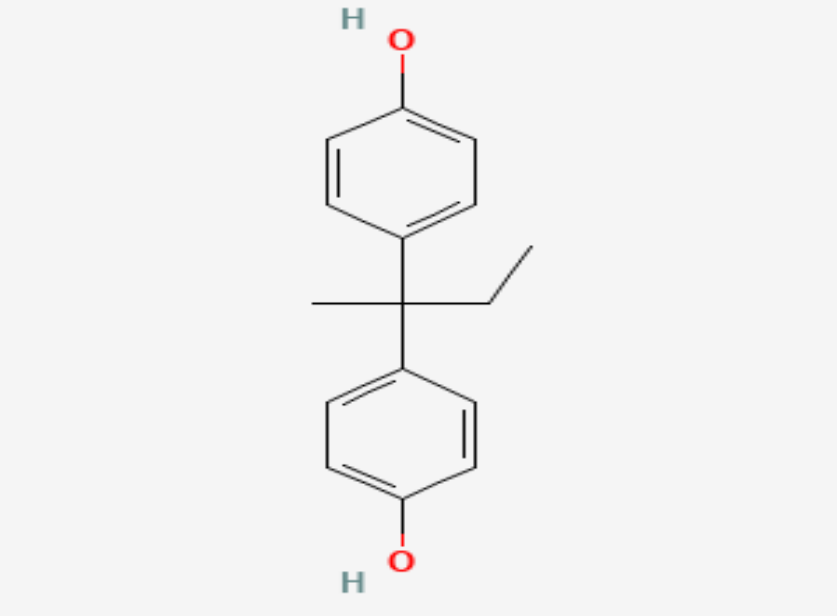


Fig. 2.6 Structure of Bisphenol B

BPB/2,2-Bis(4-hydroxyphenyl) butane is a solid in white crystals form with the same melting point as BPA, but with a long alkyl chain. It is a diphenolic acid composed of two phenol functional groups joined by a butylidene group. BPB use has raised harmful effects on health and the environment as human health side effects such as reproductive and developmental issues might occur; it also raises bioaccumulation and persistence. Approval agencies are examining whether BPB is safe, considering controls to cut dangers, and stressing the need for ongoing research and thoughtful regulation.

2.2.5 Bisphenol Z (BPZ)

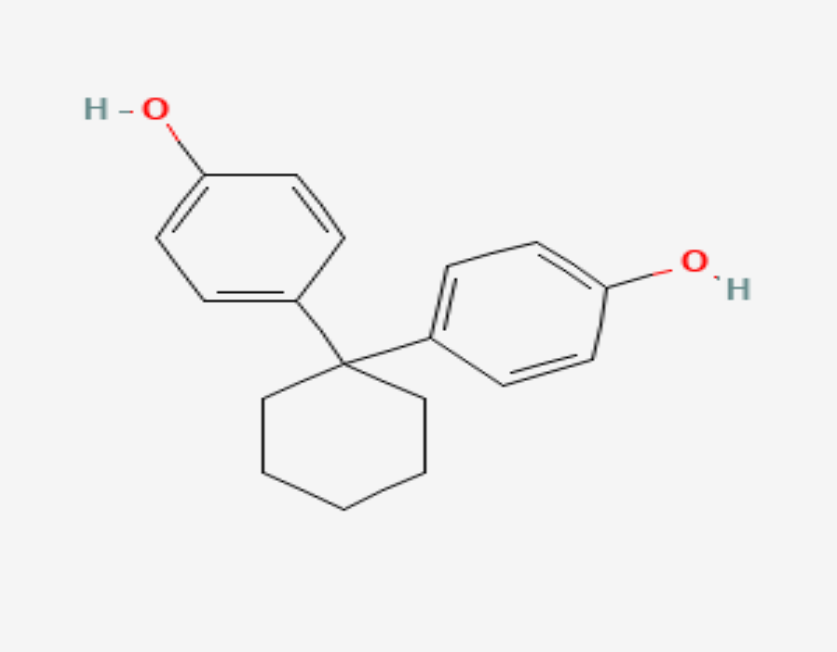


Fig. 2.7 Structure of Bisphenol Z

Bisphenol Z (BPZ) is a unique intermediate compound synthesised by the condensation of phenol with formaldehyde, which possesses excellent thermal, chemical resistance, and electrical insulation properties. The formula of the chemical is C12H10O2 and the molecular weight is 186.2g/mole. It is widely used as a feedstock for specialty polymers, resins, and coatings used in industrial applications; however, limited studies have focused on the toxicological and environmental concerns of BPZ. Because there is limited published information on BPZ, concern arises that knowledge of its potential risks and consequences remains incomplete, and reducing doubt might lead to a more recent assessment of its risk on environment and human health [10]. Uses of BPZ is amazingly wide used as a everyday replacement for BPA hence leading to the inexorable buildup of BPZ in human environment [11].

2.3 ROUTES OF EXPOSURE

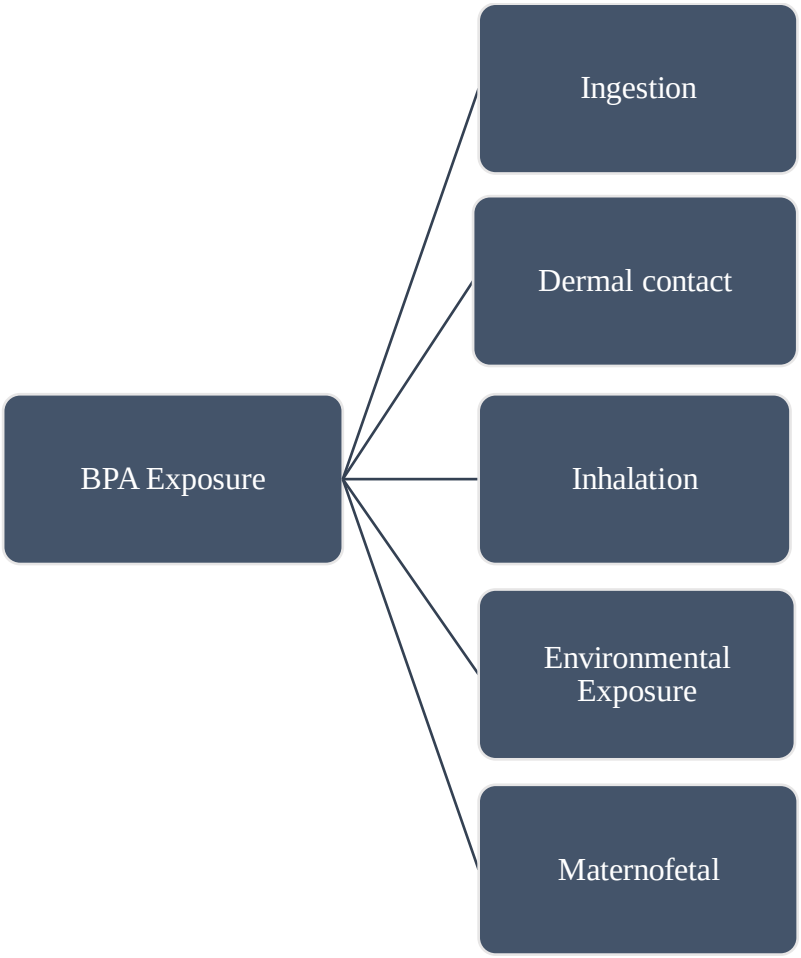


Fig. 2.8 BPA exposure routes

Human exposure normally happens as the following:

2.3.1 Ingestion

Bisphenol A and its analogs are predominantly consumed through dietary sources, where it leaches into food and beverages from BPA-containing containers. These containers, such as polycarbonate plastics and epoxy resins, can be heated, scraped, or subjected to acidic or high-temperature contents, which accelerates BPA leaching. BPA can also be present in food packaging and plastic utensils, which adds to its

ingestion. When consumed, BPA is absorbed through the digestive tract, potentially causing health problems.

Beverages having internal epoxy resin coating can leach out the BPA into the drinks especially when the containers are washed or heated.

Dietary intake of BPA and its analogs can take place through packaged goods, especially those stored in plastic wrap, which can potentially lead to exposure to BPA.

2.3.2 Skin and Eye Contact

Dermal exposure to bisphenol A and its analogs occurs when the skin comes into touch with BPA-containing goods, causing chemicals to penetrate the skin. Handling thermal paper or using products containing BPA and its analogs, such as medical devices, household products, and personal care items, are common exposure sources. Although skin penetration is less important than ingestion, frequent and sustained exposure can increase the overall BPA burden in the body, potentially compromising health due to its hormone-disrupting effects.

2.3.3 Inhalation

Inhalation of Bisphenol A takes place while BPA particles or vapors are inside the air and are breathed in. This can be in an environment where bisphenol A and its analogs are used in commercial approaches, leading to the discharge of airborne BPA. Workers in production plants that produce BPA-containing goods are at higher risk because of ability inhalation of fumes containing BPA/ BPA analogs. Moreover, BPA may be determined in household dust, contributing to inhalation publicity in general places like indoor environments in which dirt accumulates. Kids, who often play on the floors and feature nearer proximity to dirt, maybe in particular susceptible. BPA can enter the respiratory pathway and doubtlessly penetrate the bloodstream, contributing to its typical exposure.

2.3.4 Environmental Exposure

BPA is a harmful compound found in water, soil, and air, which can enter the environment through industrial waste, breakdown of BPA-containing products, and landfill by leaching. It can contaminate water sources, soil, and sediments, potentially affecting agricultural products and wildlife. BPA can be inhaled in the air as dust particles, leading to indirect human exposure. Continuous low-level exposure from these sources can contribute to the overall BPA burden in the body, raising concerns about its potential health effects due to its ability to disrupt the endocrine system.
Water contamination occurs due to BPA leaching out of pipelines and bottles.

Soil exposure occurs as BPA can enter the environment through waste streams and be present in soil and sediments, indirectly causing human exposure and contributing to human health issues.

2.3.5 Maternofetal

Maternofetal publicity to BPA refers to the transfer of BPA from a pregnant lady to her developing fetus. This switch occurs ordinarily through the placenta, as BPA can go through the placental barrier, allowing it to go into the fetus's bloodstream. BPA has been detected in maternal blood, placental tissue, and amniotic fluid, indicating that the fetus is exposed to the chemical at some stage in critical intervals of development. resources of maternal BPA publicity encompass the ingestion of meals and beverages from BPA-containing bins, dermal absorption from coping with products like thermal paper receipts, and inhalation of dust particles infected with BPA. As soon as transferred to the fetus, BPA can interfere with developmental techniques, doubtlessly leading to negative health outcomes along with disruptions in endocrine characteristics, reproductive machine development, and brain improvement. decreasing maternal BPA exposure is crucial to minimizing those capability dangers to fetus health.

2.4 RECEPTORS-BPA INTERACTION

BPA can mimic estrogen, a natural hormone, because of its phenolic structure. It interacts ordinarily with estrogen receptors via binding to the ligand-binding domain of these receptors. This binding can prompt or inhibit the estrogenic pathway, main to numerous organic responses. It also interacts with other hormone receptors, together with the thyroid receptor (TR) and the androgenic receptor (AR), with lower affinity. These interactions can disrupt everyday endocrine functions, doubtlessly leading to damaging health results including reproductive issues, metabolic troubles, and developmental issues. The capacity of BPA as well as its NextGen analogs to bind to twenty-one nuclear receptors pf humans was assessed in a study and the findings indicated that BPA and the NextGen bisphenols are extremely disruptive to non-ribosomal proteins (NRs) e.g. ERα, ERβ, ERγ, and GR and CAR [12].

2.4.1 Interaction with Estrogenic Receptors

Estrogens, regulated by Erα and Erβ receptors, play a necessary role in tissue development, homeostasis, and growth. These receptors can also bind to various compounds like BPA and its analogs with varying binding affinities [13]. Studies show estrogen and BPA have similar effects on adipogenic transcription factors gene expression and stop adiponectin secretion from adipocytes of people in a non-monotonic dose-dependent manner, potentially affecting body weight. BPA is also responsible for binding to ERs causing carcinogenesis, as it promotes the cell division and migration of ovarian cancer cell lines.

2.4.2 Interaction with Androgenic Receptors

BPA, a plasticizer, has been shown to have anti-androgenic properties due to its capacity to compare with DHT for binding to androgenic receptors (AR). BPA has been demonstrated to attach to various locations on AR surfaces via hydrophobic interactions, causing detrimental effects on spermatogenesis, steroidogenesis, testicular atrophy, and changes in mature sperm parameters. BPA also affects pituitary, hypothalamic, and testicular tasks by regulating estrogen/androgen synthesis as well as receptor work.

2.5 TRANSCRIPTION FACTORS AND BPA

BPA happens to be a powerful endocrine-disrupting compound/ chemical (EDC) that can drastically alter gene expression by influencing transcription factors. This can result in negative health consequences such as hormone imbalances, reproductive problems, and carcinogenesis. BPA's widespread action on transcription factors highlights its importance in gene regulation and cellular function.

2.6 EFFECTS OF BPA ON HUMAN HEALTH

BPA is a chemical with serious health consequences. In humans, BPA affects the endocrine system, causing metabolic, cardiovascular, and reproductive problems. It also raises the risk of certain malignancies, including breast and prostate cancer, since it alters gene expression and promotes cellular proliferation. The main sources of BPA exposure include toys, dental products, and food packaging [14]. It is broken down in the liver to produce bisphenol A glucuronide, which interacts with estrogen receptors to cause hormone-dependent cancers, metabolic problems, and infertility, among other endocrine illnesses[15].

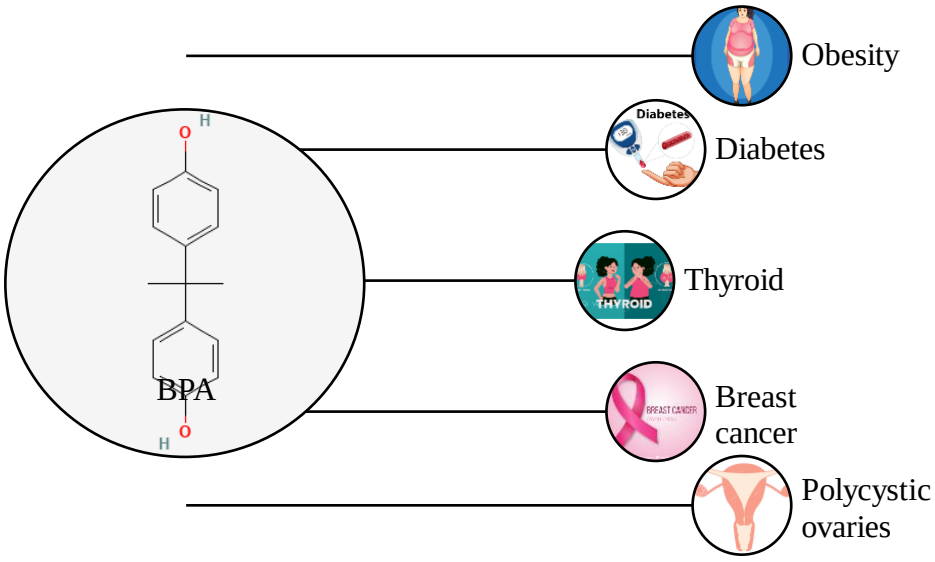


Fig. 2.9 BPA Effects on Human

2.6.1 Metabolic Syndrome Like Obesity

BPA exposure raises the risk of obesity, metabolic disorders, and IL-17A levels in human adipose tissue, which may result in increased inflammatory responses, weight gain, and insulin resistance [16]. BPA reaction in the company of estrogen receptors fills in as an antagonist by an estrogen receptor based on a signaling pathway. It increases adipogenesis, which results in more lipid buildup and adipogenic markers [17]. BPA disrupts cellular evenness by boosting oxidation while lowering antioxidant enzymes, causing mitochondrial dysfunction. BPA exposure causes endocrine disruption, which leads to the metabolic syndrome.

2.6.2 Diabetes

Summary of Diabetes mellitus (Type-2DM) is a progressive disorder or metabolic disease due to resistance of insulin and pancreatic β-cell dysfunction; BPA is an endocrine disrupting substance that has been implicated in the pathogenesis of T2DM [18]. BPA announced that it also affects the structure of mitochondria, changes gene expression and, by interfering with glucose stability and cell functions of pancreas, it may cause insulin hampering, causing additional metabolic disturbances after exposure to a developing fetus and a newborn during the fetal period [19]. BPA has been the focus of scientific investigation for its potential to function as a risk factor for diabetes by binding to the receptors of natural estrogen as an estrogen and mimicking [20].

2.6.3 Polycystic/Multicysts Ovary Syndrome (PCOS)

Polycystic/ multicystic ovarian syndrome (PCOS) is a well-known polymorph metabotrophism illness manifesting in young women before menopause. Over here it leads to hypertension, bad monthly cycle and pregnancy issues too and symptoms e.g. hair fall [21]. Endocrine disruptors, notably Bisphenol A, maybe a contributing factor to the condition, as they have been associated with metabolic and reproductive abnormalities comparable to PCOS. Exposure to these chemicals may exacerbate symptoms in affected females or contribute to the syndrome's final phenotype in genetically predisposed people [21].

2.6.4 Breast Cancer

BPA, like to diethylstilbestrol, attaches itself to steroid receptors and can disrupt endocrine functions, potentially leading to hormone-dependent tumors [22]. BPA interacts with ER: ERα and ERβ in MCF-7 breast cancerous cells [22]. Which leads to increased transcriptional activity and proliferation. The MCF-7 cell line expresses both ERα and ERβ, with ERβ indicated as a cancer treatment target [23].

2.6.5 Thyroid Function

The studies suggest that BPA potentially hamper the action of the thyroid hormone [24]. BPA and its variants bind to TR, specifically TRβ, and serve as antagonists, similar to T3. BPA decreased TR-mediated transcription of T3-response genes, indicating that it can impair thyroid hormone activity. BPA's TR-antagonistic impact may be the primary mechanism by which it impairs thyroid function, as it has been shown to decrease TR-mediated transcription of T3-response genes at low concentrations. In a study, it is also predicted that BPA exposure can also cause thyroid cancer in some people [25].

2.6.6 Cardiovascular

The study looked at the impacts of BPA on the cardiovascular system and found a possible relationship between BPA and hypertension [26]. BPA significantly impacts the circulatory system during hypoxic events by increasing the synthesis of vascular endothelial development factor, that leads to not controlled neovascularization [27]. It promotes the making of vascular endothelial growth factor, resulting in neovascularization which was not controlled, angiogenesis [28] and intraventricular thickness increases.

2.6.7 ASD- autism spectrum disorder

The illness of the neurological network known as an autism spectrum disorder (ASD) is characterized by difficulty in talking, interacting with people, and repeating the same activities. It often results in issues with language development, connection formation, and social cue comprehension. Without the use of a single test, an extensive assessment of behavior and developmental history is used to diagnose ASD. although the precise etiology is uncertain, environmental and genetic factors are thought to have a role [29]. For people with ASD, prior discovery and support systems such as behavioral and talking therapy can greatly improve outcomes by assisting in the development of clinical abilities and assisting in overcoming obstacles, thereby

improving the person’s quality of life. Recent research shows that prenatal BPA exposure affects ASD-linked gene expression, brain processes, and behaviors in a sex-specific way, although the molecular mechanisms are unknown[30].

2.6.8 DNA Damage

The Ames test, CHO/HGPRT mutation assay, chromosomal aberration tests, comet assay, micronucleus assay, cellular proliferation, cell transformation, and expression of p53 or Y2HAX are some of the assays utilized in vitro investigations in DNA damage and toxicity. The results of these studies revealed an increase in genotoxicity; however, cytotoxicity was not consistently shown. BPAF and BPB were discovered to activate the tumor suppressor gene p53, with the mitochondrial toxicity test exhibiting the highest sensitivity to cell stress [31].

2.6.9 Skin Irritation

There was a lack of prediction for the development of respiratory allergies among the six chemicals examined for skin and respiratory sensitization, whereas all six showed the characteristics of allergic responses. It seems that BPA and BPS do not normally cause direct skin damage or inflammation, since they were determined to be negative for skin irritation. According to the predictions, BPB and BPF will not irritate the skin when touched, therefore they won't do any immediate damage [32].

2.7 EFFECTS OF BPA ON THE ENVIRONMENT

BPA pollution is a major concern because it enters waterways through landfill leaching, the degradation of BPA-containing items, and industrial discharge. Aquatic animals, such as amphibians and fishes, are especially affected by BPA, which harms their reproductive systems and causes the population to decline. BPA bioaccumulates, endangering the entire food chain, including humans who consume contaminated seafood and wildlife [33].

2.7.1 Vertebrates Affected by BPA

Bisphenol A (BPA) is predominantly found in rivers and lakes, with most studies on its effects on wildlife focusing on aquatic species, particularly fish and organisms that live in both water and on land, with some data also available for birds as well as of reptiles [33]. Fish are mostly exposed to BPA by inhalation through their gills, which is less efficient than liver metabolism. As a result, waterborne BPA regularly causes estrogenic illness in fish, adding the initiation of vitellogenin in males, and demonstrating its ability to reproduce.

2.7.2 Effect of BPA on Plants

Higher BPA exposure causes an increase in ROS levels, which accelerates the oxidation of UFA, resulting in decreased membrane fluidity and lipid peroxidation due to self-catalytic processes [34].

2.7.3 Effects on Soil and Water

BPA, a hazardous chemical, can pollute soil via sludge, wastewater, and biosolids made use of as soil amendments, and has a half-life of 30 days, causing land degradation and accumulation. BPA leaches into water from plastic containers and poses a health danger to individuals who consume it. Certain situations, such as high temperatures, prolonged storage, and physical damage, might cause the chemical to leak into the water. BPA can alter the endocrine system by mimicking the estrogen hormone, resulting in hormonal abnormalities, reproductive disorders, and developmental issues in the fetus and young children. This leaching is especially concerning because water is a daily necessity, resulting in constant exposure [35].

2.8 ENZYMATIC DEGRADATION OF BPA

Extracellular fungal and bacterial enzymes have several advantages for decomposing endocrine disruptor chemicals, including high substrate specificity, adaptability in a variety of environmental circumstances, simplicity, and easy process, making them an attractive alternative [36]. Microbial degradation, both pure and mixed cultures, has been discovered as a promising approach for BPA detoxification, providing a safer and more cost-effective alternative to classic physicochemical processes [37]. Through hydrophobic interactions, enzymes cling to the polymer surface to form hydrolases, which catalyze the hydrolysis or hydroperoxidation of polymer bonds. Enzyme accessibility is increased by the hydrophobic gap in the active region of the enzyme, which permits the absorption of hydrophobic groups. By reducing BPA pollution, this procedure can save human health and the ecosystem for generations.

2.8.1 Carboxylesterase

Carboxylesterases are esterases that catalyze the breakdown of ester bonds. Numerous novel enzymes have been discovered to recover their physiological and biochemical features [38]. These numerous enzymes are found in various sources, including humans and microbes. Carboxylesterases are lipolytic enzymes that effectively hydrolyze a wide range of structurally varied molecules, including carboxylic acid esters, amides, and certain thioesters [39]. They also catalyze synthetic and transesterification events and due to this, they take part of main role in the hydrolysis activity of many substances.

2.8.2 Lignin Peroxidase

Lignin peroxidase (LiP), an enzyme with oxidoreductase properties, is found in various microorganisms, particularly white-rot basidiomycetes. LiP is made up of two domains, proximal and distal, separated by heme to ensure full incorporation into the proteins [40]. It performs the oxidative depolymerization of substances like lignin. Lignin peroxidase was first extracted from *P. chrysosporium* fungus culture and has since been discovered in various fungi [41]. Lignin peroxidases are monomeric hemoproteins with molecular weights of 40kDa, identical to horseradish peroxidase (HRP) [42]. They feature a peroxides catalytic cycle similar to HRP. The LiP enzyme performs three catalytic reaction cycles [43]. It is oxidized by hydrogen peroxide, yielding compound 1 and water. Compound 1 catalyzes the production of substance 2, which produces free radicals and transfers electrons from the substrate. Compound two then interacts with the substrate molecule, generating another free radical and water while reducing the enzymes to their native form [44].

2.8.3 IsPETase

IsPETase is a PET hydrolase enzyme that shares similarities with lipases and cutinases, but it also has unique properties that set it apart from cutinases previously identified for PET hydrolysis [45]. To build the crystal structure, an E. coli protein called IsPETase was recombinantly synthesized from a codon-enhanced gene in several hosts [46]. The enzyme, a member of the α/β serine hydrolase family, hydrolyzes PET by attacking the substrate's ester bond through a nucleophilic attack by serine, which is stratd by other triad remainders [47]. Serine forms a covalent tetrahedral intermediate containing an ester carbonyl group, which is evened by hydrogen bonds betwixt amide bonds in an oxyanion hole [48]. IsPETase's α or β hydrolase fold have 9 β-strands in a twisted core β-sheet, near by 6 α-helices [49].

2.9 MOLECULAR DOCKING

Scientists must first understand how protein receptors recall, relate with, and attach to molecular substrates and inhibitors to find new drugs [50]. The scoring function is an essential component in structure/form-based drug design [51]. These protein-molecule interactions are evaluated with a computational technique called molecular docking. Molecular docking is an important computer approach for drug development, structural biology, and biomolecular interaction studies. It involves determining how a tiny chemical, will bond with a target biomolecule. This technique assists in the finding of new drug nominees/candidates, the refinement of existing molecules, and the study of the complex interaction between ligands and receptors. It compares and ranks various ligand-enzyme conformations based on binding energies, separating high-affinity ligands from low ones. It has applications in a variety of drug development disciplines, including structure-based medicine development, virtual screening, and lead optimization [52]. Pollutant degradation is aided by the combination of an enzyme and a substrate, which is more favorable when the binding energy between the two is low. Molecular docking of protein form changes and ligand binding relies on designing effective potentials that meet accuracy and speed requirements, and efficient algorithms to sample these potentials. This review emphasizes strategies for achieving these goals in different molecular modeling contexts, particularly in structural biology [53].

CHAPTER 3. METHODOLOGY

3.1 Preparation of the Fungal and Bacterial Enzyme

Three enzymes were employed in the investigation for molecular docking studies: IsPETase (*Piscinibacter sakaiensis*), lignin peroxidase (*Phanerodontia chrysosporium),* and carboxylesterase (*Pseudomonas aeruginosa*). These enzymes's structure was downloaded in 3D format from the Protein Data Bank (PDB), which may

be accessed in PDB format at (https://www.rcsb.org/). PyMol and BIOVIA were both utilized by the researchers to produce the receptor, however only BIOVIA was employed in this investigation. A software application for materials science, biochemical analysis, and drug development in the life sciences is called BIOVIA. It provides molecular modeling simulation, data management, and visualization to facilitate effective biological system analysis. Its user-friendly interface accelerates scientific advancements in academic research, biotechnology, and pharmaceuticals while streamlining processes and improving cooperation. Water molecules were removed from fungal and bacterial enzyme structures after initially loading it into the BIOVIA tool as it may prevent the binding process. Secondly in the pursuit of improved strength of docking protocols to align fungal and bacterial enzyme binding a polar hydrogen atoms were introduced to fungus and bacterium enzyme scaffolds.

3.2 Preparation of BPA and its Analogs as Ligands

The chemical or compound database for BPA and its another derivatives; BPS, BPF, BPZ, BPB, and BPAF were gathered from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). It serves as a embryonic database of the molecular functions of small molecules PubChem provides details on a number, ranging from chemical structures to physical properties and disease-related to the pharmaceutical activities, and the related references to the original scientific literature you need. Because PubChem allows researchers to search its massive amount of information on the biological activities of chemicals and the result of its screening experiments, it is a very useful tool for scientists working on the fields of chemical biology, toxicology and drug development. Importantly, PubChem is critical to the worldwide progress of science as well as the development of new drugs. It was then converted into a three-dimensional SDF (structure data file) format. It requires a good understanding of molecular geometry which is essential for accurate modeling studies. Following acquisition, the 3D structure of the molecule was manually analyzed and manipulated in order to be prepared for a docking analysis and make sure the next docking studies were more accurate and reliable. Building up the construction of BPA

and it is products adequately that these were well prepared to possibly be analyzed seriously during docking investigation.

3.3 Exploration of Molecular Docking Utilizing PyRx

BPA and its derivatives which are BPF, BPB, BPZ, BPAF, and BPS were docked onto three enzymes which were IsPETase (*Piscinibacter sakaiensis*), lignin peroxidase (*Phanerodontia chrysosporium*), and carboxylesterase (*Pseudomonas aeruginosa*) using PyRx software and AutoDock Vina technique. PyRx is a free open-sourced software for all those who need a visual molecular docking with AutoDock. This means that there is an entire interface that makes it easier to do complex experiments for people who do not have the most sophisticated of the hardware. PyRx can bring these in Python with the help of a number of libraries and computational tools, such as AutoDock Vina one of the reasons why this well-known software is widely popular is that it is able to rapidly predict the binding affinity and orientation of smaller molecules in the binding site of a target protein. This quickely screened databse of large small molecules to identify lead drug candidates with good building affinities and desirable interactions with targets using PyRx and AutoDock Vina. The program PyRx AutoDock was used for the docking ligands to freely move around enzyme structures. It enabled them to explore possible binding sites, and identify potential high-affinity binding sites. This method reliably assessed ligand receptor interactions which is a significant point for understanding the binding of BPA and its derivatives with their targets.

3.4 Determining Ligand-Enzyme Interaction with BIOVIA

The enzyme-BPA complex of compounds after docking simulations were analyzed on BIOVIA discovery studio. This software platform allowed us to visualize the interactions between enzymes and BPA ligands and analyze the protein of enzyme of interest to determine the properties and binding mechanism of these proteins. This visualization gave us a better understanding of the ligand- receptor and its therapeutic implications by giving a clue into the molecular recognition and binding kinetics of BPA with putative enzymes of bacterial origin. Application BIOVIA software product

lines are used in markets where scientific research and innovation are mission-critical in industries such as academia, biotechnology, chemicals, consumer-packed goods, energy, engineering, materials, health, and medicine. Sophisticated computational and informative technologies are used to support scientists and engineers in solving complex problems, accelerating research, and incorporate them into the in cities in their studies, and it can offer a far more sophisticated visualization and signaling features. these let users generate great visualization and illustrate for quotes and reports, learn about molecular properties and multi-dimensional figures.

CHAPTER 4

RESULTS

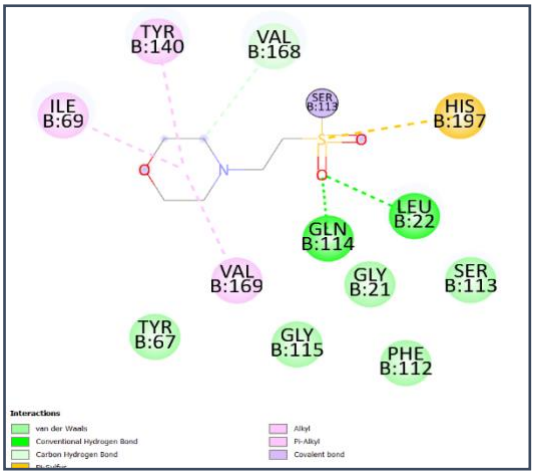
Such work explores how degradation is mediated by diverse enzymatic capacities among enzyme-expressing organisms, e.g. bacteria and fungi, to cleave chains such as polycarbonate, which comprise BPA and its derivatives. The BPA degradation potential of these enzymes as tools for the efficient removal of BPA pollution in the ecosystem must be validated. Using a computational technique, molecular docking was performed to predict the interaction between the fungal and bacterial enzymes with BPA and its derivatives. This was coupled to three enzymes that break down plastics (‘PlasticBreaking Enzymes 1-3; PBEnz1-3) and tested against BPA and a panel of its organic chemicals. Hydrophobic interactions, hydrogen bonding, and the binding affinity of the compounds were also evaluated using extra parameters. The significance of comprehending the molecular interactions like van der Waal or hydrogen bonding between the three enzymes and BPA and its derivatives in this study, emphasizes the necessity of developing effective solutions for the deletion of BPA contamination from the ecosystem.

Table. I illustrate the Binding Affinities Between the Three Enzymes, and the BPA and its Derivatives.

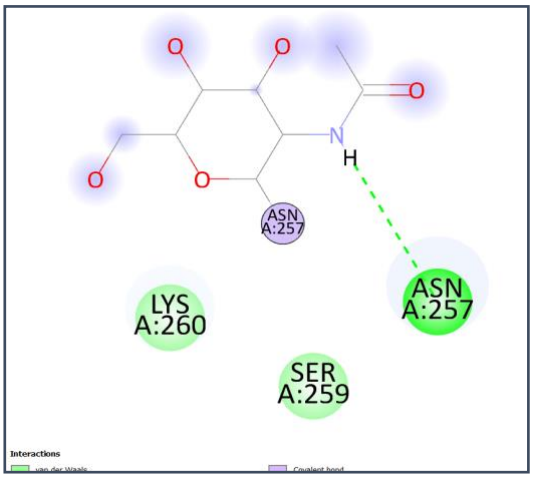
S.No.	Compound	Compound ID	Binding Affinity with Enzymes		
			Carboxylesterase	LiP	IsPETase
1.	Bisphenol A (BPA)	6623	-6.7	-6.4	-6.1
2.	Bisphenol F (BPF)	12111	-6.1	-6	-5.5
3.	Bisphenol S (BPS)	6626	-6.8	-6.1	-6.3
4.	Bisphenol AF (BPAF)	73864	-6.9	-6.7	-6.7
5.	Bisphenol Z (BPZ)	232446	-6.6	-6.7	-6
6.	Bisphenol B (BPB)	66166	-6.6	-6.6	-5.9

The table above shows various binding affinity scores with each enzyme. The BPA and its derivatives have different binding affinities with each of the three enzymes which are IsPETase (Piscinibacter sakaiensis), lignin peroxidase (Phanerodontia chrysosporium), and carboxylesterase (Pseudomonas aeruginosa), suggests the potential enzyme for the degradation as more negative score symbolizes that the binding affinity would be better and also the binding potential of that enzyme.

BPA Interaction with Carboxylesterase



BPA Interaction with Lignin Peroxidase



BPA Interaction with IsPETase

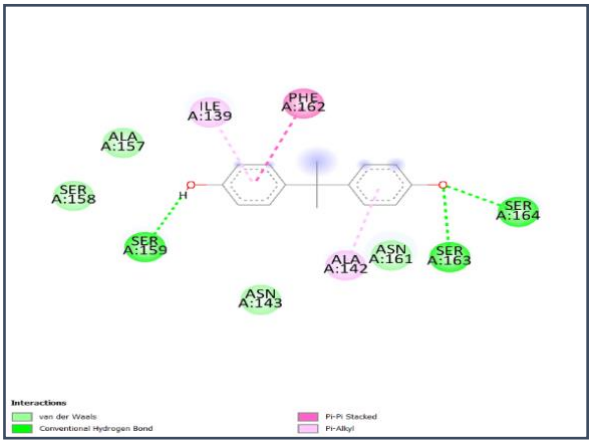
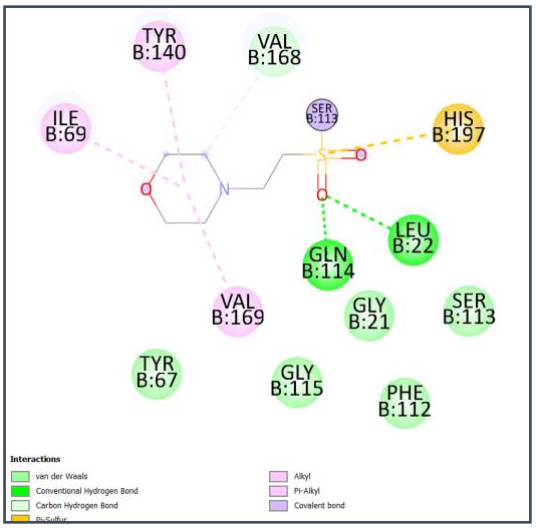


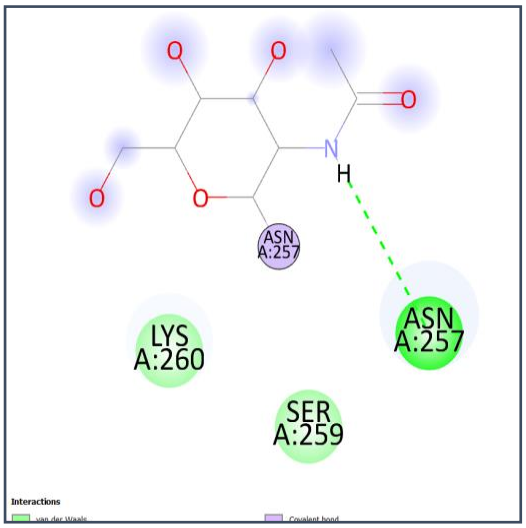
Fig. 4.1 2D interaction between BPA with Carboxylesterase, IsPETase, and LiP.

Fig. 4.1 shows the 2D interactions between the enzymes and BPA. The binding affinities of BPA with Carboxylesterase is -6.7, LiP is -6.4, and IsPETase is -6.1 which shows that Carboxylesterase enzyme would be better suitable for the degradation of BPA as it has the highest binding energy as compared to LiP and IsPETase. The binding affinities were in the order of Carboxylesterase> LiP> IsPETase.

BPF Interaction with Carboxylesterase



BPF Interaction with Lignin Peroxidase



BPF Interaction with IsPETase

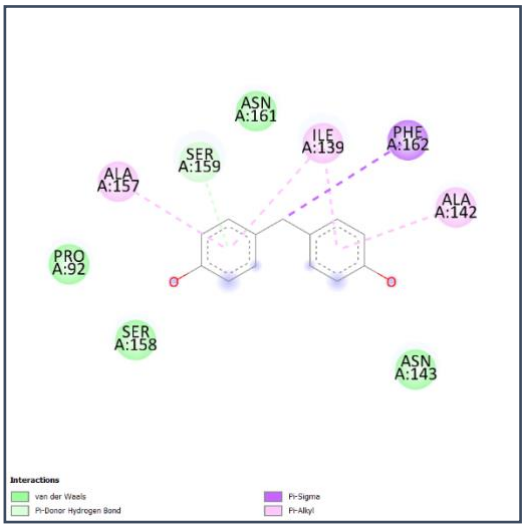
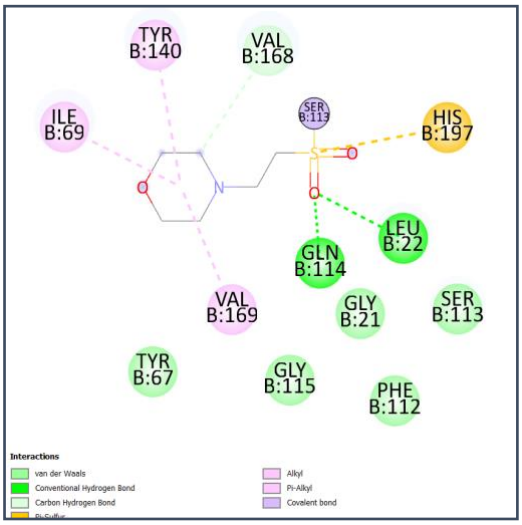


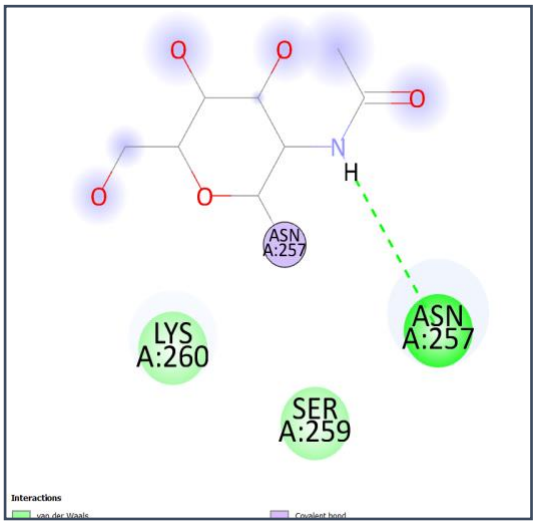
Fig. 4.2 2D interaction between BPF with Carboxylesterase, LiP, and IsPETase.

Fig. 4.2 shows the 2D interaction between the enzymes and BPF. The binding affinities of BPF with Carboxylesterase is -6.1, LiP is -6, and IsPETase is -5.5 which shows that Carboxylesterase enzyme would be better suitable for the degradation of BPF as it has the highest binding energy as compared to LiP and IsPETase. The binding affinities

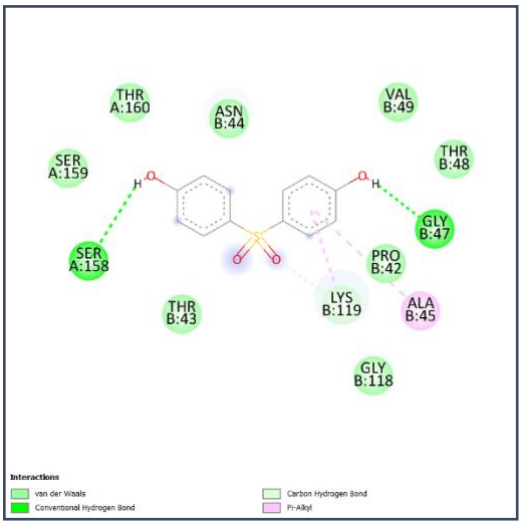
BPS Interaction with Carboxylesterase



BPS Interaction with Lignin Peroxidase



BPS Interaction with IsPETase

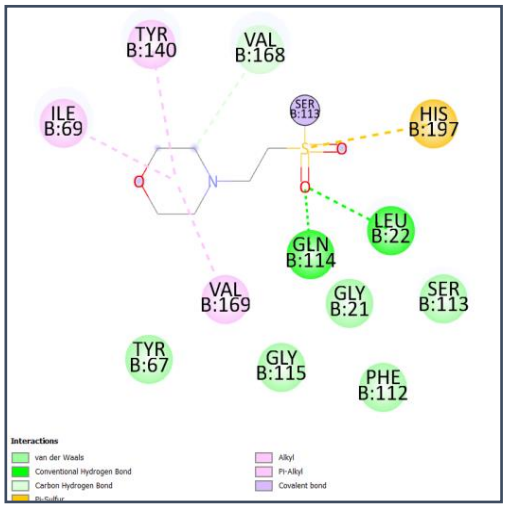


were in the order of Carboxylesterase> LiP> IsPETase.

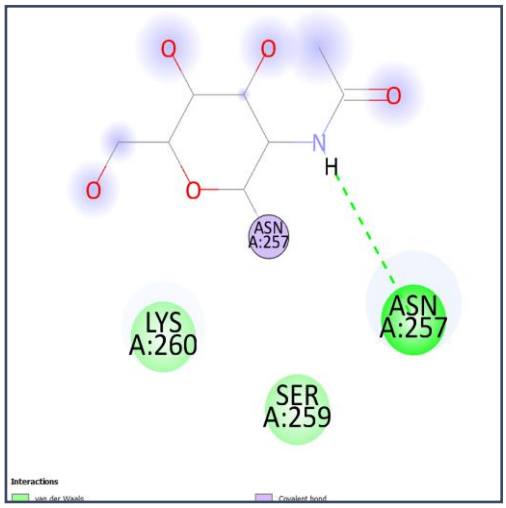
Fig. 4.3 2D interaction between BPS with Carboxylesterase, LiP, and IsPETase.

Fig. 4.3 shows the 2D interaction between the three enzymes and BPS. The binding affinities of BPS with Carboxylesterase is -6.8, LiP is -6.1, and IsPETase is -6.3 which shows that Carboxylesterase enzyme would be better suitable for the degradation of BPS as it has the highest binding energy as compared to LiP and IsPETase. The binding affinities were in the order of Carboxylesterase> IsPETase> LiP.

BPAF Interaction with Carboxylesterase



BPAF Interaction with Lignin Peroxidase



BPAF Interaction with IsPETase

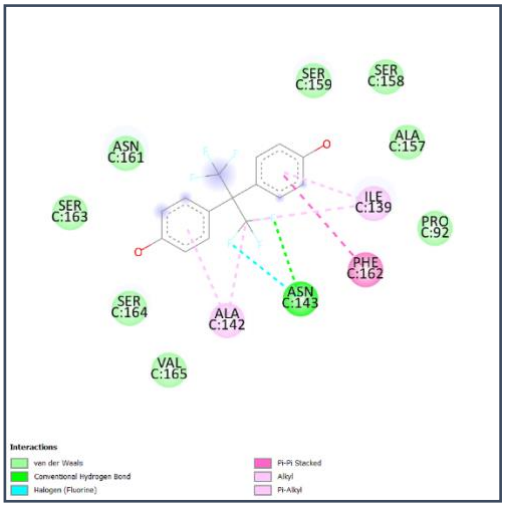
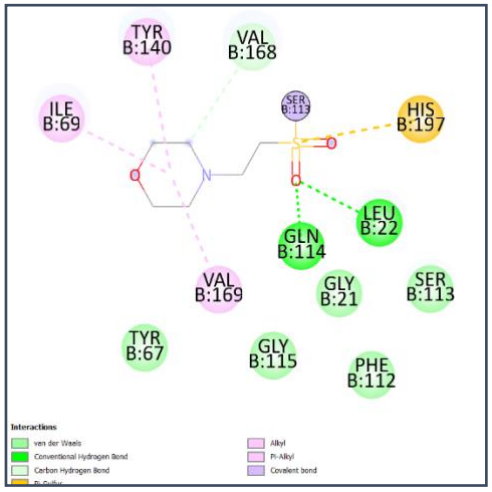


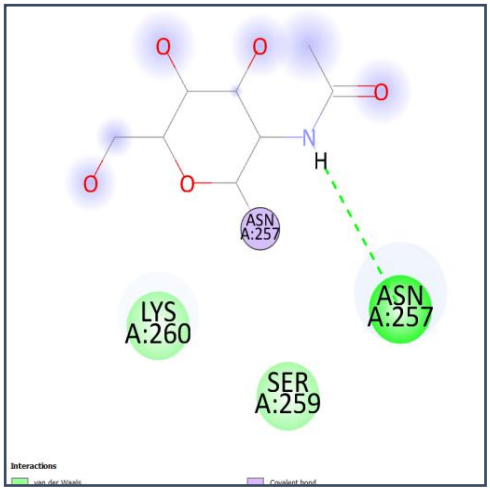
Fig. 4.4 2D interaction between BPAF with Carboxylesterase, LiP, and IsPETase.

Fig. 4.4 shows the 2D interaction between the three enzymes and BPAF. The binding affinities of BPAF with Carboxylesterase is -6.9, LiP is -6.7, and IsPETase is -6.7 which shows that Carboxylesterase enzyme would be better suitable for the degradation of BPAF as it has the highest binding energy as compared to LiP and IsPETase. The binding affinities were in the order of Carboxylesterase> LiP=IsPETase.

BPZ Interaction with Carboxylesterase



BPZ Interaction with Lignin Peroxidase



BPZ Interaction with IsPETase

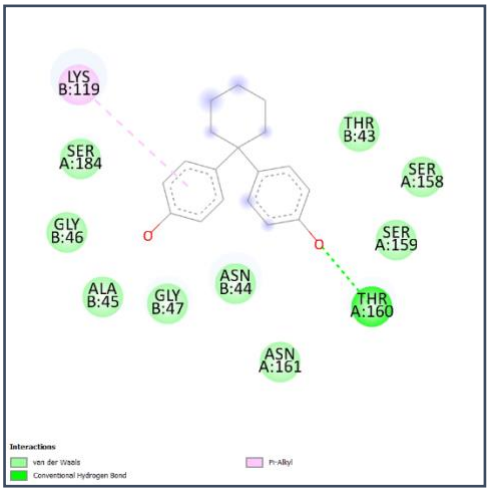
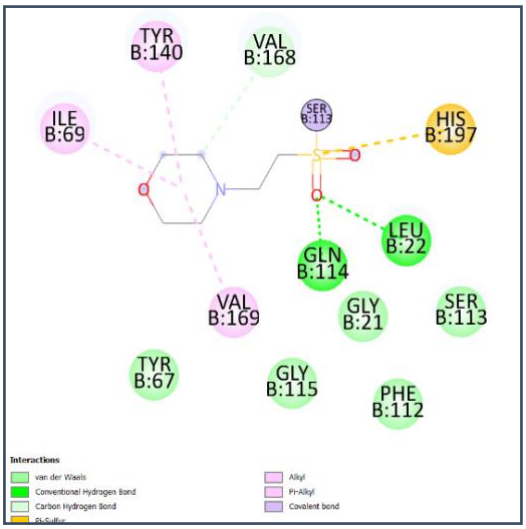


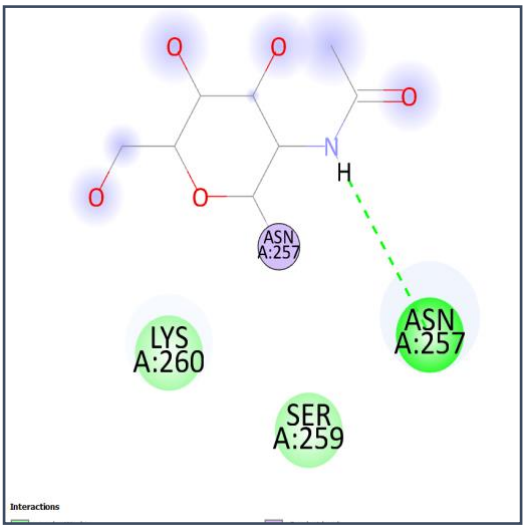
Fig. 4.5 2D interaction between BPZ with Carboxylesterase, LiP, and IsPETase.

Fig. 4.5 shows the 2D interaction between the three enzymes and BPZ. The binding affinities of BPZ with Carboxylesterase is -6.6, LiP is -6.7, and IsPETase is -6, which shows that LiP enzyme would be better suitable for the degradation of BPAF as it has the highest binding energy as compared to Carboxylesterase and IsPETase. The binding affinities were in the order of LiP> Carboxylesterase> IsPETase.

BPB Interaction with Carboxylesterase



BPB Interaction with Lignin Peroxidase



BPB Interaction with IsPETase

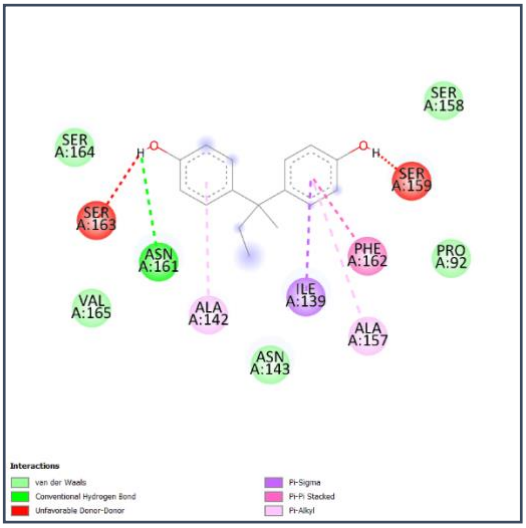


Fig. 4.6 2D interaction between BPB with Carboxylesterase, LiP, and IsPETase.

Fig. 4.6 shows the 2D relation between the three enzymes and BPB. The binding affinities/score of BPB with Carboxylesterase is -6.6, LiP is -6.6, and IsPETase is -5.9, that shows that Carboxylesterase and IsPETase enzyme can be better suitable for the deterioration of BPB as it has the highest binding energy as compared to LiP. The binding affinities were in the order of Carboxylesterase= IsPETase> LiP.

CONCLUSION AND DISCUSSION

Consumer goods and household dust contain BPA derivatives, which have toxicological effects that are similar to or less severe than BPA itself. Since they are present in consumer goods and samples taken from human biomonitoring, it is crucial to understand their possible biological actions. Studies suggest that the harmful effects were observed due to the structural similarity of bisphenol A and its derivatives with the human hormone estrogen. Bisphenol A (BPA) and its equivalents pose serious threats to human and environmental health due to their overuse in industries like food packaging, toy making, beverage wrapping, and containers. Disruption of the endocrine system by mimicking the human estrogen and other health problems like polycystic ovaries, thyroid, diabetes, and obesity caused by these contaminants that enter the human body via soil, water, and rivers. These persistent pollutants are still piling up in the ecosystem and in the human body, therefore finding an effective bioremediation solution is critical. Bioremediation solutions include enzymatic degradation as BPA and its analogs can be broken down effectively with no need for heat or pressure, making this process both economical and better for the environment. Enzymes reduce the toxicity and environmental persistence of bisphenol compounds by selectively breaking them down into less hazardous chemicals. In order, to potentially degrade the Bisphenols, enzymes must have a higher binding affinity with this synthetic chemical. This study aims to predict the potential microbial enzymes for the biodegradation of Bisphenol A and its equally toxic derivatives. The interaction between fungal and bacterial enzymes and bisphenol A and its equivalents which are BPS, BPB, BPZ, BPF, and BPAF were thoroughly investigated and this investigation in this study was done with the help of a molecular docking tool called PyRx. Some enzymes can degrade these dangerous compounds; examples include carboxylesterase, IsPETase, and lignin peroxidase. Ester bonds may be hydrolyzed by carboxylesterase, while complex aromatic compounds can be degraded by lignin peroxidase. The strong catalytic characteristics of IsPETase suggest that enzymes like these might be modified to degrade BPA as well as its derivatives like BPF, BPZ, BPB, BPS, and BPAF.

According to this study, carboxylesterase was the best-suited enzyme over IsPETase and lignin peroxide for the degradation of BPA and its harmful derivatives because it has the highest binding affinity with them, which suggests it is the potential biodegrading enzyme for bisphenols. Extensive research, public education, and a combination of scientific innovation and public participation are necessary for this step toward bioremediation to be successful.

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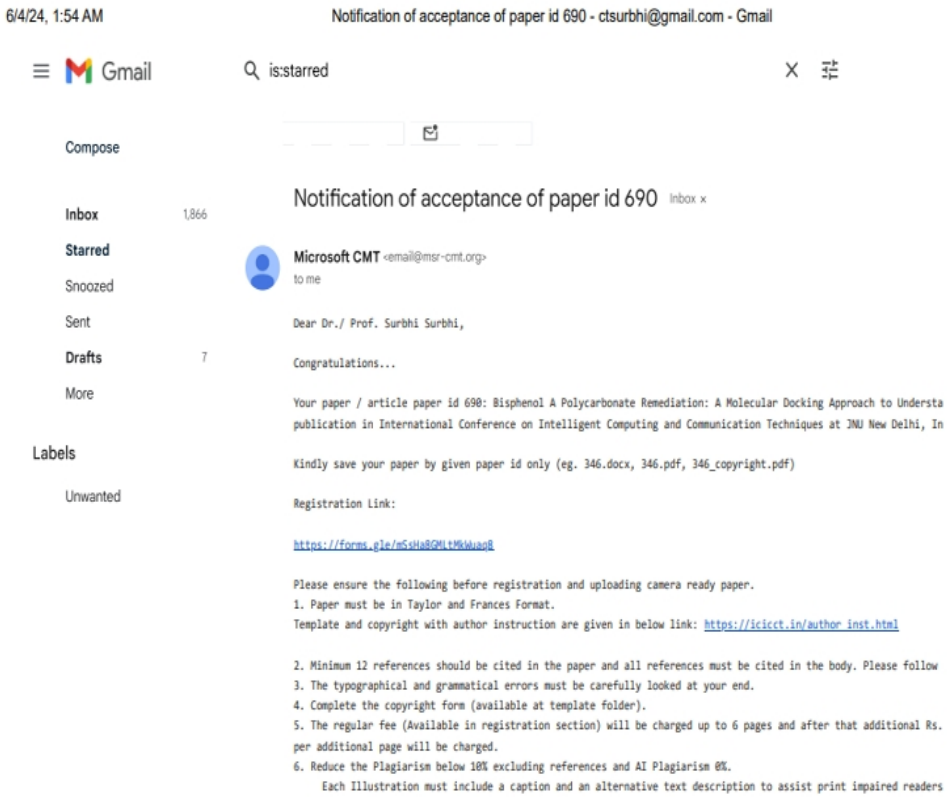

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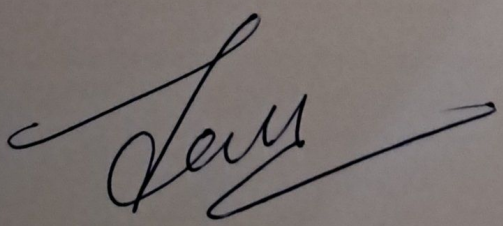

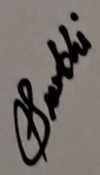

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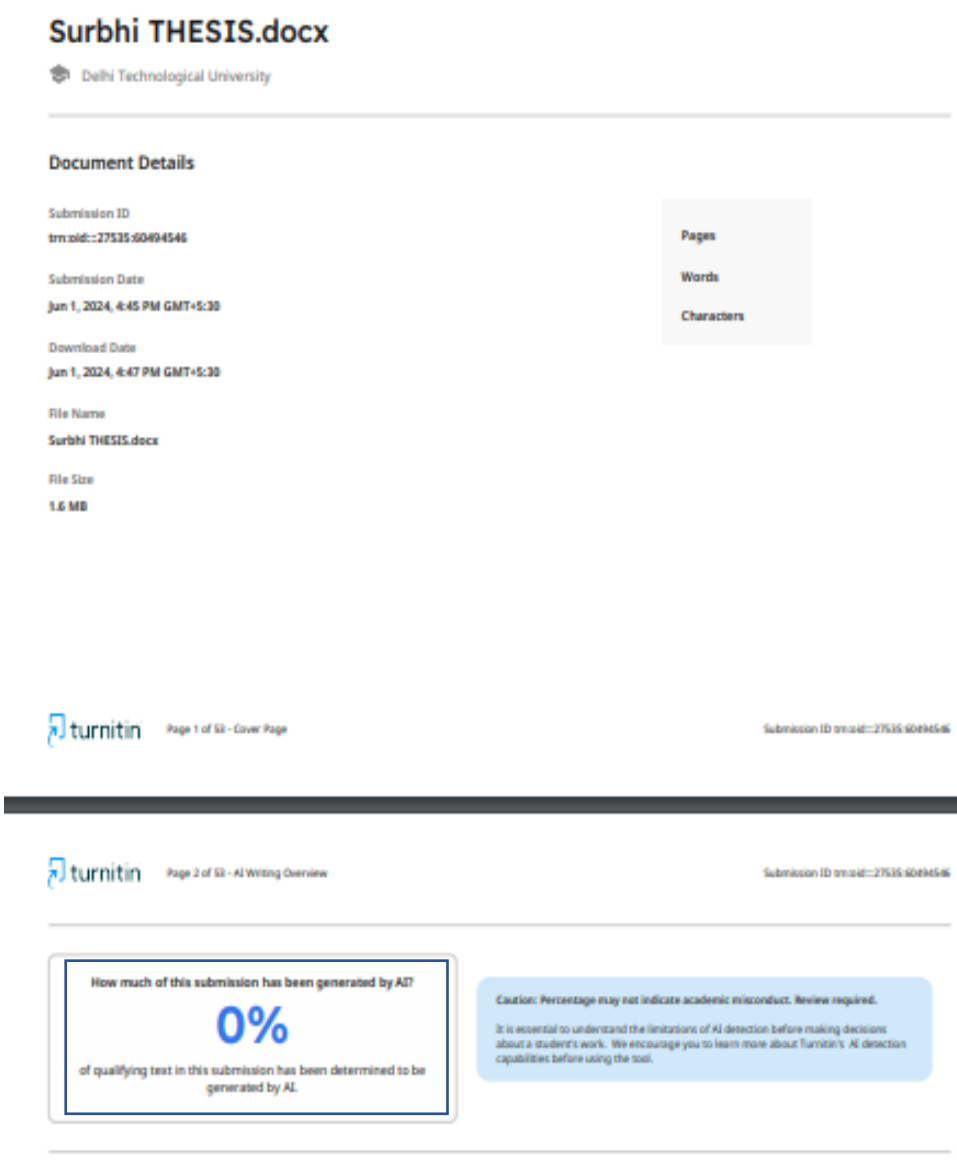

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