MOLECULAR DOCKING AND MOLECULAR DYNAMICS SIMULATION OF MUTANT CARBOXYLESTERASE IN ENHANCING MICROPLASTICS BINDING AFFINITY

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DEDICATION

This dissertation is dedicated to all my beloved family members, especially my parents. My mother “Rabia Lameh” who supported me in every challenging moment and undertook all the efforts to let me make my career, and my father “Shah Hakim Lameh” who allowed me to cross the oceans to achieve my goal.

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ABSTRACT

Literature survey has shown that microbial and biodegradation of polyethylene terephthalate (PET) by PETases are eco-friendly. However, microbes capable of such feat are few in conjunction with being time-consuming and the laborious bioprospecting efforts are undesirable. Therefore, mutation by *in silico* means of current isomer of PETase to introduce PET degradative capability could be a better approach to resolve this issue. Previously, BTA-hydrolase was reported capable of degrading PET. This study aimed to convert a carboxylesterase from *Archaeoglobus fulgidus* (AFEST) to BTA-hydrolase of *Thermobifida fusca* by *in silico* site-directed mutagenesis of six amino acids. This was followed by molecular docking analysis with PET and polypropylene (PP) to compare their interactions. The best-docked enzyme-substrate complex was further subjected to molecular dynamics (MD) simulation using GROMACS to gauge the binding quality of the above-said proteins PET. Results of molecular docking revealed the mutated residues, Glu34Asn, Gly177Lys, Asp179 Ala, Leu120Phe, Ala168 Met, and Leu82Thr on the AFEST yielded the lowest binding energy for the wild-type AFEST-PP complex (-7.5 kcal/mol), followed by mutant AFEST-PP complex (-7.1 kcal/mol) and lastly, the BTA-hydrolase-PP complex with (-5.9 kcal/mol). The mutant-AFEST also showed lower binding energy (- 6.7 kcal/mol) than BTA-hydrolase (-5.6 kcal/mol) when complexed with PET. The energy-minimized wild-type-, mutant-AFEST and BTA-hydrolase docked ligand complexes showed that the RMSD value for the BTA-hydrolase-PET complex was stable (0.12 – 0.18 nm) after 5 ns compared to the mutant AFEST-PET complex (~0.22 nm) after 18 ns. The RMSF for the mutant AFEST-PET complex fluctuated at 0.43 nm for the mutated residue Lys177, while the RMSF value of the BTA-hydrolase-PET complex was 0.32 nm for Leu248. Finally, the Rg value for BTA-hydrolase-PET complex (~1.68 nm) was the lowest compared to the mutant-AFEST-PET and wild-type AFEST-PET complexes which both showed the same range (~1.80 – 1.84 nm). The collective *in silico* data conveyed the six residue mutations on the wild-type AFEST imparted a minimal change in the ability of the mutant-AFEST to bind to PET. This suggests that amino acid mutations that are closer and more centrally-located in the tunnel leading up to the catalytic site might yield a mutant-AFEST with better PET-degrading ability.

ABSTRAK

Kajian literatur telah menunjukkan bahawa mikrob dan biodegradasi polietilena terefthalat (PET) oleh PETase lebih mesra alam. Namun, mikrob yang mampu melakukan perkara ini hanya "jauh dan terlalu sedikit di antara" serta usahanya memakan yang masa dan usaha bioprospek yang tidak diingini serta menyukarkan. Oleh itu, mutasi dengan cara siliko terhadap enzim berkait dengan PETase dimana kemampuan degradasi PET merupakan suatu pendekatan yang lebih baik bagi menyelesaikan masalah ini. Sebelum ini, hidrolase BTA dilaporkan mampu mendegradasi PET. Kajian ini bertujuan untuk menukar karboksilesterase dari *Archaeoglobus fulgidus* (AFEST) menjadi hidrolase BTA *Thermobifida fusca* dengan menggunakan mutagenesis terarah enam asid amino secara *in siliko*. Ini diikuti oleh analisa molekul terikat dengan PET dan polipropilena (PP) untuk membandingkan interaksi mereka. Kompleks enzim-ligand yang terikat terbaik kemudiannya akan menjalani simulasi dinamik molekul (MD) dalam GROMACS untuk mengukur kualiti pengikatan protein PET yang disebutkan di atas. Keputusan analisis ikatan molekul mendedahkan residu termutasi, Glu34Asn, Gly177Lys, Asp179 Ala, Leu120Phe, Ala168 Met, dan Leu82Thr pada AFEST menghasilkan tenaga pengikat terendah untuk kompleks AFEST-PP pada asal (-7,5 kcal / mol), diikuti oleh kompleks AFEST-PP mutan (-7.1 kcal / mol) dan terakhir, kompleks BTA hidrolase-PP (-5.9 kcal / mol). Mutan-AFEST juga menunjukkan tenaga pengikat yang lebih rendah (-6,7 kcal / mol) daripada hydrolase BTA (-5,6 kcal / mol) ketika dikomplekskan dengan PET. Kompleks ligan ikatan asal, mutan-AFEST dan hidrolase BTA yang ikatan tenaga rendah menunjukkan bahawa nilai RMSD untuk kompleks hidrolase BTA-PET stabil (0.12-0.18 nm) selepas 5 ns berbanding dengan kompleks AFEST-PET mutan (~ 0.22 nm) selepas 18 ns. RMSF untuk kompleks mutan AFEST-PET turun naik pada 0.43 nm untuk residu termutasi Lys177, sementara nilai RMSF kompleks hidrolase BTA-PET adalah 0.32 nm untuk Leu248. Akhirnya, nilai Rg untuk kompleks hidrolase BTA-PET (~ 1.68 nm) adalah yang paling rendah berbanding kompleks AFEST-PET mutan (~ 1.80 – 1.84 nm) atau AFEST asal (~ 1.80 – 1.84 nm). Data terkumpul *in siliko* menunjukkan mutasi enam residu pada AFEST asal memberikan perubahan minimum dalam kemampuan AFEST mutan untuk mengikat PET. Ini menunjukkan bahawa mutasi asid amino yang lebih dekat dan terletak di sepanjang terowong yang menuju ke lokasi pemangkin mungkin AFEST mutan yang lebih berkemampuan untuk mendegradasi PET dengan lebih baik.

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LIST OF ABBREVIATIONS

AFEST	-	*Archaeoglobus fulgidus esterase*
PDB	-	Protein Data Bank
HI	-	Hydropathy index
PET	-	polyethylene terephtalate
PP	-	polypropolene
RMSD	-	Root-Mean-Square Deviation
MD	-	Molecular dynamic
3D	-	3-Dimension
RMSF	-	Root-Mean Square Fluctuation
MSA	-	Multiple Sequence Alignment
DNA	-	Deoxyribonucleic acid
RNA	-	Ribonucleic acid
GRAVY	-	Grand average of hydropathicity
ExPASy	-	Expert Protein Analysis System
MultAlin	-	Multiple Alignment
pI	-	Protein Isoelectric point
K	-	Kelvin- unit of temperature in the international system of units (SI)
G+C	-	Guanine+Cytosine
nm	-	nanometer
bp	-	Base pair
ns	-	nanosecond
Rg	-	Radius of gyration
Arg	-	Arginine
Lys	-	Lysine
Glu	-	Glutamic acid
Leu	-	Leucine
Ala	-	Alanine
Gly	-	Glycine
Asp	-	Aspartic acid

Thr	-	Threonine
Met	-	Methionine
Phe	-	Phenylalanine
Asn	-	Asparagine

LIST OF SYMBOLS

ψ	-	psi
φ	-	phi
~	-	Equivalent to
β	-	Beta
α	-	Alpha
μ	-	Micron
Å	-	Angstrom
Na^+	-	Sodium ion
%	-	Percentage

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The high demand for plastics has seen its raising in daily life, such as in medical products, household goods, toys, personal care products, manufacture and so on. While plastic products make human life easier and bring comfort to daily life, they pollute the environment. The issue is exacerbated by poor waste management and the lack of a proper recycling system of the products (Hu et al., 2019). Exposure of plastic products to environmental chemicals, physical and biological conditions shreds the plastics into small pieces of nano plastics and microplastics with the diameter of (<100nm) and (<5mm) respectively (Ren et al., 2020). Moreover, it takes hundreds to thousands of years for microplastics to decompose into their monomers (Hu et al., 2019). Microplastic can be found in both terrestrial (Horton et al., 2017) and marine (Zhang & Chen, 2020) environment. Almost every ocean of the world is contaminated with at least 10% of all plastic production, while the microplastic pollution is less studied in freshwater (Free et al., 2014). Based on the source, microplastics are classified into primary and secondary microplastics. Primary microplastics are industrially synthesized in the form of pellets, microbeads, and synthetic fibers. In comparison, secondary microplastics are generated due to the large plastic particle's breakdown into smaller fragments, which depends on environmental situation and polymer types (Blair, 2017).

Among hundreds of other synthetic polymers, polyethylene terephthalate (PET) is the most popular polyester in the market. PET is polymerized from terephthalic acid (TPA) and ethylene glycol (EG), both of which are derivatives of crude oil. Persistence, stability, transparency, and low production cost are the main properties of PET that make it a highly utilized polyester worldwide (Liu et al., 2019). In retrospect, the same attributes can be problematic for PET product's

degradation (Taniguchi et al., 2019). While many degrading mechanisms have been suggested to decompose PET, but they are pricy, time-consuming, produce other wastes into the environment. Conversely, the biodegradation of plastics by microbes and their enzymes are more reliable and friendlier methods to rid plastics' from the environment (Ma et al., 2018). Biodegradation is a biological approach in which microbes release enzymes on the plastic to break down its polymer chain into small oligomers, dimers, or monomers and utilize them as their sole carbon and energy source (Samak et al., 2020). Some microbial enzymes from family members of cutinase, lipase, and esterase can hydrolyze PET to some extent (Liu et al., 2019). For instance, the *Thermobifida fusca* PET-hydrolase is a cutinase that degrades the PET at a higher temperature (Kumar et al., 2017).

The biodegradation of plastic is far from satisfactory, and the process is time-consuming as extensive bioprospecting for effective microorganisms is required to do the job. A better way is to use existing microbial enzymes and tailor their enzymes to be partial in degrading plastics. For this purpose, the bioinformatics tools are the best approach for predicting biological mechanisms computationally while saving time and costs (Wang et al., 2019). Having said that, a good start to "design" a novel enzyme capable of degrading plastics is to mutate an enzyme from the member of the α/β-hydrolase family, a family that PETase (PET hydrolase) also belongs. Our target enzyme is the carboxylesterase from *Archaeoglobus fulgidus* (AFEST) which exhibits high thermostability (Rusnak et al., 2005). Mutating the carboxylesterase to endow it with the degradative characteristics of a PETase is possible since the sequence and the three-dimensional (3D) structure of the enzyme is available in the literature (De Simone et al., 2001). Carboxylesterase is serine hydrolases which structural and functional characteristics closely matches the α/ß hydrolase fold enzyme (Rusnak et al., 2005). The catalytic mechanism of AFEST comprised a catalytic triad which consists of Ser160, His285, and Asp255. The AFEST structure has been successfully crystallized in complex with a sulphonyl derivative and deposited to the Protein Data Bank (accession code 1JJI) (De Simone et al., 2001). The most interesting feature of AFEST is its unusual spectrum of pH activity. The enzyme exhibited the optimal activity at 70 ◦C in pH 10 –11 and significant activity at pH 12. Therefore, this enzyme might be of particular interest

for approaches involving directed evolution for the generation of valuable catalysts for industrial applications (Rusnak et al., 2005). *In silico* site-directed mutagenesis of AFEST can be performed to enhance and assess the enzyme's ability to degrade plastic compared to a well-known PET-hydrolase, the BTA-hydrolase (Hartanti et al., 2016).

1.2 Problem statement

The non-renewable nature of fossil fuel-derived plastics and their last long-lasting accumulation can seriously pollute the environment (Satti & Shah, 2020). It is an ongoing hazardous predicament that threatens all living organisms' livelihood, warrants developing a safer remediation technique. A practical and eco-friendly means to remove plastics from the environment is biodegradation by PETase-producing microorganisms with a penchant for plastics as the growth substrate. However, the laborious and time-consuming bioprospecting efforts are undesirable in conjunction with being costly. Mutation by *in silico* means of a current isomer of the PETase to introduce PET degradative capability could be a better approach to resolve this issue.

Herein, a rational mutation on the wild-type AFEST binding sites of *A. fulgidus* for a higher plastic degradability using a known PET-degrading enzyme as the template, is proposed. This approach is feasible compared to a blind mutation on any sort of enzyme. The course is likely viable as the two enzymes originate from the same α/β hydrolase fold family and the full 3D structure of AFEST is available in the literature. In this work, the mutation is based on an *in silico* data of the PETase from *Thermobifida fusca* in complexed with PET. The AFEST'S multiple amino acid mutations attempt to emulate the PETase amino acid interactions with the PET substrate. It is hypothesized that the target multiple mutation sites could boost the mutant-AFEST to degrade PET.

1.3 Objectives

The following objectives were set to achieve the goal of the work:

1. To identify the possible substrate-binding residues of the AFEST to be mutated by sequence alignment with the PETase from the BTA-hydrolase.
2. To carry out molecular docking assessments of two different ligands polyethylene terephthalate (PET) and polypropylene (PP), with enzymes, BTA-hydrolase, wild-type- and the mutant-AFEST.
3. To compare the molecular dynamic (MD) simulations of the best docked mutant-AFEST-ligand structure against the BTA-hydrolase-ligand complex.

1.4 Scopes of study

The research was conducted in three stages to achieve the aforesaid objectives. For the first stage of work, the FASTA format of amino acids sequence of carboxylesterase (AFEST) and BTA-hydrolase (PET-hydrolase) were retrieved from Protein Data Bank with PDB ID (1JJI) and (5zoa) respectively. The multiple sequence alignment of AFEST and BTA-hydrolase was conducted via Multalin software to find binding sits of AFEST on the conserved regions. The AFEST sequence was then visualized on PyMol program to identify the residues for mutations. Furthermore, the physicochemical properties of the three above proteins were characterized through ExPASy server for the later comparison with the BTA-hydrolase and mutant-AFEST. After, the structural validation of mutant-AFEST through software packages of PROCHECK, ERRAT, and VERIFY-3D, the PYMOL software was used to view the protein structure.

This study's second phase involved the molecular docking of ligands, polyethylene terephthalate (PET), and polypropylene (PP) with the BTA-hydrolase, wild-type- and mutant-AFEST, using the software AutoDock 4.2.6. Before initiating the process, each ligand's SDF file was extracted from the PubChem database. Afterward, each ligand and protein was prepared with a default setting. Then, the

results were compared to decide the residues to be mutated in the wild-type AFEST substrate binding site. At the end of docking, the PDBQT file format was generated, and the result was analyzed using Autodock vina. The molecular interaction between the mutant-AFEST and the two ligands, such as binding energy, hydrogen bonds, hydrophobic interactions, were assessed to identify the best enzyme-ligand for the subsequent MD simulation study.

At the last phase, docked protein-ligand complexes and the interactions of wild-type AFEST, mutant-AFEST, and BTA-hydrolase models with substrates were analyzed by molecular dynamics (MD) simulation using a parallel version of GROMACS 5.1.2 by employing the Gromos96 53a7 force- field. Before employing MD simulation, the models were further refined to ensure that the gained native states at the global minimum (Feig, 2017). The protein models were checked to be free from any errors by comparing them to their native structure. Consequently, the MD simulation result was calculated for RMSD, RMSF, and Rg score to compare with the BTA-hydrolase-ligand results.

1.5 Significance of the study

The use of rational-design of existing enzymes bioinformatic tools is a rapid resolution to solve the slow degradation of plastics by microbes in the environment. By rationally mutating the AFEST enzyme, knowledge on the germane residues that impart PET-degradative capability may prove applicable to other enzymes in the hydrolase fold family for plastic degradation.

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