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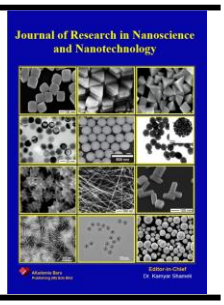

In Silico Molecular Docking Simulation of *Chromolaena Odorata* Phytoconstituents Against Matrix Metalloproteinase Proteins – 9 (MMP-9)

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ABSTRACT

The purpose of this study is to investigate the potential ligands of *Chromolaena Odorata* plants which contributes to the wound healing process. The ligands involved were phytol, ß-Caryophyllene, and 3,3-Dimethyl-1,2,4-cyclopentanetrione. This work addressed molecular docking simulations between the chosen ligands and Matrix Metalloproteinases (MMP) as the primary viral protein/receptor. The binding modes of the protein-ligand interactions were analysed. 9 poses of docking modes were obtained from the simulation. The ligand-receptor with the lowest interaction energy is the potential candidate for wound healing treatment. In summary, 3,3-Dimethyl-1,2,4-cyclopentanetrione has been chosen to be the best docked complexes as it shows the lowest energy among the other ligands with value of -7.1 kcal/mol.

Keywords:
Chromolaena Odorata; wound healing;Matrix Metalloproteinases; molecular docking

1. Introduction

The anatomical of a human being is considered as a complex structure where it has many different parts with various interactions in terms of its behavior. The main organ of a human body is the skin, which plays a crucial function in fluid balance, thermoregulation, protection against infection and negative impact such as UV radiation. This associated with the continuous destructions and renewal of body cells which can be known as a part of the wound healing process. This is an important process for every human for their constant growth and development through the biochemical process that occur inside the body. Based on a review by Saeed and friends, wound is defined as disruption or an abrasion which mainly occurs on a healthy skin or towards the skin epithelium [1]. Wound healing

is a complex process that involve the interaction of several cell types which inhibits multiple tissue compartments and considered to be the same as in tissue types.

A proteolytic enzyme known as one of the important components for skin repair which is Matrix Metalloproteinase (MMP), functioning as an influence towards the wound-healing responses such as re-epithelialization. The ability of MMP-9 is to regulate the extracellular matrix (ECM) by regulating and releasing cytokines, growth factors, and other biologically active components found in the ECM. In other words, MMP works by inhibit natural inhibitors not only in Tissue Inhibitor for Metalloproteinases (TIMP) but also several non-MMP serine proteases for delaying wound healing [2]. It was discovered that the interaction between cancer cells and ECM components serves an important role in the development of cancer [3].

Demonstration of the usage of medicinal plants or herbs has been shown from almost all ancient civilizations. Due to the limited access to the health facilities and economically deprived, indigenous people benefit the plants traditionally by extracting its natural oil for treating wounds. However, problem arise when they often mix the impurified plants which lead to a serious health problem such as infections, especially when it comes to wound dressing. In addition, they have insufficient information on biological activities of the plants in which it contains various ingredients which sometimes can cause allergic reactions. Improper wound treatment may pose to mobility limitation in which terrible itching was likely to occur during the night that was cause by the pain.

Chromolaena Odorata was known as a perennial scandent from the family of *Asteraceae* [4]. During the Second World War, *C. Odorata*, a native flowering semi-woody shrub in North and Central America has been brought into India and has been widely spread along the roadsides of the local towns and rapidly growth in some parts of the Asia, Australia and Africa. It can travel for a long distance by the wind and stick to the fur and clothing [5]. Other names for C. Odorata are butterfly weed, eupatorium, Siam weed, Christmas bush and turpentine weed [6]. The various study of Siam Weed by extraction (SWE) has discovered its potential of stimulating the haemostasis and wound healing process. According to a study by Pandith and friends, the bioactive compound of *C. Odorata* stimulate a strong response to the cell proliferation when employed with fibroblast cell lines [7].

The aim of this project is to investigate the potential therapeutic components for wound healing process by investigating the binding mechanism of ligand namely: Phytol, ß-Caryophyllene, and 3,3-Dimethyl-1,2,4-cyclopentanetrione with Matrix Metalloproteinase-9 (MMP-9) as the main viral protein for wound healing, by using a molecular docking simulation approach.

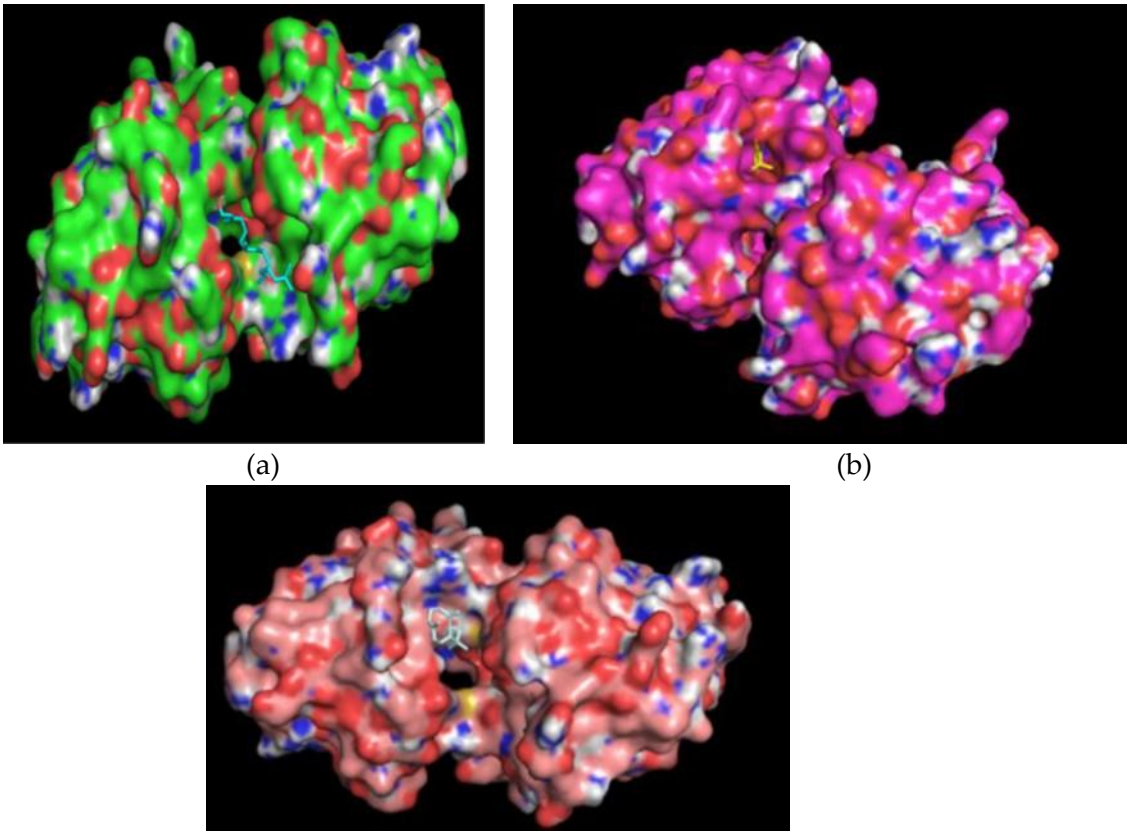
2. Materials and Methods

The protein structures used for identification and *in silico* screening of the structural site was Matrix Metalloproteinases Protein-9 (MMP-9) (RCSB Protein Data Bank codes: 4H1Q) whereas the ligands were Phytol, ß-Caryophyllene, and 3,3-Dimethyl-1,2,4-cyclopentanetrione (PubChem ID: 5280435, 5281515 and 550735, respectively). AutoDock Vina and Pymol Visualization software were used to prepare the protein receptor. In this step, water molecules were removed, and Kollman charges were added. The active site size and coordination for Grid box production may be easily found using the inbound ligand. The ligands were prepared using Pymol software. The generated box file was then used as input for the GRID programme, which calculates information about the steric and electrostatic environment of MMP-9 protein. DOCK was used to screen the entire database of small molecules within the protein grid, with the selected spheres representing as theoretical binding sites.

The small molecule output was then ranked based on predicted energy scores composed of electrostatic interactions and van der Waals' forces.

3. Results and Discussion

A preferred orientation of small molecule compound (SMCs) in the active site of a target protein or receptor was predicted by molecular docking (MD). Each orientation of the ligand that was docked onto the active site gave a certain score that generally known as 'docking score' where a stronger binding was indicated by the more negative value. This will predict the binding mode and best bio affinity of SMCs with their receptor [8]. The docking result shows that the lowest binding energy for ligand phytol, ß-Caryophyllene and 3,3-Dimethyl-1,2,4-cyclopentanetrione was -5.7 kcal/mol, -5.9 kcal/mol and -7.1 kcal/mol, respectively. Table 1 shows the 9 modes of docking for each of the ligands where mode 1 was the best docked complexes. Figure 1 shows the best docked complex for phytol, ß-Caryophyllene and 3,3-Dimethyl-1,2,4-cyclopentanetrione.



(a) (b)

(c)

Figure 1. Best docked conformation for (a) Phytol (b) ß-Caryophyllene and (c) 3,3-Dimethyl-1,2,4-cyclopentanetrione

According to a study by Durhan and friends, phytol acts as their molecular docking studies for antibacterial activity which was found inside the *A.lividus* [9]. In their research paper, it was revealed that the phytol was capable to interact with protein aquaporin-z of bacteria with binding energy of -5.21 kcal/mol. Another study by Yasmeen et. al displayed that phytol showed a binding affinity of -7.06 kcal/mol with second highest drug score and could be a potent inhibitory drug for MMP-1 along with potentially safe to be developed into active pharmaceutical drug against MMP-1 [10].

Furthermore, phytol interacts with many proteins and provide protection against various microbial infections. As a comparison, the value of binding energy obtained was reasonable.

Table 1. Binding mode and binding energy (kcal/mol) of
Auto dock Vina for phytol, ß-Caryophyllene and 3,3-Dimethyl-1,2,4-cyclopentanetrione

Mode	Phytol (kcal/mol)	ß-Caryophyllene (kcal/mol)	3,3-Dimethyl-1,2,4-cyclopentanetrione (kcal/mol)
1	-5.7	-5.9	-7.1
2	-5.3	-5.8	-7.0
3	-5.2	-5.6	-7.0
4	-5.0	-5.5	-6.9
5	-4.9	-5.5	-6.7
6	-4.9	-5.2	-6.5
7	-4.8	-5.1	-6.4
8	-4.8	-5.1	-6.2
9	-4.6	-5.1	-6.2

Next, ß-Caryophyllene showed a binding energy of -5.9 kcal/mol as shown in Table 4.1 with mode 1 as best docked complexes. There was a formation of hydrogen bond between the ligand and amino acid of the protein which was Arg249(A) with a bond length of 3.15 Å. This interaction with MMP-9 main protease will further increase the potential of efficient accommodation inside the pocket of the protein, thus, will provide a promising basis in inhibiting viral protease. Mini research by Narkhede and colleagues showed that ß-Caryophyllene worked as a potential candidate for exerting the anti-viral activity against SARS-CoV-2 infection with binding affinity of -7.2 kcal/mol [11]. However, it is still not chosen as the favourable drug-like properties in treating the COVID-19 main protease inhibitor. Furthermore, a recent study by Lisnasari and friends showed that ß-Caryophyllene inside the active compound of *Lavandula angustifolia* (lavender oil) had a binding energy of -8.02 kcal/mol when docked with N-methyl-D-aspartate (NMDA) receptor [12]. It could be developed as a treatment for depression. However, no hydrogen bond was formed.

For 3,3-Dimethyl-1,2,4-cyclopentanetrione, the binding energy obtained was -7.1 kcal/mol which was the lowest among the other ligands. It was observed that the hydrophobic interactions of the ligand and the active site of the protein was the factor of the increase of the binding affinity. By incorporating the hydrophobic interaction at the site of the hydrogen bond, the binding affinity and drug efficacy can be optimized. The appearance of water molecules in hydrophobic regions makes the region quite flexible, thus, can be a leading method for drug designing. However, there was less information regarding this ligand as there is limited research ongoing with this compound [13].

4. Conclusions

As a conclusion to this study, 3,3-Dimethyl-1,2,4-cyclopentanetrione is chosen as the best suitable compound in wound healing therapy based on the energy value compared among the docked complexes. Regardless of the results gained in this thesis, some of the ligands are required to be tested empirically in vitro. Those who demonstrate wound healing therapy in experimental investigations are likely to be strong candidates for subsequent clinical trials. Based on the results, phytol, ß-Caryophyllene, and 3,3-Dimethyl-1,2,4-cyclopentanetrione may be beneficial drugs for wound healing treatment, but further study is required to validate this finding.

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Chemical Energy Conversions and Applications (ChECA), Department of Chemical and Environmental Engineering, Malaysia-Japan International Institute of Technology, Universiti Teknologi Malaysia.

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