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In silico Analysis of Phytochemicals from *Mucuna pruriens (L.) DC* against *Mycobacterium tuberculosis* Causing Tuberculosis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors DD, SD and DB conceived and planned the study, while author DD performed the computational framework and analyzed the statistical data. Author SD carried out the implementation. Author DD wrote the first draft of the manuscript. Authors DD and SD managed the analyses of the study. Author SD took lead in the literature searches. Author MP read and approved the final manuscript and provided assistance throughout the study. While author DB supervised and guided the whole study. All authors read and approved the final manuscript.

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ABSTRACT

Tuberculosis is somewhat a disease of poverty that mainly targets the low-income populations of developing countries. At the same time, the disease act as a barrier for economic growth to affected people and families caring for them which in turn results into increased poverty in the community. Thesepopulation below the poverty line lacks access due to higher retail price and unavailability of the medicines. To overcome these obstacles researchers are nowadays opting to derive medicines from plant extract containing phytochemicals rather than synthesizing new chemicals which proved to be more expensive and unsafe compared to their organic counterpart. Phytochemicals are non-nutritive compounds obtained from plants. It has been reported that *Mucuna pruriens* plant extract is expected to cure Tuberculosis, which is caused by

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Mycobacterium tuberculosis. The said microbe contains 3-hydroxyacyl-CoA dehydrogenase enzyme which is reported to be very crucial for the survival of the organism. The molecular docking of the phytochemicals with the microbial enzyme was studied using Biovia Discovery Studio. The machine learning protocols analyze and predict the volume of the molecular interactions occurring between the plant phytochemical and the bacterial enzyme occurring at the active site of the enzyme. The strength of the interaction was evaluated based on -CDocker energy and -CDocker interaction energy. Subsequently the study displays high positive values for both the parameters indicating that out of different phytochemicals present in *Mucuna pruriens,* L-Dopa can effectively deactivate the enzymatic metabolic activity by interrupting β-oxidation of fatty acid in the microbial cell which causes termination of the life cycle of *Mycobacterium tuberculosis*.

Keywords: Phytochemical; Biovia; discovery studio; Mucuna pruriens; Mycobacterium tuberculosis.

1. INTRODUCTION

Tuberculosis is a disease of poverty that are more prevalent in low-income populations of developing countries. Tuberculosis (TB) is closely related to lifestyles of poverty, overcrowded conditions, alcoholism, stress, drug addiction and malnutrition. This disease spreads quickly among people who are undernourished [1]. While, the disease act as a great hinderance for economic growth to affected people and families caring for them which in turn results into increased poverty in the community. According to WHO, medical strategies report, approximately 30% of the global population does not have regular access to medicines. In the poorest parts of Africa and Asia, this percent goes up to 50% [2]. The population below the poverty line lacks access due to higher retail price and unavailability of the medicines due to high expenses of synthesizing artificial chemical drugs [3]. Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been derived from natural source [4]. The medicinal value of the plants lies in some chemical substances that produce a definite physiological action on the human body, these substances are called phytochemicals, which can be used for therapeutic purpose. Plants based medicinal constituents can be derived from any part of plant like bark, leaves, flowers, roots, fruits, and seeds [5]. Various medicinal plants and their phytoextracts have shown numerous medicinal properties like anti-oxidant, anti-inflammatory, anti-cancer, anti-microbial, anti-diabetes action etc [6]. Among different sources of natural products, plants have been a source of novel chemical substance, which serves as starting materials for a number of old and new pharmaceutical products while proving to be safe and cost effective.

Medicinal plants are the foundation of many drugs prescribed today in modern medicinal system. About 25% of modern pharmaceutical drugs have botanical origins. Research needs in the field of medicinal plants are huge, but are balanced by the potential health benefits and the enormous size of the market. Research into the quality, safety, biological activity, and clinical efficacy of the numerous plants in common usage is required. Newly emerging scientific techniques and approaches have been used in the growing area of medicinal plant research, for the investigation of constituents and determination of biological activity of medicinal plants. Evidence for the beneficial effects of selected plants is generally based on experiments demonstrating a biological activity in a relevant in vitro bioassay or experiments using animal models [7]. Plants that demonstrated anticancer, antioxidant, anti-inflammatory, immunostimulatory, and antimicrobial properties have received research attention.

Kaunch Beej belongs to family fabaceae. Kaunch Beej leaves extract is used to cure disease like tuberculosis (reference). The plant is an annual, climbing shrub with long vines that can reach over 15 meters in length. When the plant is young, it is almost completely covered with fuzzy hairs, shed with age. *Mucunapruriens* bears white, lavender or purple flowers [8]. Globally this species is widely distributed in the tropical regions of Asia and Pan Tropics. It is found in most part of India. Kaunch Beej is known to contain phytochemicals like Gallic Acid, Ascporbic Acid, L-dopa, Beta-carboline, Bufotenine, Linoleic Acid, S-nicotine, Palmitic Acid, Serotonine, Oleic Acid, Steraric Acidetc [9,10]. There is high possibility that these phytochemicals play a major role in curing tuberculosis. However, there is no report identifying the specific phytochemical responsible to cure tuberculosis.

A group of bacteria belonging to genus Mycobacterium generally cause tuberculosis [11]. *Mycobacterium tuberculosis* are large nonmotile rod shaped which can appear either Gram-negative or Gram-positive bacteria [12]. Tuberculosis (TB) is a disease that primarily affects the lungs, although it can attack other parts of the body. The classic symptoms of active TB are a chronic cough with blood-containing mucus, fever, night sweats, and weight loss [11]. It spreads much like a cold or the flu through the expelled airborne droplets from a person with infectious TB. When inhaled, the bacterium can settle in the lungs, where it begins to grow. If not treated, it can spread to areas such as the kidneys, spine, and brain. It can be life-threatening [11,13]. However, it is possible to control the disease by inhibiting the metabolic pathway of the microbe. Mycobacterial lipid metabolism is very crucial for the said bacterium for its survival. The enzyme 3-hydroxyacyl-CoA dehydrogenaseplays a crucial role in the β-oxidation of fatty acid.

This study focuses on the identification of the phytochemical of *Mucuna pruriens* responsible to cure Tuberculosis caused by *Mycobacterium tuberculosis* by inhibiting the lipid metabolism pathway.

2. MATERIALS AND METHODS

2.1 Software Used

Discovery studio module of Biovia software (Dassault Systemes of France) was used for analysis. The software utilizes machine learning techniques to predict the level of molecular interaction.

2.2 Methodology

2.2.1 List of phytochemicals

Phytochemicals are produced by plants as secondary metabolites to protect them from predators. The potential threats to plants include bacteria, viruses, fungi etc. When these plants or their parts are consumed by humans these phytochemicals fight off threats to health. Some phytochemicals have been used as poisons and others as traditional medicine. Published works showed that *Mucuna pruriens* contains Gallic Acid, Ascporbic Acid, L-dopa, Beta-carboline, Bufotenine, Linoleic Acid, S-nicotine, Palmitic Acid, Serotonine, Oleic Acid, Steraric Acid etc. It has already been established that *Mucuna pruriens* plant belonging to Fabaceae family has potential to help controlling Tuberculosis. This work is focused on identification of the particular phytochemical responsible for inhibiting and controlling of Tuberculosis.

2.2.2 Enzyme found in *Mycobacterium tuberculosis*

It has been reported that Tuberculosis can cause as a result of *Mycobacterium tuberculosis* infestation. Various metabolic cycles have been seen in the bacterial life cycle for its survival. These metabolic cycles are regulated by different enzymes. Brenda enzyme database was used to identify and list different enzymes found in *Mycobacterium tuberculosis* bacteria. It has been found that 3-hydroxyacyl-CoA dehydrogenase enzyme (protein database code 3PPI) is involved in lipid metabolism (KEGG), (BRENDA) and very crucial for β-oxidation of fatty acids presents in microbial cell wall in order to survive.

2.2.3 Molecular docking

Molecular docking method has been used to identify the phytochemical from the plant extract, that act as a ligand and form a strong covalent bond with the bacterial protein to successfully inhibit the microbe. The Discovery studio module of Biovia software was used for identifying molecular interaction and perform molecular docking. In this process first the sdf files for the phytochemicals found in the *Mucuna pruriens* plant were downloaded from the website [14]. The protein database code of the enzyme was identified from the website [15]. The active site of the enzyme was identified via “receptor cavity” protocol found under "receptor-ligand interaction" menu. Molecular docking was done using the CDocker protocol of Biovia software under “receptor-ligand interaction”. The enzyme molecule was treated as the receptor molecule and the phytochemical was treated as the ligand. The “-CDOCKER_ENERGY” and “-CDOCKER_INTERACTION_ENERGY” were used as indicator for the quality of molecular docking. The high positive value of those indicators presented a good interaction between the ligand and the receptor. Thus, the interactions with high values might indicate the major phytochemical responsible for curing the disease.

3. RESULTS AND DISCUSSION

Fig. 1 shows the active site of the 3-hydroxyacyl-CoA dehydrogenase enzyme. It appears as light green color. CDOCK is a molecular dynamics (MD) simulated-annealing-based algorithm. It is a grid-based molecular docking method and optimized for accuracy. The ligand conformations were obtained by Molecular Dynamic methods.

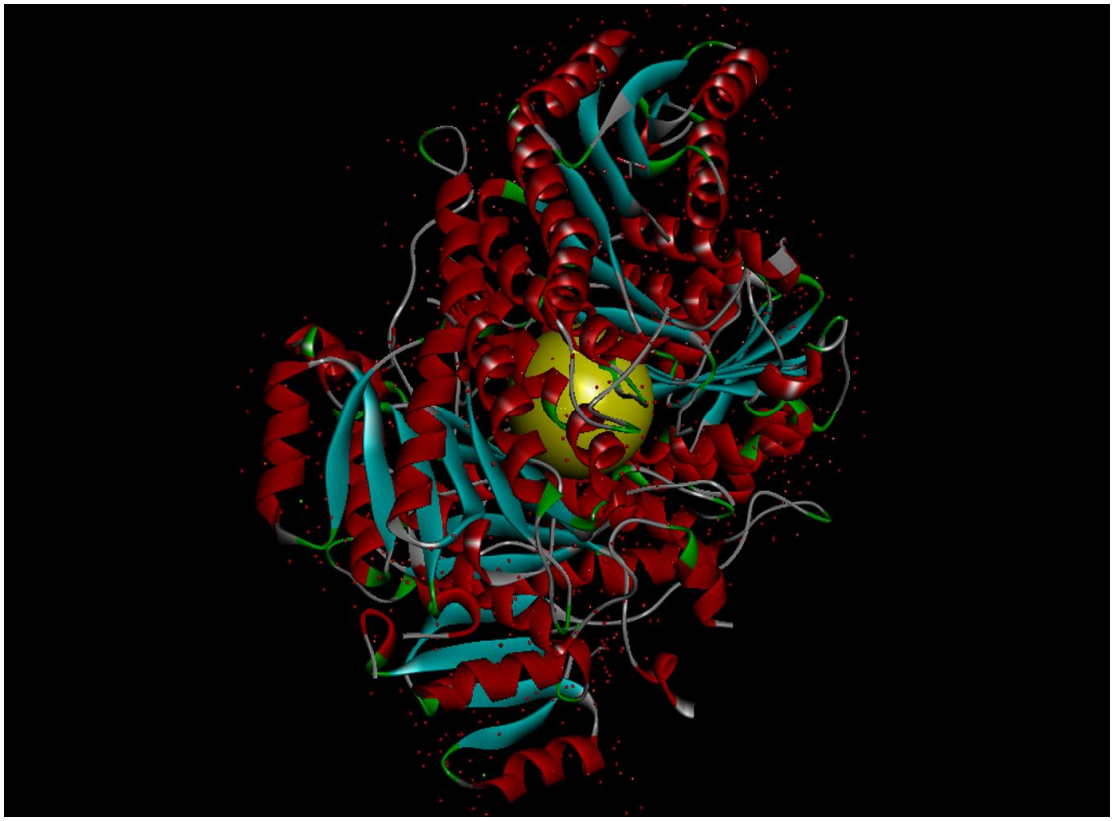

Fig. 1. Active site of 3-hydroxyacyl-CoA dehydrogenase enzyme

Table 1. Results of CDocking of phytochemicals with 3-hydroxyacyl-CoA dehydrogenase (receptor)

SL no	Ligand	- C DOCKER energy	- C DOCKER interaction energy	Difference between - C DOCKER interaction energy and - C DOCKER energy
1	L-dopa	37.1352	36.4247	-0.7105
2	Gallic Acid	32.0445	28.7722	-3.363
3	Palmitic Acid	28.8911	40.9454	12.0543
4	Steraric Acid	28.4452	37.6954	9.2502
5	Bufotenine	25.0849	31.7944	6.7095
6	Serotonine	24.9626	29.7026	4.74
7	Ascporbic Acid	11.2438	27.6216	16.3778
8	Oleic Acid	8.63143	32.3249	23.69347
9	Beta-carboline	6.91207	21.0322	14.12013
10	Linoleic Acid	-1.00773	41.8964	42.90413

-CDOCKER energy was calculated based on the internal ligand strain energy and receptor-ligand interaction energy. -CDOCKER interaction signifies the energy of the nonbonded interaction that exists between the protein and the ligand. The criteria for best interaction was chosen based on a) high positive value of -CDOCKER energy and b) small difference between -CDOCKER energy and -CDOCKER interaction energy [16].

Table 1 shows that (L-Dopa)-(3-hydroxyacyl-CoA dehydrogenase) interaction has the highest positive value of -CDOCKER energy (37.1352) and minimum value of the difference (-0.7105) between - C DOCKER interaction energy and - C DOCKER energy followed by Gallic Acid, Palmitic Acid, Steraric Acid, Bufotenine, Serotonine, Oleic Acid, Ascporbic Acid. Thus, the results indicated that L-Dopa can effectively deactivate the 3-hydroxyacyl-CoA dehydrogenase enzyme thereby interrupting the lipid metabolically cycle of *Mycobacterium tuberculosis*. Higher positive values for L-Dopa indicated that it was the most active ingredient against *Mycobacterium tuberculosis*. On the other hand, Linoleic Acid can deactivate the enzyme to a small extent (negative -CDocker energy but positive -CDocker interaction energy). Thus, the key phytochemicals preventing Tuberculosis caused by *Mycobacterium tuberculosis* is L-Dopa.

4. CONCLUSION

It was previously identified that *Mucuna pruriens* plant has medicinal action against Tuberculosis. Tuberculosis is caused by *Mycobacterium tuberculosis*. This study provides the theoretical basis of this observation. Using Discovery studio module of Biovia software, molecular docking operation displays the regularity of interactions of the plant phytochemicals (Gallic Acid, Ascporbic Acid, L-dopa, Beta-carboline, Bufotenine, Linoleic Acid, Palmitic Acid, Serotonine, Oleic Acid, Steraric Acid), with the vital enzyme 3-hydroxyacyl-CoA dehydrogenase of the microbe. It was concluded that L-dopa can form strong bond with the enzyme according to the high interaction values followed by Gallic Acid, Palmitic Acid, Steraric Acid, Bufotenine, Serotonine, Oleic Acid, Ascporbic Acid. A positive interaction successfully inhibits the lipid metabolic cycle of the microbe. Nevertheless, Linoleic Acid can not be much effective in deactivating the enzyme of the microbe due to negative outcomes. Thus, this study can explain that the presence of L-Dopa provides the therapeutic values to *Mucuna pruriens* against Tuberculosis caused by *Mycobacterium tuberculosis*.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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