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Cardamom Derived Phytochemicals against *Mycobacterium tuberculosis* Causing Tuberculosis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Tuberculosis is a disease caused by severe infections by *Mycobacterium tuberculosis,* a pathogenic bacteria. These bacteria cause infections in humans and thus lead to an unhealthy life. Phytochemicals from *cardamom* plant extract are traditionally used to cure Tuberculosis. Molecular docking method applied using "Biovia Discovery Studio". "High positive values of -CDOCKER energy and -CDOCKER interaction energy" suggested that acetic acid can effectively deactivate histidinol dehydrogenase (H37Rv) thereby interrupting the life cycle of the organism.

Keywords: Phytochemical; Cardamom; Mycobacterium tuberculosis.

1. INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* bacteria. Tuberculos is generally affects the lungs, but can also spread to other parts of the body. Active infection occurs more often in smokers and people with HIV/AIDS. In 2018, there were more than 10

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million cases of active TB which resulted in 1.5 million deaths. Nature is a major source of medicines [1] to fight against many diseases like Tuberculosis. The medicinal value of the plants is due to the phytochemicals present in it. Phytochemicals can be derived from different parts of plants. Different medicinal plants and their phytoextracts have shown anti-microbial action [2]. These medicinal plants play a key role in human health care. Many people rely on the use of traditional medicine [3]. Cardamom extract is traditionally used to cure diseases like Tuberculosis.

Cardamom emerges from the coastal area of India. It is now grown in Cambodia, Guatemala, Tanzania, El Salvador, Vietnam, Laos, and Sri Lanka. India is the main trader of dried Cardamom. Cardamom is known as the "Queen of the Species". Cardamom belongs to family Zingiberaceae. Cardamom contains"4-terpineol, acetic acid, cinnamaldehyde, eucalyptol, 3,7-dimethyl, Santolina alcohol". These phytochemicals might act against Tuberculosis. However, there is no such study available.

This objective of the study is to identify the phytochemical of Cardamom capable of curing Tuberculosis.

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 *Cardamom* contains 4terpineol, acetic acid, cinnamaldehyde, eucalyptol,3,7-dimethyl, Santolina alcohol, etc. It has already been established that *Cardamom* plant belonging to the Zingiberaceae family has the potential to help controlling Tuberculosis. This work is focused on the identification of the particular phytochemical responsible for inhibiting and controlling Tuberculosis.

2.2.2 Enzyme found in *Mycobacterium*

It has been reported that Tuberculosis is caused as a result of *Mycobacterium sp.* 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 sp.* bacteria. It has been found that histidinol dehydrogenase (H37Rv) enzyme (protein database code5HKF) is involved in glycerolipid metabolism (KEGG) and very crucial for the survival of the particular microbe.

2.2.3 Molecular Docking

The molecular docking method has been used to identify the phytochemicals from the plant extract, which acts as a ligand and forms 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 *cardamom* plant were downloaded from the website (www.molinstinct.com). The protein database code of the histidinol dehydrogenase (H37Rv) enzyme was identified from the website (www.rcsb.org). The active site of the enzyme was identified via the "receptor cavity" protocol found under the "receptor-ligand interaction" menu. Molecular docking was done using the CDOCKER protocol of Bioviasoftwere 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

-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

Table 1. Results of C docking of phytochemicals with histidinol dehydrogenase (H37Rv) (receptor)

Sl. no.	Ligand	-CDOCKER energy	-CDOCKER interaction energy	Difference between -CDOCKER interaction energy and -CDOCKER energy	Remarks
1	4-terpineol	-823.001	-253.653	569.348	Maximum inhibition of microbial enzyme
2	acetic acid	13.1516	10.7878	2.3638	
3	cinnamaldehyde	-175.704	-74.9785	100.7255	
4	eucalyptol	Failed	Failed	NA	
5	3,7-dimethyl	Failed	Failed	NA	
6	Santolina alcohol	Failed	Failed	NA	

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 [4,5]. Table 1 shows that histidinol dehydrogenase (H37Rv) enzyme-acetic acid interaction has the highest positive value of -CDOCKER energy (13.1516) and the difference (2.3638) between - C DOCKER interaction energy and - C DOCKER energy. Thus the results indicated that acetic acid can effectively deactivate the histidinol dehydrogenase (H37Rv) enzyme thereby interrupting the biological cycle of *Mycobacterium sp*. Higher positive values of acetic acid indicated that it was the most active ingredient against *mycobacterium sp*. Eucalyptol, 3,7-dimethyl and Santolina alcohol can not interact with histidinol dehydrogenase (H37Rv) enzyme. Thus, the key phytochemicals preventing Tuberculosis caused by *mycobacterium sp.* is acetic acid.

4. CONCLUSIONS

It was previously known that *Cardmom* plant has medicinal action against Tuberculosis. Tuberculosis is caused by *Mycobacterium sp*. This study was carried out to provide the theoretical basis of this observation. Using Discovery studio module of Biovia software, molecular docking operation was performed to identify the phytochemical (4-terpineol, acetic acid, cinnamaldehyde, eucalyptol,3,7-dimethyl, Santolina alcohol), which can have significant interaction with the vital enzyme [histidinol dehydrogenase (H37Rv)]of the microbe. It was found that acetic acid can form a strong bond with the enzyme successfully inhibiting the metabolic cycle of the microbe. 4-terpineol and cinnamaldehyde were found to be not much effective in deactivating the enzyme of the microbe.eucalyptol,3,7-dimethyl, Santolina alcohol cannot deactivate the enzyme. Thus, this study could explain that the presence of acetic acid provided the medicinal values to *Cardamom* against Tuberculosis caused by *Mycobacterium sp*.

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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