

# **In Silico Analysis of Effects of Phytochemicals From *Michelia champaca* Against Peptidase Do of Bordetella Pertussis Causing Cough**

## **ABSTRACT:**

Phytochemicals are non-nutritive compounds obtained from plants. It has been reported that *Micheliachampaca* extract is used to cough. The plant extract contains different phytochemicals. Cough is caused by *Bordetella pertussis*. One of the key enzymes involved in its biochemical pathway peptidase Do enzymes. The molecular docking of the phytochemicals with the enzyme was studied using Biovia Discovery Studio. The strength of the interaction was evaluated based on -CDocker energy and -CDocker interaction energy. High positive values for both the parameters indicate that out of different phytochemicals magnoflorinecan effectively deactivate the peptidase Do enzymes thereby interrupting the life cycle of cough.

**KEYWORDS:** Phytochemical, Biovia, Discovery studio, *champa* flower.

## **1. INTRODUCTION:**

In olden days, life was natural, slow, difficult at times but healthy. Today, in modern times, life is fast paced, comfortable, readymade, stressful and unhealthy. Changing work condition, less physical activity, sedentary jobs, comfortable but stressful life and bad eating habits has exposed us to some dangerous health hazards like blood pressure, diabetes, ageing, obesity and also

immunosuppression etc. A little caution, small changes in lifestyle and care if taken, we can prevent these lifestyle related diseases from increasing. The most effective path to diminish the action of free radicals which causes the oxidative stress is antioxidant defence mechanisms. Cough is the most common symptom for which medical treatment is sought in the outpatient setting. It can also be a warning sign of several respiratory and non-respiratory diseases and is one of the most common reasons for adults seeking medical treatment [1]. Acute or short-lived cough, which often occurs in association with upper respiratory tract infection, is usually self-limiting and usually resolves within three weeks. However, a persistently troublesome chronic cough (*i.e.*, >8 weeks in duration) of obscure aetiology has been shown to be one of the most common reasons for new patient visits to respiratory physicians in secondary/tertiary care [2,3].

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. The medicinal value of the plants lies in some chemical substances that produce a definite physiological actions on the human body, these substances are called phytochemicals, which can be used for therapeutic purpose. Phytochemicals (from the Greek word phyto, meaning plant) are biologically active, naturally occurring chemical compounds found in plants, which provide health benefits for humans further than those attributed to macronutrients and micronutrients. They protect plants from disease and damage and contribute to the plant's color, aroma and flavor. Plants based medicinal constituents can be derived from any part of plant like bark, leaves, flowers, roots, fruits, and seeds. The WHO endorses and promotes the addition of herbal drugs in national health care programs because they are easily accessible at a price within the reach of a common man and are time tested and thus considered to be much safer than the modern synthetic drugs [4]. Also these phytochemicals present in different plants parts are used up by the local people for healing certain disorder [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. Limited quantities of nicotine, pyrethrins and rotenone are used as pesticides [6]. Medicinal plants play a key role in human health care. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plants, the reasons of this popularity are the safety, efficacy of medicinal plants and their cost effectiveness. Many of the medicinal plants are used as spices and food items. Tanins generally act as an astringent [7]. Quinones e.g., hypericin can be used as antimicrobial agent [8]. They also played an important role in many medicines like allopathic medicine, herbal medicine, alternative medicine, homeopathy and aromatherapy. Among different sources of natural products, plants have been a source of novel chemical substances, which serve as starting materials for a number of old and new pharmaceutical products.

*Plumeria* (/plu:'meriə/) is a genus of flowering plants in the family Apocynaceae. Most species are deciduous shrubs or small trees. The species variously are indigenous to Mexico, Central America and the Caribbean, and as far south as Brazil and north as Florida, but are grown as cosmopolitan ornamentals in warm regions. Common names for plants in the genus vary widely according to region, variety, and whim, but **frangipani** or variations on that theme are the most common. *Plumeria* is also used as a common name, especially in horticultural circles. A cough can be the result of a respiratory tract infection such as the common cold, acute bronchitis, pneumonia, pertussis, or tuberculosis. In the vast majority of cases, acute coughs, i.e. coughs shorter than 3 weeks, are due to the common cold. In people with a normal chest X-ray, tuberculosis is a rare finding. Pertussis is increasingly being recognised as a cause of troublesome coughing in adults. After a respiratory tract infection has cleared, the person may be left with a postinfectious cough. This typically is a dry, non-productive cough that produces no phlegm. Symptoms may include a tightness in the chest, and a tickle in the throat. This cough may often persist for weeks after an illness. The cause of the cough may be inflammation similar to that observed in repetitive stress disorders such as carpal tunnel syndrome. The repetition of coughing

produces inflammation which produces discomfort, which in turn produces more coughing. Postinfectious cough typically does not respond to conventional cough treatments. Treatment consists of any anti-inflammatory medicine (such as ipratropium) to treat the inflammation, and a cough suppressant to reduce frequency of the cough until inflammation clears.<sup>1</sup> Inflammation may increase sensitivity to other existing issues such as allergies, and treatment of other causes of coughs (such as use of an air purifier or allergy medicines) may help speed recovery. A bronchodilator, which helps open up the airways, may also help treat this type of cough. Cough may also be caused by conditions affecting the lung tissue such as bronchiectasis, cystic fibrosis, interstitial lung diseases and sarcoidosis. Coughing can also be triggered by benign or malignant lung tumors or mediastinal masses. Through irritation of the nerve, diseases of the external auditory canal (wax, for example) can also cause cough [9]. Cough is an important natural defense mechanism of the respiratory tract[10]. Cardiovascular diseases associated with cough are heart failure, pulmonary infarction and aortic aneurysm. Nocturnal cough is associated with heart failure, as the heart does not compensate for the increased volume shift to the pulmonary circulation, in turn causing pulmonary edema and resultant cough. Other causes of nocturnal cough include asthma, post-nasal drip and gastroesophageal reflux disease (GERD). Chronic cough is reported in approximately 10-20% of the general population [11]. Another cause of cough occurring preferentially in supine position is recurrent aspiration. Given its irritant nature to mammal tissues, capsaicin is widely used to determine the cough threshold and as a tussive stimulant in clinical research of cough suppressants. Capsaicin is what makes chili peppers spicy, and might explain why workers in factories with these fruits can develop a cough. Coughing may also be used for social reasons, such as coughing before giving a speech. Coughing is not always involuntary, and can be used in social situations. Coughing can be used to attract attention, release internal psychological tension, or become a maladaptive displacement behaviour. It is believed that the frequency of such coughing increases in

environments vulnerable to psychological tension and social conflict. In such environments, coughing may become one of many displacement behaviors or defense mechanisms.

## **2. MATERIALS & METHODS**

### **Software used:**

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

### **Methodology:**

#### **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 work shows that *Micheliachampaca* flowers $\beta$ -sitosterol, germacranolide, liriodenine, magnoflorine, parthenolide, ushinsunine. It has already been established that *Micheliachampaca* plant belonging to family magnoliaceae has potential to help controlling cough. This work is focused on identification of the particular phytochemical responsible for inhibiting and controlling of cough.

#### **Enzyme found in Bordetella pertussis:**

It has been reported that cough can cause as a result of *Bordetellapertussis*.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 *Bordetella pertussis* bacteria. It has been found that peptidase Do enzyme(protein database code 3IVL).

Peptidase Do enzymes has a major role in metabolic pathway of *Bordetella pertussis* as lipoprotein biosynthesis(signal peptide cleavage)which is a part of protein modification.

It has another metabolic pathway known as peptidoglycan biosynthesis which is a part of cell wall biogenesis.

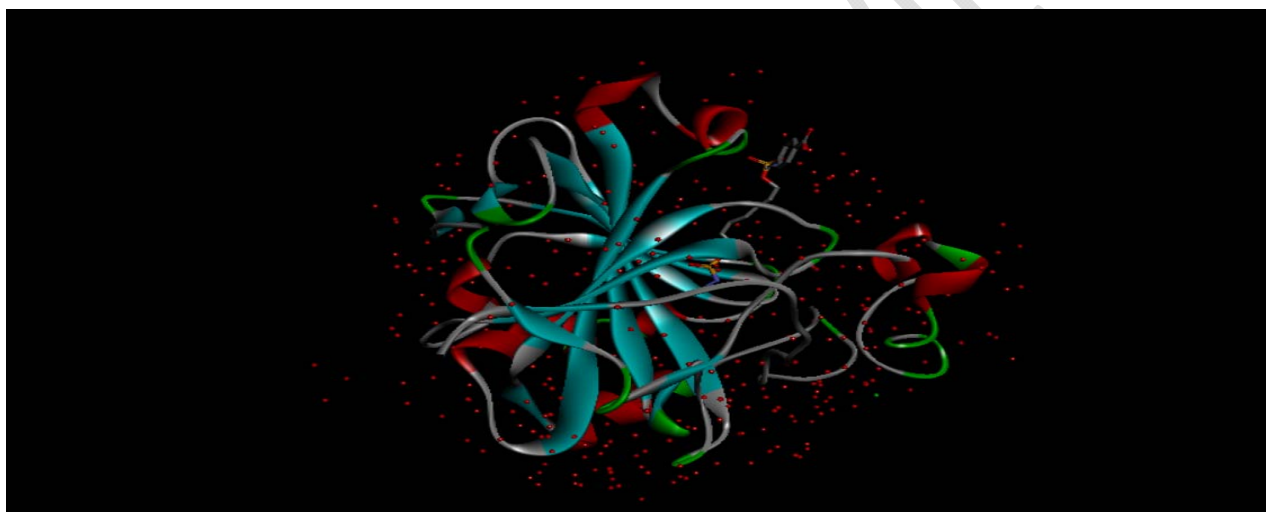
### **Molecular docking:**

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 *Micheliachampac* plant were downloaded from the website (<https://pubchem.ncbi.nlm.nih.gov/>). The protein database code of the peptidase Do enzyme was identified from the website (<https://www.rcsb.org/structure/3IVL>). 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. RESULT AND DISCUSSION

Fig. 1 shows the active site of the peptidase Do enzyme. It appears as light green color. CDOCKER 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.



**Figure 1. Active site of peptidase Do enzyme**

-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 [12]. Table 1 shows that peptidase Do-magnoflorine interaction has the highest positive value of -CDOCKER energy (6.50793) and minimum value of the difference (34.66487) between -CDOCKER interaction energy and -CDOCKER energy followed by

parthenolide. Thus the results indicated that magnoflorine can effectively deactivate the peptidase Do enzyme thereby interrupting the biological cycle of *Bordetella pertussis*.

**Table 1. Results of CDocking of phytochemicals with peptidase Do (receptor)**

SL NO	LIGAND	- C DOCKER ENERGY	- C DOCKER INTERACTION ENERGY	DIFFERENCE BETWEEN - C DOCKER INTERACTION ENERGY AND - C DOCKER ENERGY
1	Magnoflorine	6.50793	41.1728	34.66487
2	Ushinsunine	-4.64953	31.4747	36.12423
3	Liriodenine	-14.3424	26.8966	41.236
4	Germacranolide	-18.5597	32.6054	51.1651
5	Parthenolide	-31.6875	30.6494	62.3369
6	$\beta$ -sitosterol	-35.4176	41.1406	76.4936

#### 4. CONCLUSION

It was previously known that *Micheliachampac* plant has medicinal action against cough is caused by *Bordetella pertussis*. 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 (Germacranolide,  $\beta$ -sitosterol, liriodenine, magnoflorine,



parthenolide,ushinsunine), which can have a significant interaction with the vital enzyme (peptidase Do) of the microbe.From the above study it can be concluded that magnoflorine has successfully inhibiting the metabolic cycle of the microbe. Ushinsunine is found to be less effective in deactivating the enzyme of the microbe. Liriodenine, Germacranolide, parthenolide, $\beta$ -sitosterolcan not interact with peptidase Do enzyme. Thus the key phytochemicals in preventing cough caused by bordetella pertussis is magnoflorine.

#### **COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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