Journal of Pharmaceutical Research International

32(6): 128-131, 2020; Article no.JPRI.56450
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Capsicum Derived Phytochemicals against Shikimate Dehydrogenase of *Haemophilus influenza* causing Bronchitis

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Authors' contributions

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

Article Information

DOI: 10.9734/JPRI/2020/v32i630507
Editor(s):
(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.
Reviewers:
(1) Sandeep Onkar Waghulde, University of Mumbai, India.
(2) Bhaskar Sharma, Suresh Gyan Vihar University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/56450

Original Research Article

Received 09 April 2020
Accepted 13 May 2020
Published 15 May 2020

ABSTRACT

Phytochemicals from *Capsicum* plant extract are traditionally used to cure Bronchitis. It is caused by *Haemophilus influenzae.* Molecular docking method applied using "Biovia Discovery Studio". "High positive values of -CDOCKER energy and -CDOCKER interaction energy" suggested that Apigenin can effectively deactivate the Shikimate dehydrogenase enzyme thereby interrupting the life cycle of the organism.

Keywords: Phytochemical; capsicum; Haemophilus influenza.

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. Nature is a major source of medicines [1]. 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

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in human health care. Many people rely on the use of traditional medicine [3]. Capsicum belongs to family Solanaceae. Capsicum extract is used to cure disease like Bronchitis. The objective of the study is to identify the phytochemical responsible to cure the disease.

Published works showed that *Capsicum* contains "1,8-cineole, Apigenin, camphene, capsaicin, linalool, luteolin, myrcene, quercetin, rutin, β-carotene" etc. These phytochemicals might act against Bronchitis. However, there is no such study available.

This objective of the study is to identify the phytochemical of *Capsicum* capable of curing bronchitis

2. MATERIALS AND METHODS

2.1 Software Used

Discovery studio module of Biovia software (Dassault Systems 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 *Capsicum* contains1,8-cineole, Apigenin, camphene, capsaicin, linalool, luteolin, myrcene, quercetin, rutin, β-carotene.It has already been established that *Capsicum* plant belonging to Solanaceae family has potential to help controlling bronchitis. This work is focused on identification of the particular phytochemical responsible for inhibiting and controlling of bronchitis.

2.2.2 Enzyme found in *Haemophilus influenzae*

It has been reported that bronchitis can causeas a result of *Haemophilus influenza* 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 *Haemophilus influenza* bacteria. It has been found that shikimate dehydrogenase enzyme (protein database code1P74) is involved in shikimate pathway (KEGG) and very crucial for survival of the particular microbe. The shikimate pathway occupies a central position for aromatic biosynthesis in microbes and plants but is not present in humans and other higher animals. The absence of the shikimate pathway in animals makes it an ideal target for herbicide and anti-microbial drug design. Recent studies have also shown that glyphosate blocks the shikimate pathway in apicomplexan parasites and is effective in controlling their growth. The shikimate pathway consists of seven enzymatic steps initiated by the condensation of phosphoenolpyruvate and erythrose-4-phosphate by 3-deoxy-d-arabino-heptolosonate 7-phosphate synthase. The last enzymatic step produces the branch point intermediate, chorismate, which serves in turn as the precursor for a number of pathways including those involved in aromatic amino acid, phytoalexin, flavanoid, and lignin biosynthesis.

The fourth enzyme in the pathway, shikimate dehydrogenase (shikimate: NADP+ oxidoreductase; EC 1.1.1.25), is involved in the NADPH-dependent reduction of dehydroshikimate to shikimate. This enzymatic reaction proceeds in both the forward and reverse direction with similar rates and similar Michaelis constants for substrates in either direction. Kinetic studies with substrate analogues and isotope exchange demonstrated that the shikimate dehydrogenase-catalyzed reaction is consistent with an ordered sequential mechanism. Two types of shikimate dehydrogenases from bacteria have been characterized to date, AroE and YdiB (quinate/shikimate dehydrogenase, EC 1.1.1.282). Although AroE has been established as the enzyme responsible for flux through the main trunk of the shikimate pathway, YdiB has been implicated in a branch point involving the metabolism of quinate.

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 [4]. 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 *Capsicum* plant were downloaded from the website (https://pubchem.ncbi.nlm.nih.gov/). The protein database code of the shikimate dehydrogenase enzyme was identified from the website (https://www.rcsb.org/structure/1P74). 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 Bioviasoftware under "receptor-ligand interaction". The enzyme molecule was treated as the receptor molecule and the phytochemical was treated as the ligand [5]. 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 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 [6]. Table 1 shows that shikimate dehydrogenase-luSSteolin interaction has the higher positive value of -CDOCKER energy (32.4718) and minimum value of the difference (3.9218) between - C DOCKER interaction energy and - C DOCKER energy followed by apigenin and quercetin. Thus, the results indicated that luteolin, apigeninand quercetincan effectively deactivate the shikimate dehydrogenase enzyme thereby interrupting the biological cycle of *Haemophilus influenzae*. Higher positive values for luteolin indicated that it was the most active ingredient against *Haemophilus influenzae*. On the other hand, 1,8-cineole, camphene,linalool andmyrcenecan deactivate the enzymeto a small extent (negative -CDOCKER energy but positive -CDOCKER interaction energy). β-carotenecannot interact with shikimate dehydrogenase enzyme. Thus, the key phytochemicals preventing bronchitis caused by *Haemophilus influenzae* are luteolin, apigenin and quercetin.

Table 1. Results of Cdocking of phytochemicals with shikimate dehydrogenase (receptor)

SL no	Ligand	-CDOCKER energy	-CDOCKER interaction energy	Difference between -CDOCKER interaction energy and -CDOCKER energy	Remarks
1	1,8-cineole	-11.5286	15.6269	27.1555	
2	Apigenin	27.8637	33.265	5.4013	Maximum inhibition
3	Camphene	-49.0282	16.5946	66.1177	
4	Capsaicin	26.4834	41.2432	14.7598	
5	Linalool	-7.15223	25.1919	32.34413	
6	Luteolin	32.4718	36.3936	3.9218	
7	Myrcene	-10.88	19.4237	30.3037	
8	Quercetin	32.7969	38.92	6.1231	
9	Rutin	1.6057	62.023	60.8373	
10	β-carotene	Failed	Failed	NA	

4. CONCLUSIONS

It was previously known that *Capsicum* plant has medicinal action against bronchitis. Bronchitis is caused by *Haemophilus influenzae*. 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 (1,8-cineole, Apigenin, camphene, capsaicin, linalool, luteolin, myrcene, quercetin, rutin and β-carotene), which can have a significant interaction with the vital enzyme (shikimate dehydrogenase) of the microbe.It was found thatluteolin, apigenin and quercetincan form strong bond with the enzyme successfully inhibiting the metabolic cycle of the microbe.1,8-cineole, camphene, capsaicin, linalool, myrcene, rutinwere found to be not much effective in deactivating the enzyme of the microbe. β-carotene cannot deactivate the enzyme.Thus, this study could explain that the presence of luteolin, apigenin and quercetin provided the medicinal values to *Capsicum* against bronchitis caused by *Haemophilus influenzae.*

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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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/56450