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IN SILICO MOLECULAR DOCKING OF PHYTOCHEMICAL OF CINNAMON-CINNAMALDEHYDE, CINNAMATE AND CINNAMIC ACID AGAINST CAMPYLOBACTER SPECIES

TYPE OF STUDY: In Silico study

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ABSTRACT:
Cinnamomum is an ethno-medicinal plant which has very essential activity against bacteria and fungi. It has been reported that this plant extract is used to cure campylobacter infections. Multiple Research work emphasize the therapeutic importance of bioactive principles of Cinnamomum in the treatment of intestinal infections. This plant extract contains different phytochemicals which prevents the activity of campylobacter infections. That is the causative agent of campylobacter jejunum. The molecular docking of the phytochemicals with the enzyme was studied using PubChem database in SDF format and were converted into Protein data bank (PDB) format using SDF to PDB online converter tool.Molecular docking was carried out using Hex dock software (ver 8.0.0) with default settings. Interaction of the drug including pharmacological effects and mechanism of action, adverse effects and side effects were predicted using Passonline web server(Way2drug). The physicochemical properties, lipophilicity, water solubility, pharmacokinetics and drug- likeliness were assessed using the SwissADME online server program. SMILES of each drug was used as the input.

KEYWORDS:
Phytochemicals, Cinnamate, cinnamaldehyde, cinnamic acid, PubChem database, way2drug, Swiss ADME

INTRODUCTION:

In recent decades , lifestyles, an important factor of health, are more interesting to researchers. According to WHO 60% of health factors are directly related to the way of living. Millions of people follow an unhealthy lifestyle like unhealthy diet, smoking, alcohol consumption, drug abuse, stress and so on(1). Hence, they encounter illness, disability and problems like joint pain, cardiovascular disease, hypertension(2), overweight , skin lesions, low vision and low hearing problems in early age is very common in now –a – days world. From Vedic period, nature has been the best doctor of all individuals .According to the great scholar Charaka ,every plant has its own medicinal properties. The main component of the plants which are used in therapeutic purposes is called phytochemicals(3). These phytochemicals produce definite physiological actions in the human body. The presence of phytochemicals has revealed the presence of numerous chemicals including Alkaloids, tannin, flavonoids, saponins etc. these are secondary metabolites of plants . serves as a defense mechanism against bacteria, insects and many microorganisms(4,5). Based on current research

it seems that medicinal plants will play an important role in the health condition of society. The use of traditional medicinal plants in most of the developing countries ,as a normative basis for the maintenance of good health, has been widely observed (UNISCO ,1996). In order to a comprehensive compilation of medicinal plants that can be used in disease prevention(6). is obtained ,collation of the original data from the traditional knowledge is essential. For knowing ethno-botanical values of medicinal plants a survey should be conducted. Various phyto extracts have numerous properties like anti cancer, antioxidant, anti-inflammatory, anti microbial, anti diabetic etc. .The popularity of the medicinal plants are due to their safety, efficacy and their cost effectiveness(7). For preparing a drug from botanical origin it can be any part of the plants like roots, stem, seeds, fruits etc. For example, the anticancer property of Neem leaves (Azadirachta indica) has phytochemicals like terpenoids and steroids.(8) This plant has very preventive, protective, immune modulatory and apoptotic effects against various types of cancer Allium sativum (Garlic) constituents allicin, disulfide, diallyl trisulfide have a chemopreventive agent for lung and breast cancer. Research should be emphasized in the field of medicinal plants. which will be beneficial for both economical side and therapeutic purpose.

Cinnamaldehyde (CM) is an interesting drug development base because it can be obtained from synthesis and isolation of natural ingredients. CM is the main component of cinnamon bark essential oil, which has been widely used as a herbal medicine, especially in tropical and subtropical areas.(9) It demonstrates as an antiallergenic, antimicrobial, antiviral, antioxidant, gastroprotective agent, and anti-Alzheimer's, which has attracted the attention of several research studies. Additionally, CM has anti angiogenic properties among which being an active compound used as an antitumour and anticancer agent (Kuswandi et al., 2016).
The term "cinnamic" derives from the spice cinnamon (Cinnamomum zeilanicum) which has been used since antiquity as a flavoring agent and for its stimulant, carminative, antiseptic and insecticide properties. The bark of several species of Cinnamomum contain considerable amounts of (E)-cinnamaldehyde, a volatile aldehyde responsible for the pungent, sweet and hot flavor of cinnamon, Cinnamaldehyde and the essential oils of the species of Cinnamomum have antimicrobial activity both against bacteria and fungi.(10)The addition of functional groups contained in Cinnamaldehyde makes it possible to have some interesting CM derivatives to study.

Materials and Methods

Data

The 3D structure of TolB protein of Campylobacter jejuni was not available in the protein data bank. Hence, the protein was modeled using the Swiss-Model online server program (https://swissmodel.expasy.org/). Template search with BLAST and HHblits has been performed against the SWISS-MODEL template library. Models are built based on the target-template alignment using ProMod3. Coordinates which are conserved between the target and the template are copied from the template to the model. Phytochemicals identified from honey namely, caffeic acid, cinnamic acid, gallic acid, syringic acid, ellagic acid were selected for the study. The two-dimensional chemical structures in structured data format (SDF) were retrieved from PubChem database and were converted into Protein data bank (PDB) format using Pymol. Antifungal drug, fluconazole was processed similarly and considered as controls.
Interaction of the drug including pharmacological effects and mechanism of action. interaction with metabolic enzymes and transporters, influence on gene expression, possible adverse effects and side effects were predicted using Passonline web server (http://www.way2drug.com/passonline). SMILES (Simplified Molecular Input Line Entry System) of each drug was fed as the input for each drug. Ten interactions with the highest Pa value is shown in Table 1 and 2. Pa (probability "to be active") is an estimate of the probability

of the drug belonging to the sub-class of active compounds resembling the established set of actives in the server training set. Similarly, Pi is the probability "to be inactive" that is estimated by the server.

The physicochemical properties, lipophilicity, water solubility, pharmacokinetics and drug-likeliness were assessed using the SwissADME online server program. SMILES of each drug was used as the input.

Optimal docking areas were calculated using molsoft online server (http://www.molsoft.com). The output was viewed using an ICM-browser.

Molecular Docking

Molecular docking was carried out using Hex Protein Docking server (). The receptor and the ligand were fed as a .pdb file and the resulting interactions with the docking score were recorded.

Results

MOMP: Total Structure Weight:

Prediction of biological activity for Cinnamoldehyde

Pa	Pi	Activity
0,916	0,004	Antidiabetic

There were no possible adverse effects or side effects (Pi >0.7) predicted for cinnamaldehyde

Prediction of biological activity for Cinnamic acid

Pa	Pi	Activity
0,969	0,001	Feruloyl esterase inhibitor
0,938	0,004	Membrane integrity agonist
0,928	0,004	Mucomembranous protector

Analysis of cinnamate yielded no results due to its less molecular charge (-1).

Prediction of possible adverse effects and side effects for Cinnamic acid (>0.8)

Pa	Pi	Activity
0,894	0,003	Skin irritation, corrosive
0,934	0,003	Ulcer, aphthous

ADME

Table 1: Important ADME parameters of the drugs

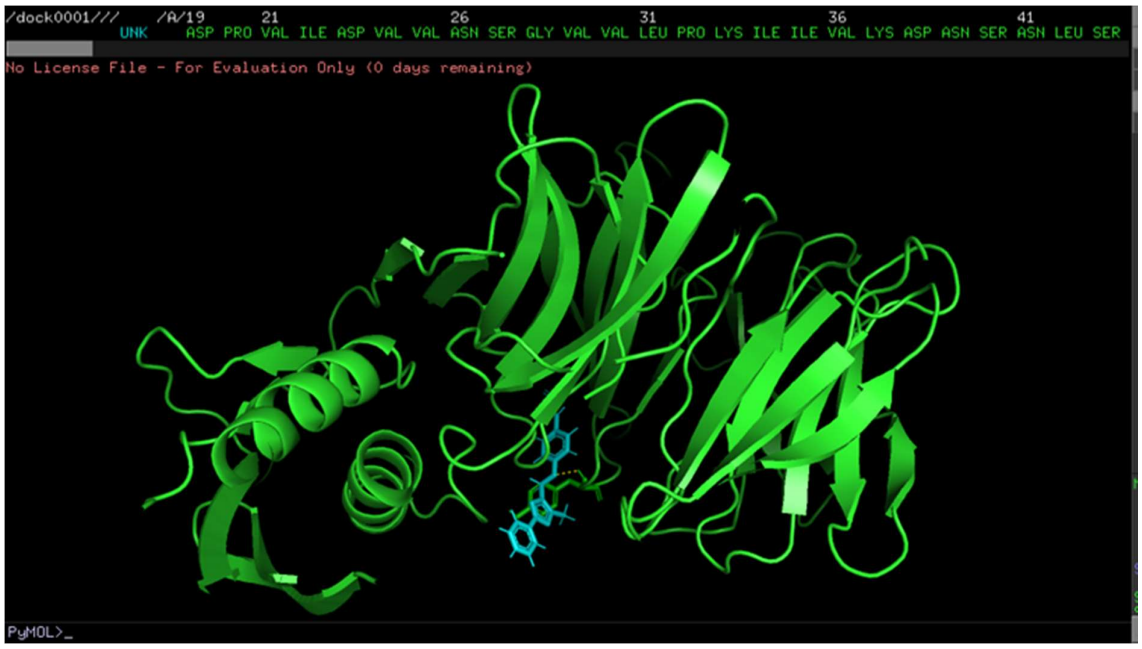
Parameters	Cinnamaldehyde	Cinnamate	Cinnamic acid

TPSA	17.07 Å²	26.30 Å²	37.30 Å²
Consensus Log Po/w	1.97	2.22	1.79
Water solubility	Soluble	Soluble	Soluble
GI absorption	High	High	High
Inhibitors of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4	No	No	No
Lipinkski (drug likeliness	Yes; 0 violation	Yes;0 violation	Yes;0 violation
Bioavailability score	0.55	0.55	0.85
Synthetic accessibility	1.65	1.91	1.67

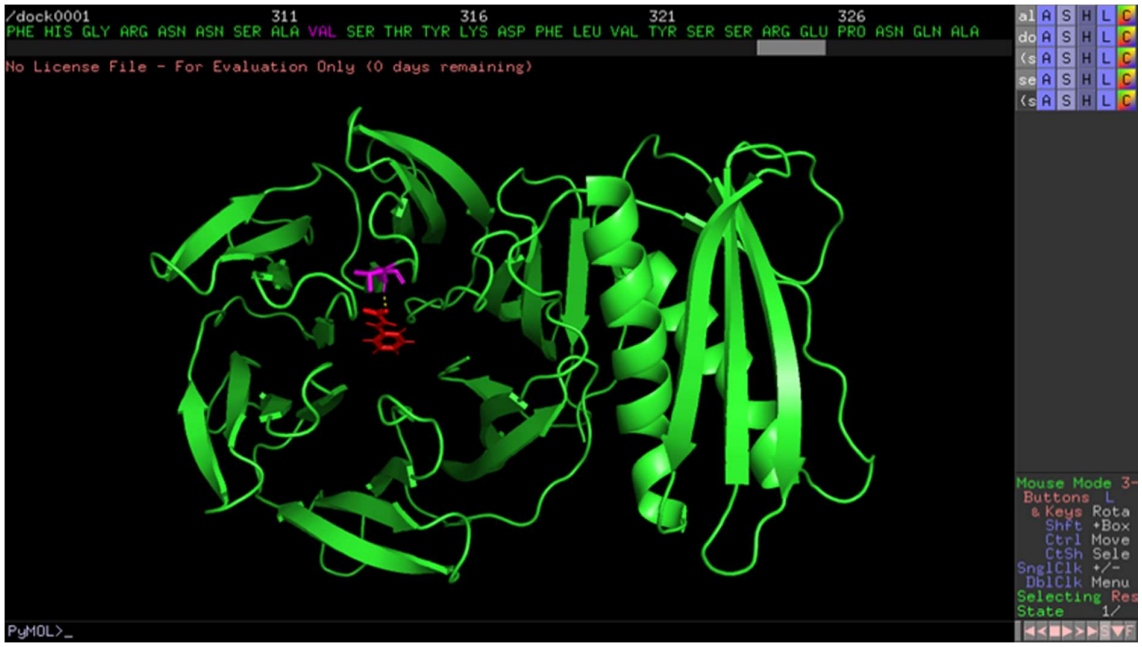
Docking results

S.No	Phytochemicals	PubChem ID	Binding Residues	E-total
1	Cinnamaldehyde	53888831	Tyr-315	-252.95
2	cinnamate	5957728	Val-312	-162.65
3	Cinnamic acid	444539	Val-312	-156.60

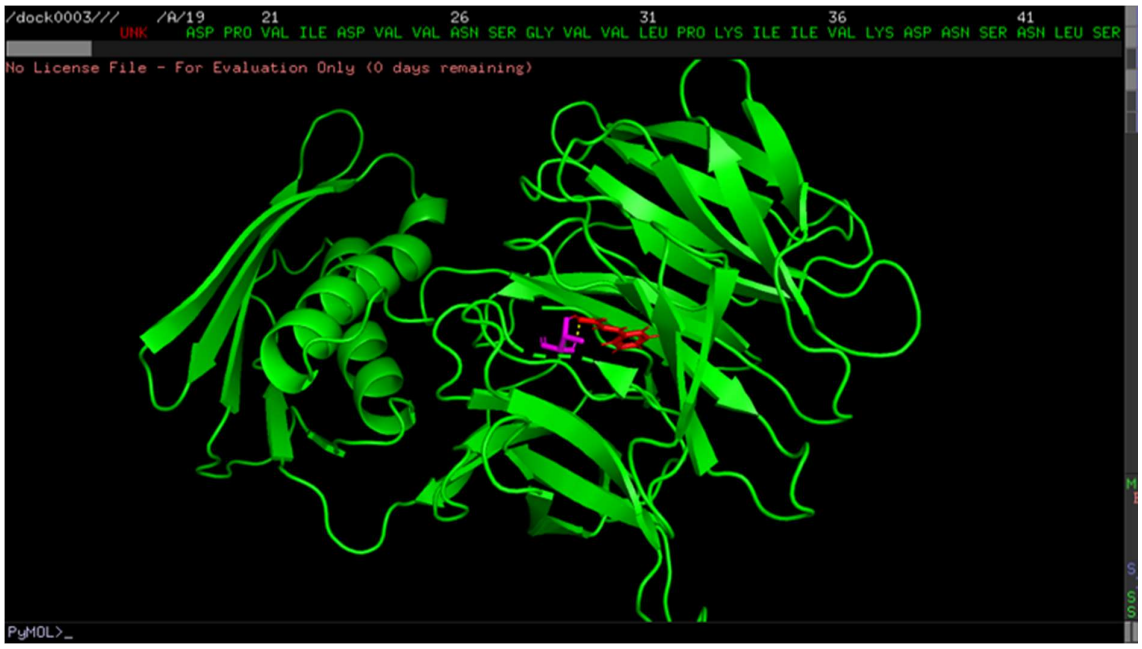
DOCKED COMPLEX-CINNAMALDEHYDE



DOCKED COMPLEX-CINNAMATE



DOCKED COMPLEX-CINNAMIC ACID



DISCUSSION:

Molecular docking is one of the crucial techniques in drug design and validation process. It gives accurate and preferred orientations of the ligand at the active site of the enzyme.(11) It was previously known that that Cinnamon plant has medicinal action against campylobacter. This study was carried out to provide the theoretical knowledge of this observation.(11,12) Using Discovery studio module of BIOVIA software, molecular docking operation was performed to identify the phytochemical (cinnamic acid,vallinin,quercetin, catechin , eugenol 3D, curcumin, nicotin,procyanidin A2),(13) which can have a significant interaction with the vital enzyme (aspartate semialdehyde dehydrogenase) of the microbe .It was found can form strong bond with the enzyme successfully inhibiting the metabolic cycle of the microbe(11,12,14). Curcumin and nicotin were found to be not much effective in deactivating the enzyme of the microbe. Procyanidin A2 cannot deactivate the enzyme(15).Thus, this study could explain that the presence of cinnamate,cinnamic acid, cinnamaldehyde provided the medicinal values to Cinnamomum against intestinal damage caused by campylobacter. Cinnamaldehyde had the lowest E score indicating strong interaction. All the three drugs had one hydrogen bond each with the binding residue. Of the three compounds, cinnamic acid had a high TPSA score. All the three drugs were water soluble and had similar bioavailability scores. All these three drugs had good binding interactions with the TolB protein of Campylobacter. The ADMET properties of the three drugs indicate the drug-likeliness favourable. Further study will help develop potent drugs based on these compounds against Campylobacter species.

CONCLUSION:

Our study showed the importance of specific phytochemicals of cinnamon that could be potentially developed as a drug compared to cinnamic acid, cinnamaldehyde against Campylobacter species.

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CONFLICT OF INTEREST:

All the authors declare that there was no conflict of interest in the present study.

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