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ARTICLE

Combatting the Coronavirus Utilizing Natural Cinnamon and Its Derived Products

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ABSTRACT

The entire world health system has collapsed because of the attack by Coronavirus and currently, no vaccines are available to treat patients affected by this virus. In this work, we discuss the natural remedies to fight against Coronavirus. Based on an extensive review of existing literature and our comprehensive understanding of the efficacy of natural products in combating diseases, based on findings that cinnamon and its derived product exhibit substantial potential as a very effective therapeutic agent for the treatment of Covid-19. The physico-chemical and geometrical parameters obtained from DFT calculations are also presented to validate the present findings. Cinnamon, their constituents and products derived from them were not tested against Covid19. However, this study may open up a way to include new treatment strategies against coronavirus.

INTRODUCTION

During 2020-2022, the entire world has collapsed because of the attack by Coronavirus. The Covid-19 pandemic, caused by the novel coronavirus, has had a significant impact on several aspects of daily life and has resulted in a slowdown of the worldwide economy. The ongoing pandemic has had a profound impact on a significant number of individuals, resulting in either illness or mortality as a consequence of the disease's transmission. Currently, no effective vaccines are available to treat patients as covid virus has changes its variants around thousand times and and sets of mutations potentially linked to changes in the viral properties [1]. Similarly, effective medicines are not available to treat diseases caused by covid-19. Therefore, alternative constructive ideas based upon natural remedies should be used.

Cinnamon is one of the most important spices from the genus *Cinnamomum* and belongs to the Lauraceae family. The bark of various cinnamon species is used worldwide not only for cooking but also in traditional and modern medicines. In *Cinnamomum* genus, more or less 250 species have been identified [2]. They are classified into four groups *viz*. true cinnamon or Ceylon cinnamon or Mexican cinnamon (*Cinnamomum zeylanicum*); Indonesian cinnamon (*Cinnamomum burmanni*); Vietnamese cinnamon (*Cinnamomum loureiroi*); Cassia cinnamon or Chinese cinnamon (*Cinnamomum aromaticum*). Among them, only few *Cinnamomum* species are grown commercially for spice. Even though *Cinnamomum verum* is sometimes consi-

dered to be true cinnamon, most cinnamon in international commerce is derived from the related species named *C. cassia.* Cinnamon is mainly used in the aroma and essence industries due to its fragrance, which can be incorporated into different varieties of foodstuffs, perfumes and medicinal products [3].

In addition to applications as a spice and flavouring agent, cinnamon is also added to flavour chewing gums to get rid of bad breath and to make mouth refreshing effects [4]. Cinnamon can reduce the risk of cancer [5] and it can act as a coagulant [6]. Along with these applications, its other components (for example essential oils) also have important activities, such as antioxidant [7], antifungal [8], antidiabetic [9], antimicrobial [10], anti-inflammatory [11], nematicidal [12], antitermitic [11], mosquito larvicidal [13], antimycotic [14], insecticidal [15] and anticancer [16].

Cinnamon has been used by patients suffering from diverse viral diseases for centuries. For instance, an increasing trend is observed among HIV patients towards the use of cinnamon, expecially the oil as a therapy against HIV [17]. Among the ingredients cinnamaldehyde, eugenol and cinnamic acid have shown antiviral activities. The main ingredients of cinnamon include eugenol (**1**), cinnamaldehyde (**2**), cinnamyl acetate (**3**) cinnamic acid (**4**), ethyl cinnamate (**5**), estragole (**6**), linalool (**7**), caryophyllene (**8**), coumarin (**9**), O-methoxy cinnamaldehyde (**10**) and benzylbenzoate (**11**) (Fig. 1). Table-1 shows the concentrations of different ingredients in different parts of the plant.

Since cinnamaldehyde and eugenol are the active components present in cinnamon, we describe them in detail.

Cinnamaldehyde: Cinnamaldehyde is an important aldehyde found in cinnamon bark in high concentrations (65-80%). It has a wide range of medicinal applications. Usually, cinnamon bark is used medicinally in doses of 1-6 g orally. About 6 g of cinnamon can contain 42-189 mg of cinnamaldehyde. Cinnamon carries approximately 1-3.5% essential oil. The essential oil is around 70-90% cinnamaldehyde. *In vitro* tests using human skin, homogenates show that cinnamaldehyde is metabolized by aldehyde dehydrogenase. This action helps to develop cinnamic acid, which is a known metabolite of cinnamaldehyde. Another important metabolite of cinnamon is cinnamyl alcohol. Cinnamaldehyde extracted from the *C. cassia Presl* plant has anti-inflammatory [19], antibacterial [20] and antitumor effects [21].

TABLE-1
CONCENTRATIONS OF DIFFERENT CHEMICAL CONSTITUENTS OF DIFFERENT PARTS OF CINNAMON [18]

Component of the plant	Compound	Amount
Leaves	Eugenol	70.00-95.00%
	Cinnamaldehyde	1.00-5.00%
Bark	Eugenol	5.00-10.00%
	Cinnamaldehyde	65.00-80.00%
Root bark	Camphor	60.00%
Fruit	*trans*-Cinnamyl acetate	42.00-54.00%
	Caryophyllene	9.00-14.00%
C. zeylanicum flowers	(E)-Cinnamyl acetate	41.98%
	trans-α-Bergamotene	7.97%
	Caryophyllene oxide	7.20%
C. zeylanicum buds	Terpene hydrocarbons	78.00%
	α-Bergamotene	27.38%
	α-Copaene	23.05%
	Oxygenated terpenoids	9.00%

Antiviral activities of cinnamaldehyde: Hyashi *et al.* [22] investigated the inhibitory effect of *trans*-cinnamaldehyde from *Cinnamomi cortex* on the growth of influenza A/PR/8 virus *in vitro* and *in vivo*. Liu *et al.* [23] reported the inhibitory effect of cinnamaldehyde from *Cinnamomi cortex* on adenovirus type 3 (ADV3). The results have shown that the aldehyde (0.0195-0.315 mg/mL) has inhibited the growth of ADV3 in a

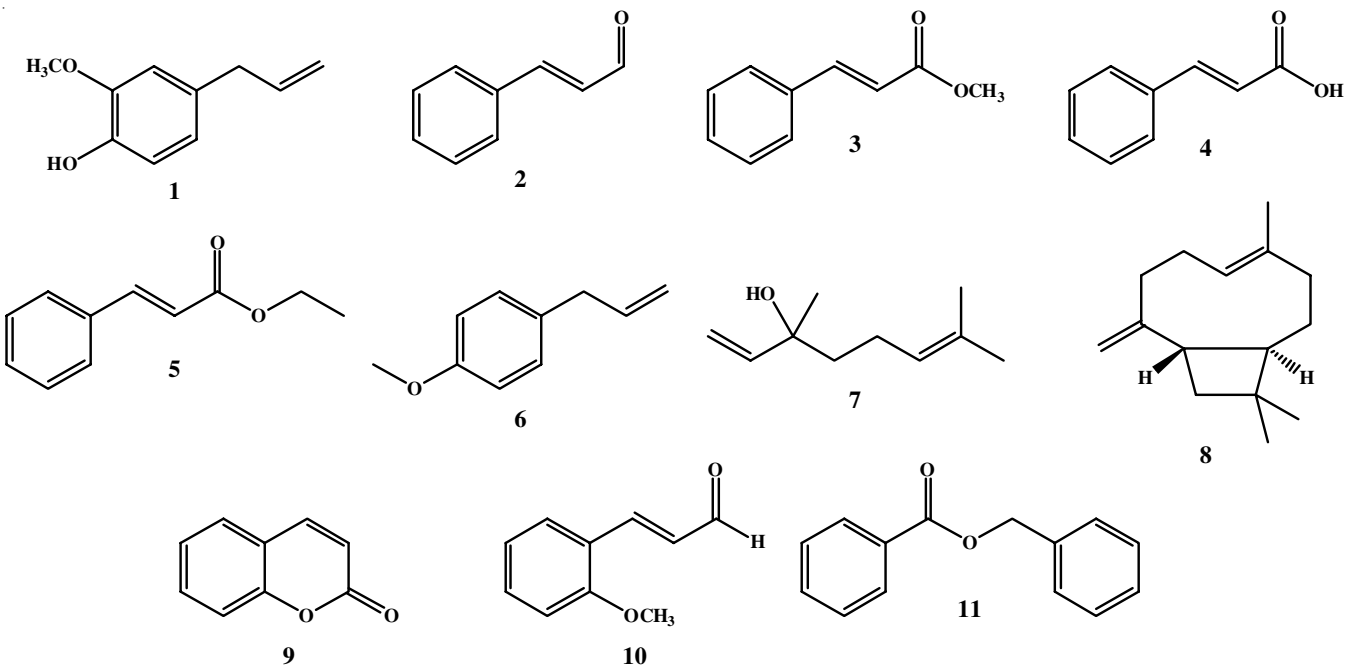


Fig. 1. Chemical structure of the main ingredients of cinnamon

concentration-dependent manner with the virus inhibition rate of 3-58.6%. The anti-ADV3 capabilities of this aldehyde may associate with decreasing the apoptosis level and inhibiting the caspase-3, caspase-8 and caspase-9 protein expression. Fabra *et al.* [24] investigated cinnamaldehyde's virucidal activity on norovirus surrogates, hepatitis A virus (HAV), murine 26 noroviruses (MNV) and feline calicivirus (FCV). They also have evaluated the antiviral activity of cinnamaldehyde-derived benzimidazole against porcine reproductive and respiratory syndrome virus (PRRSV) grown *in vitro* on MARC-145 cells. Goswami *et al.* [25] described the antiviral activity of (*E*)-cinnamaldehyde. The mode of action of this double-stranded DNA virus is close to HIV and Ebola virus.

Eugenol: Eugenol belongs to the allylbenzene class of chemical compounds. It can be extracted from cinnamon, cloves, nutmeg lemongrass, tulsi, basil and bay leaf. It has analgesic, anti-inflammatory, anticancer, analgesic and anesthetic activities. Studies have shown that eugenol (**1**) is metabolized by cytochrome P450 and converted into a cytotoxic quinone methide (**12**) [26] (Fig. 2). Quinone methides deplete intracellular glutathione levels, react with macromolecules in living cells and they are considered as cytotoxic in general.

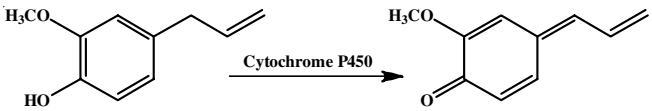


Fig. 2. Metabolic activation of eugenol

Antiviral activities of eugenol: As a potent natural product, eugenol is analyzed to understand its biological activity and therapeutic potential as an antiviral agent. Studies also have shown a synergistic effect between eugenol and acyclovir in the inhibition of herpes virus *in vitro* [27]. Eugenol has exhibited ovicidal activity against *Haemonchus contortus*, a parasite that resides in the gastrointestinal tract [28], antiprotozoal activity against *Leishmania*, which is an assembly of diseases responsible for a wide spectrum of clinical manifestations [29] and virucidal activity against HSV1 and HSV2 viruses [30].

Antibacterial activities of eugenol: Reports have shown that eugenol plays a crucial role in inhibiting the growth of bacteria [31]. It alters protein and reacts with phospholipids in the cell membrane and also can affect the transport of ions and ATP and changes the fatty acid profile of different bacteria [32]. Eugenol is active against, both Gram-negative and Gram-positive, as well as fastidious and facultative anaerobic oral bacteria. It is also reported that the antimicrobial mechanism of eugenol is affecting not only the membrane but also the envelope of fungal and bacterial cells [33].

Our research groups have been engaged in the synthesis and biological evaluation of diverse natural products of medicinal significances for example, we have used eugenol, curcumin and ascorbic acid in our study [34-36]. Considering the available literature and our background on the effectiveness of natural products against diseases, herein the possible effectiveness of cinnamon and a product obtained from it for the treatment of Covid-19 is reported. Cinnamon, their constituents and products derived from them were not tested against Covid-19 either individually and in combination with other agents. Cinnamon has a considerable amount of eugenol and unsaturated aldehydes.

EXPERIMENTAL

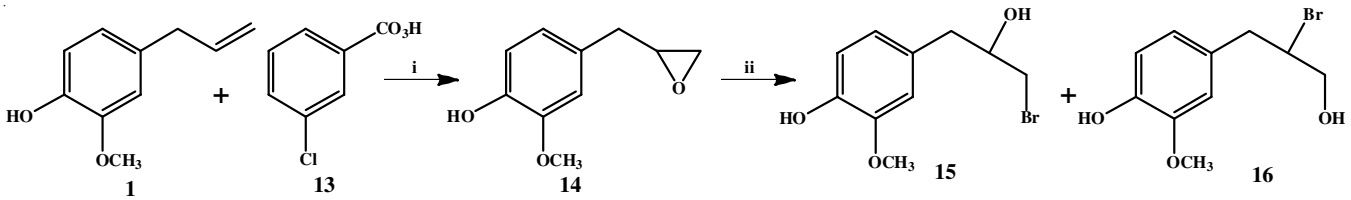
Eugenol **1** (5 mmol) was taken in a small flask with dry dichloromethane (5 mL). To it was added chloroperbenzoic acid **13** (10 mmol) and the reaction mixture was stirred for 6h at room temperature. It was then washed with saturated sodium bicarbonate solution (5 mL), brine (5 mL) and dried with anhydrous sodium sulfate (3 g). The solvent was evaporated and dried to afford the epoxide **14**.

To the epoxide **14** was added a saturated aqueous solution of KBr (5 mL). After being stirred for 2 h, the reaction was extracted with dichloromethane (5 mL), solvent was evaporated and dried to afford the bromo alcohol **15** (90%).

In another method eugenol **1** (5 mol) was heated with dry dichloroethane (5 mL) in an automated microwave oven for 3 min at 60°C. After bringing the reaction mixture to room temperature, a saturated aqueous solution of KBr was added to it (5 mL). The reaction was again irradiated at the automated microwave oven for 3 min at 60 °C. Following an identical method of extraction as mentioned above the bromoalcohol **15** was obtained in more than 90% yield [35].

RESULTS AND DISCUSSION

Our group has extensively studied the synthesis and antimicrobial activity of eugenol and its derivatives [Fig. 1(a-b)]. The distillation method was applied to isolate eugenol from cinnamon. The alkene group of eugenol (**1**) was converted to an epoxide **14** using 3-chloroperoxybenzoic acid in good yield at room temperature. Peroxybezoic acid was also used successfully for this purpose. The epoxide ring was then opened by treat-ment with an aqueous solution of potassium bromide. This reaction, in principle, may produce two alcohols **15** and **16**. However, only single secondary alcohol **15** was formed regioselectively.



Scheme-I: Synthesis of eugenol epoxide and bromo alcohol. Reagents and conditions: (i) 3-chloroperbenzoic acid $CH_2Cl.CH_2Cl$, MW; (ii) KBr, H_2O, MW

Considering the sequence of the above reactions and conditions of the experiments, we realized that the bromo alcohol **15** can also be prepared in a one-pot method under microwave-assisted reactions. Thus, the microwave-induced reaction of eugenol (**1**) and 3-chloroperoxybenzoic acid in dichloroethane was performed for 2 min. After completion of the reaction, an aqueous solution of KBr was added to the reaction flask. The reaction mixture was irradiated in a domestic microwave oven for 2 min. A single bromo alcohol **15** was isolated from this one-pot reaction as well (**Scheme-I**).

Compounds eugenol (**1**), epoxide (**14**) and bromo alcohol (**15**) were tested for antimicrobial activity against *S. aureus* (ATCC 25923). The results are shown in Table-2. The minimum bactericidal concentrations for eugenol, epoxide and bromo alcohol were 230, 115 and 230 µg/mL, respectively. The minimum inhibitory concentrations were 57, 115 and 115 µg/mL, respectively. Epoxide was found to be the most effective antimicrobial agent among the three compounds tested.

TABLE-2
ANTIBACTERIAL ACTIVITY, MIC (µg/mL) AND MBC (µg/mL) OF EUGENOL, EXPOXIDE-EUGENOL AND BROMO-ALCOHOL

Compounds	Eugenol	Epoxide-eugenol	Bromo-alcohol
Minimum bactericidal concentration (MBC)	230	115	230
Minimum inhibitory concentration (MIC)	115	57	115

The higher antimicrobial activity of epoxide with respect to eugenol deserves special attention. The metabolic process of eugenol can lead to the formation of quinone methide as a result of the formation of a conjugated structure. Because of the phenolic hydroxyl group, such a quinone method intermediate is still possible even if the molecule has no alkene group. It is, however, understandable that the alkene group facilitates oxidation of the aromatic group due to extended conjugation. In contrast, a reaction of the epoxide ring with a nucleophilic reagent may proceed at a faster rate than the oxidation of the aromatic group in eugenol epoxide. In addition, the electronegativity of the oxygen atom in the epoxide ring may retard the oxidation of the aromatic system further. The epoxide may alter protein and react with phospholipids in the cell membrane much more effectively than eugenol itself due to the high reactivity of the oxygen atom into the three-membered ring. Thus, we believe that mechanistically quinine methide route (oxidation) is not a favourable process in the metabolism of the eugenol epoxide compared to a nucleophilic reaction that is possible with this particular substrate. Thus, the superior antibacterial activities of the epoxide compared to eugenol are due to a nucleophilic reaction. On this basis, it is anticipated that epoxide may also act against the COVID virus through this pathway, although the concept of multiple mechanisms is not overruled.

Quantum chemical calculations: Compounds eugenol, epoxide eugenol and cinnamaldehyde structures were optimized using the 6-31G* basis sets at the B3LYP level using Spartan 18 software. The energy minimized structures of these compounds are shown in Fig. 3. The physico-chemical and geometries properties obtained from density functional theory (DFT) calculations are presented in Table-3. These data are helpful in the identification of several parameters of these compounds and a similar series of compounds. Some quantitative differences in the values of these parameters are observed. These data analyses indicate that all these molecules follow Lipinski's rule of five. This type of information is required to advance an explanation of the bioactivity of organic molecules of similar structures.

TABLE-3
PHYSICO-CHEMICAL AND GEOMETRICAL PARAMETERS OBTAINED FROM DFT CALCULATIONS

	Eugenol	Epoxide eugenol	Cinnamaldehyde
Molecular weight (amu)	164.2	180.2	132.16
Total energy (a.u.)	-538.68	-613.89	-422.97
Dipole moment (D)	2.21	2.15	3.79
E_{HOMO} (eV)	-5.72	-5.43	-6.47
E_{LUMO} (eV)	0.08eV	0.28	-2.12
Area (Å^2)	208.63	212.17	172.21
Volume (Å^3)	184.97	189.77	152.76
PSA (Å^2)	25.72	35.63	14.7
Ovality	1.33	1.33	1.25
Log P	0.23	-1.02	1.04
Polarizability	55.01	55.42	52.74
HBD count	1	1	0
HBA count	2	3	1

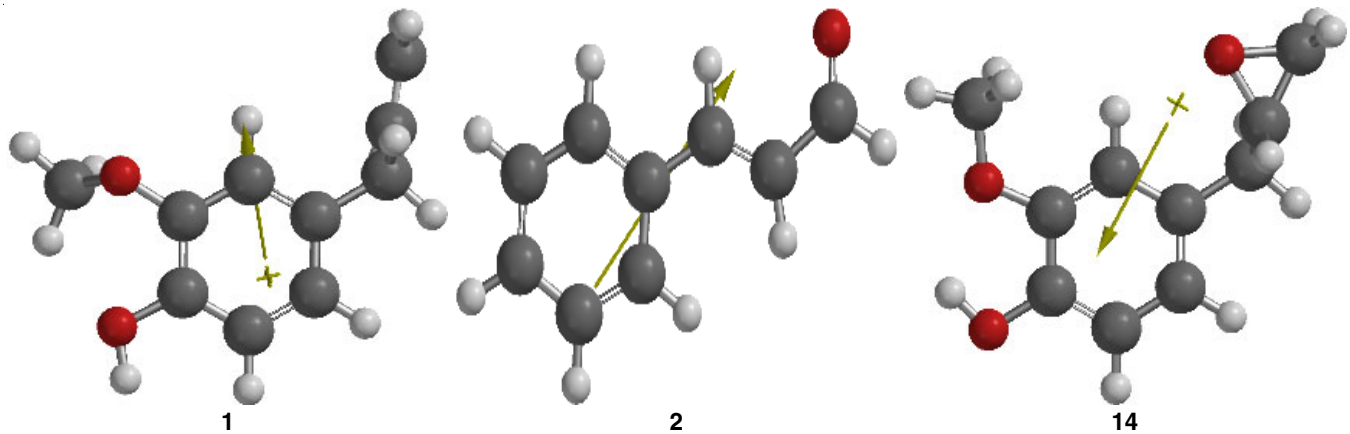


Fig. 2. Optimized geometries of the compounds eugenol (**1**), cinnamaldehyde (**2**) and epoxide-eugenol (**14**), obtained from DFT calculations

Conclusion

The antimicrobial activity of cinnamaldehyde and eugenol present in cinnamon and epoxy eugenol can also be anticipated against coronaviruses. In fact, antiviral properties (not against covid-19) of cinnamaldehyde and eugenol are reported. On the basis of results obtained, it is suggested cinnamon can be a choice in a fight against covid-19. It is important to note that unlike many common synthetic drugs, cinnamon is edible and practically there are no side effects. If cinnamon does not affect the status of covid-19, still it may help the patient because of their antibacterial nature. Most importantly, a combination of cinnamon with its epoxide may exert superior antiviral activity against coronavirus due to the synergistic effects. However, cinnamon has the potential to be transformed into many edible and non-toxic configurations, contingent upon the degree of success achieved in the experiment.

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