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Cinnamon: an immune modulator food additive to coronavirus

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Abstract

This study explores the potential role of cinnamaldehyde from cinnamon to elicit immunity against the pathogens of COVID-19. In the culture of traditional and herbal treatments, it was more valuable than gold. It has been observed that coronavirus infects cells of an organism including innate and adaptive immune cells. Cinnamaldehyde, eugenol, and other secondary metabolism of cinnamon extract, have a potential role to interact with spike protein of coronavirus. Available literature supports the suitability of cinnamon for acute respiratory infectious disease syndromes. It might be a promising source for the immune system to control viral infections like COVID-19. Preclinical and clinical trials are necessary for the safety and efficacy of the drug.

Keywords: Cinnamon; Coronavirus, COVID-19; Immunity; SARS-CoV-2.

1. Introduction

This communication is focused on the health benefits of the extracts of secondary metabolism of the compound found in cinnamon, a wonder herb for COVID-19 patients. Due to high mutation rates of SARS-CoV-2 spike protein may rise to variant of concern (VOC). Therefore, it can evade the vaccine-induced acquired immunity. Phytochemicals are considered as an effective alternative for treatment of COVID-19 infection (Chen, Wang, Wang and Wei, 2020; Jena et al., 2021; Nag et al., 2021). There are several significant risk factors for severe COVID-19 infection, such as diabetes mellitus, chronic lung disease, cardiovascular disease (CVD), obesity, and a range of other illnesses that make the patient immune compromised (Zabetakis et al., 2020; Gasmi et al., 2021). An intimate relationship exists between the immune system and the metabolic response system. The metabolic and immune systems are essential to survival (Hotamisligil, 2006). Inflammation is a flow of information in response to infection. When tissue is injured, the basic challenge for the host is to detect whether infection is present. In the event of injury and infection, a quick response is required to stop the spread of infection, even at the cost of additional tissue damage. Repairing damaged tissue caused by inflammation or that inflammation damaged is necessary (Nathan, 2002).

Our objective is to explore the potential role of cinnamon to elicit an immune response in the pathogenesis of COVID-19. For the development of this literature, an extensive database search was carried out using scientific databases like MEDLINE, BIOSIS, PubMed, EMBASE, Mendeley database, TOXLINE, and Google Scholar, Google, Google Patent. After careful examination of the literature, we consider only those literatures that fit within the scope of our target.

2. *Cinnamon* may be immunity booster agent for Covid-19 patients

Cinnamon, a tree of the Lauraceae family, grows up to the height of 10–15 meters. In our traditional culture of herbal treatment, it was more valuable than gold, commonly used in kitchens. There is suitable evidence that confirmed that cinnamon was used in the treatment of influenza and several related diseases (Ross 1906). Phytochemicals study of cinnamon identified 2- propenal, 3-phenyl (trans-cinnamaldehyde-87.013%), and Eugenol (9.317%), as major compounds. While other important phytochemicals are identified as Tricyclo [3.3.1.0 (2,8)] nona-3,6- dien-9-on (0.173%), O-Methoxy cinnamic aldehyde (0.236%), α-muurolene

(0.133%), Naphthalene, 1,2,3,4-tetrahydro-1,6-dime (0.195%) (Adinew, 2014). SARS-CoV-2 infection is associated with respiratory disease, and being a new strain, the pathogenesis of disease causation is not fully known. The interlocking of spike (S) glycoprotein with angiotensin-converting enzyme 2 (ACE2) receptor is the only donor to enter in the cells. Coronavirus infects all cells of an organism including inherent and adaptive immune cells. Coronavirus mostly affects the alveolar epithelial cells of the lungs and enterocytes of the small intestine in the initial phase (Singh et al., 2020). Infected cells release cytokines that initiate protective immunity against SARS-CoV-2. Macrophages (B lymphocytes and T lymphocytes) are immune cells that recognize viruses. Interleukin (IL2 and IL6), interferon (IFN), and tumor necrosis factor-α (TNF-α) play a critical role in Covid-19 inflammation, modulating the immune response and causing acute respiratory distress syndrome (ARDS), and multiorgan failure. Researchers confirmed that respiratory virus infection damages free radicals (Vallyathan and Shi, 1997).

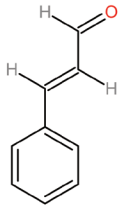
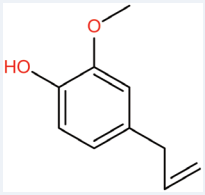
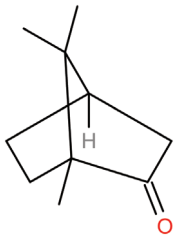
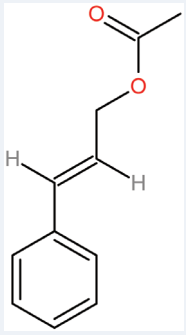
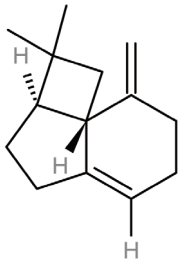
The innate immune system acts as the first line of defence, while the adaptive immune system destroys foreign pathogens like viruses, bacteria, or unwanted particles. The main organs affected by Covid 19 infection are the lungs due to collapse of alveoli, diffuse alveolar damage, destruction of alveolar epithelial cells, and formation of hyaline membranes (Carsana et al., 2020 ; Thimmulappa et al., 2021). In moderate patients, recovery depends only on the development of antibodies and the activation of the immune response (Thimmulappa et al., 2021). An antibody is a Y-shaped protein that binds to the spike (S) protein of the coronavirus and acts as a messenger for the adaptive immune system (Chen et al., 2021). It is necessary to understand how the Coronavirus infects our respiratory tract and transforms into a number of cells. As the Coronavirus invades the respiratory section of the body, its spike (S) protein couples to the receptor of angiotensin-converting enzyme 2 (ACE2-enzyme) on the alveolar cell membrane and transfers its RNA into the host cells. Due to massive viral load and the mRNA of SARS-CoV-2 combined with other cells and respiratory tract infection, the cells defused. In response to SARS-CoV-2, the immune system triggers several immune responses such as interferon (IFN)-γ, Interferon gamma-inducible protein (IP-10), monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β (Esmaeilzadeh and Elahi, 2021). Virus pathogens activate the innate immune system. Adaptive immunity plays a crucial role in viral infections. The most effective adaptive immune systems are B cells (the source of antibodies, CD4+ T cells, and CD8+ T cells) (Sette and Crotty, 2021). As a result of the innate immune response, the body's secondary or acquired immune system develops antibodies to attach to the spike-protein and neutralize the virus. Macrophages, a segment of the immune system, damage the virus cells in bulk (Kasuga et al., 2021). Functional foods increase NK cell activity, regulate cytokines specific to Th17 (RORc, IL-17A), and Th2 (IL-5, IL-13, and IL-6) immune responses, suppress IL-6, IL-1β, RORc, IL-17A, TNF-α secretion, and add to IL-10, INF-γ secretion. The research confirmed the role of food additives as immune-modulators and immune-boosters in inflammation (Gautam et al., 2020; Han et al., 2021). In a recent study on immune response, it was demonstrated that IL-6 receptors play a significant role in the trans-signaling treatment of COVID-19 cytokine storm syndrome (Chen et al., 2020). To revive the patient's health, the only prospective therapy is immune response activation against SARS-CoV-2. SARS-CoV-2 infection can be overcome by intracellular signaling pathways that modulate host immunity, and this is an area of great interest for drug development (Catanzaro et al., 2020). "Cytokine storm" in host defence is a result of excessive immune responses caused by SARS-CoV-2. Overload of free radicals is known as oxidative stress, developing chronic and degenerative diseases. This can only be rectified by antioxidants, which are produced naturally in the body or through food supplements (Pham-Huy et al, 2008; Rao and Gan, 2014). Nitric oxide (NO), plays a dominant role in both the cardiopulmonary and immune defence systems (Fang et al., 2021). Trans-cinnamaldehyde (TCA) suppresses the production of NO, modulates the expression of iNOS, IL-1β, and induces NF-κB inactivation (Fu et al., 2017; Lucas et al 2021). Cinnamaldehyde is a standard chemical allergen, which increases the histamine release, and cell-mediated Immunity (Badger-Emeka et al., 2020). The details of important phytocompounds and their interaction with coronavirus and immunity is mentioned in Table 1.

The cytokine profiles observed in covid-19 patients are activation of macrophages with high production of IL-6, IL-7, TNF and inflammatory chemokines like CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 10 (CXCL10). This observation confirms the dysregulation of mononuclear phagocyte contribution in hyper inflammation (Merad and Martin, 2020, Tay et al., 2020).

Trans-cinnamaldehyde (TCA), a principal constituent in cinnamon, has the potential to reduce the maturation of influenza A/PR/8 virus in bronchoalveolar lavage fluid. These findings support the suitability of the empirical indication of Cinnamomi cortex-containing herbal formulations for acute respiratory infectious diseases (Hayashi et al., 2007). Phenolic compounds of Cinnamomum zeylanicum like caffeic acid (IC50 = 84%) and cinnamic acid (IC50 = 53%) had the most enzyme inhibition potential. Angiotensin-converting enzyme (ACE2) and type 2 transmembrane serine protease (TMPRSS2) are the target cell contributors in SARS-CoV-2 infection (Shahwar et al., 2012; Amawi et al., 2020; Prasanth et al., 2020). The water extract of cinnamon (CWE) substantially reduced the secretion of TNF-α and IL-6 and induced macrophages, and a substantial decrease in its mRNA expression was observed (Kunnumakkara et al., 2021). Another study confirms the moderate effects of butanol fraction (containing procyanidin A2 and procyanidin B1) on Cinnamomi Cortex (CC/Fr. 2) on antiviral activity against HIV/SARS-CoV S pseudo virus infections (Zhuang et al., 2009). Researchers have noted that procyanidin type A compound (IND02) derived from cinnamon has the potential to inhibit SARS-CoV-2 at the early phase of viral infection, because of its propinquity toward ACE2 receptor and binding glycans on the spike protein of SARS-CoV2 (Ghosh, 2020). Free radical induced immunosuppression contributes to the pathogenesis of viral infection and expansion of viral pathogens. Cinnamaldehyde possesses anti-inflammatory properties. It is perceived that cinnamaldehyde suppressed NF-κB activation and inhibits the TNF-α-induced inflammation. It also suppresses hyper-expression of Toll-like receptors (TLRs) and cytosolic sensor NOD-like receptors (NLRs), PYD domain-containing protein 3 (NLRP3) inflammasome signalling pathways (Liao et al., 2008; Lee et al., 2018). Cinnamaldehyde modulates the production of prostaglandins (PGEs) by reducing IL-1β-induced COX-2 activity (Guo et al., 2006). Scientific evidence confirms that cinnamon is a potential anti-inflammatory, antioxidant functional food and could be useful in mitigation of SARS-CoV-2 induced hyper inflammation. There is an increasing demand among covid-19 patients towards the consumption of cinnamon powder as preventive functional food against SARS-CoV-2 in the developing and developed world including India.

Another important phytocompound is eugenol, which has good oral bioavailability, seen as a promising agent for the development of drugs to treat SARS-CoV-2 infection (Tallei et al., 2020). The anti-hepatitis-c antibody activity of eugenol against HSV-1(F) and HSV was strong (Tragoolpua and Jatisatienr, 2007). Combina-

Table 1. Important phytocompounds of cinnamon and their interaction with coronavirus and immune system

Phytocompounds	Chemical Formula	Molecular weight	Chemical Structure	Interaction with Coronavirus	Immune response
Cinnamaldehyde	C9H8O	132.16		Spike Protein	TLR2 and TLR4 activation, NRF2 inducer, detoxify ROS/RNS, mitigate PI3K/Akt pathway
Eugenol	C10H12O2	164.20		Spike protein	Modulates NF-kB, IL-6, IL-1β and TNFα
Camphor	C10H16O	152.23		Mpro of COVID-19 (Omar et al., 2020)	modulation of Nrf-2 and TLR4 (Salama et al., 2021)
Trans-cinnamyl acetate	C11H12O2	176.21		Binding with GLU471, ARG454, SER46 (Kulkarni et al., 2020)	inhibits the activity of NF-κB and the production of tumor necrosis factor alpha (TNFα-) induced interleukin-8 (IL-8) (Cabello et al., 2009)
Caryophyllene	C15H24	204.35		interactions with PHE 294. 3CLpro , NSP3, NSP9, and RDRP (Narkhede et al., 2020)	B cells, T cells, CD8+ lymphocytes, CD4+ lymphocytes, NK cells, neutrophils, macrophages, basophils, eosinophils, platelets, mast cells, dendritic cells, microglia, and astrocytes (Howlett and Abood, 2017; Jha et al., 2021)

tion of eugenol and acyclovir supported the inhibited herpes virus replication *in vitro*. It has been studied that eugenol delays the growth of herpes virus induced keratitis (Benencia and Courreges, 2000). Recent study observed that eugenol interlinked with spike (S1) protein of SARS-CoV-2 and strongly suppressed the entry of pseudo-type SARS-CoV-2 into human ACE2- expressing HEK293 cells. They also noticed that eugenol modulates NF-kB, IL-6, IL-1β and TNFα in human A549 lung cells (Paidi et al., 2021). Inhibiting the main 3-chymotrypsin-like protease (3CLpro), also called Nsp5 (non-structural protein 5) is the fundamental strategy for coronavirus. (Rizzuti et al., 2021), reported that eugenol inhibits the enzymatic activity of 3CLpro.

Camphor has an excellent bond against protease of SARS-CoV-2 and ACE2 receptors (Omar et al., 2020). Camphor is a solid bicyclic organic compound derived from the cinnamon tree. Camphor improves catalase and Nrf-2 activities, and reduces NO, TNF-α, TLR4 serum levels in the covid-19 infections (Salama et al., 2021). In the traditional system of medicine, camphor was

applied to the neck and chest skin for cough problems. It is also used as steam inhalation in the form of aerosol to prevent coughing (Pappas and Hendley, 2011; Eccles, 1994). Reddy et al., (2004), demonstrated the inhibition of NFkB by the cinnamon ingredients in human macrophages. A study examining the cinnamyl acetate suppression of NFκB inflammatory signaling in endothelial cells has confirmed the suppression of TNFα-induced p65 translocation (Liao et al., 2008). Another study concluded that dietary administration of cinnamyl acetate inhibited NF-κB activation through the ERK and p38 MAPK pathways in the mouse (Kim et al., 2007). Papain-Like cysteine protease (PLpro, NSP3) is required for coronavirus replication and a promising agent for antiviral drugs (Rut et al., 2020). These phytocompounds substantially act on viral main protease of SARS-CoV-2. On the basis of available literature, cinnamon inhibits the main protease of covid-19 and can be a potential drug candidate as an immunity booster.

3. Conclusion

Plenty of scientific literature confirms the antiviral and immunomodulatory potential of cinnamon extracts for influenza. Cinnamaldehyde and eugenol are effective antiviral agents and interact with spike protein of coronavirus. Cinnamon might be a promising source for the immune system to control viral infections like SARS-CoV-2. Functional food and food additives have the potential to elicit immunity against covid-19 infection and post-covid-19 care. Further preclinical and clinical trials are necessary to evaluate the efficacy level of major constituents of cinnamon extract as antiviral drugs.

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Conflict of interest

The authors confirm that this article's content has no conflicts of interest.

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