Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Cinnamon and its possible impact on COVID-19: The viewpoint of traditional and conventional medicine

Maryam Yakhchali a,*, Zahra Taghipour a, Mehran Mirabzadeh Ardakani a, Mahdi Alizadeh Vaghasloo b, Mahdi Vazirian c, Sima Sadrai d

a Traditional Pharmacy Department, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
b Traditional Medicine Department, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
c Pharmacognosy Department, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
d Pharmaceutics Department, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Cinnamomum verum
Cinnamon
COVID-19
Obstruction
Opener
Traditional Persian Medicine (TPM)

ABSTRACT

The COVID-19 global epidemic caused by coronavirus has affected the health and other aspects of life for more than one year. Despite the current pharmacotherapies, there is still no specific treatment, and studies are in progress to find a proper therapy with high efficacy and low side effects. In this way, Traditional Persian Medicine (TPM), due to its holistic view, can provide recommendations for the prevention and treatment of new diseases such as COVID-19. The muco-obstruction of the airway, which occurs in SARS-CoV-2, has similar features in TPM textbooks that can lead us to new treatment approaches. Based on TPM and pharmacological studies, Cinnamomum verum (Darchini)’s potential effective functions can contribute to SARS-CoV-2 infection treatment and has been known to be effective in corona disease in Public beliefs. From the viewpoint of TPM theories, Cinnamon can be effective in SARS-CoV-2 improvement and treatment through its anti-obstructive, diuretic, tonic and antidiote effects. In addition, there is pharmacological evidence on anti-viral, anti-inflammatory, antioxidant, organo-protective and anti-depression effects of Cinnamon that are in line with the therapeutic functions mentioned in TPM. Overall, Cinnamon and its ingredients can be recommended for SARS-CoV-2 management due to multi-targeting therapies. This review provides basic information for future studies on this drug’s effectiveness in preventing and treating COVID-19 and similar diseases.

1. Introduction

The global epidemic of Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), a member of the beta coronaviruses family, has affected the world’s physical and mental health, social relations, and economy [1]. The virus enters into type 2 alveolar epithelial cells of the lower respiratory tract by binding virus S glycoprotein to the cell membrane receptor Angiotensin-converting enzyme 2 (ACE2). The entry is followed by replication of the virus in the cell and virus release. The innate immune

Abbreviations: ACE2, Angiotensin-converting enzyme 2; IL, Interleukin; TNF-α, tumor necrosis factor-α; TPM, Traditional Persian Medicine; COPD, Chronic obstructive pulmonary disease; COVID-19; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; ARDS, acute respiratory distress syndrome; TMPRSS2, transmembrane serine protease 2; TLRs, Toll-like receptors; TCA, Trans-cinnamaldehyde; LPS, Lipopolysaccharides; ERK, extracellular signal-regulated kinases; p38 MAPK, p38 mitogen-activated protein kinases; JNK, Jun N-terminal kinases; ROS, Reactive oxygen species; BHT, butylated hydroxytoluene; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; EEC, Ethanolic extract of Cinnamon; QR, quinone reductase; GSH, Glutathione; γ-GCS, gamma-glutamylcysteine synthetase; TAPP, Type-A procyanidine polyphenols; BAL, bronchoalveolar lavage; MDA, malondialdehyde; CK-MB, creatine kinase-MB; LDH, Lactate Dehydrogenase; BUN, Blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AT1, acute tubule injury; PCNA, proliferating cell nuclear antigen; PCB2, procyanidin-B2; PKC-a, protein kinase C-a; MCP-1, Monocyte chemoattractant protein-1; VCAM-1, vascular cell adhesion molecule-1; TBARS, thiobarbituric acid reactive substances; POC, protein carbonyl; INOS, nitric oxide synthase; NAFLD, Non-alcoholic fatty liver disease; HOMA, Homeostatic Model Assessment; FBS, fasting blood glucose; TC, Total Cholesterol; TG, Triglycerides; LDL, low-density lipoprotein; GGT, gamma glutamine transpeptidase; IFN-γ, interferon-γ; BCP, β-Caryophyllene; COX-2, cyclooxygenase-2; ICU, intensive care unit.

* Correspondence to: Traditional Pharmacy Department, School of Persian Medicine, Tehran University of Medical Sciences, Giti Alley, Vafamanesh St., Heravi Sq, Tehran 141793584, Iran.

E-mail address: yakhchali_maryam@yahoo.com (M. Yakhchali).

https://doi.org/10.1016/j.biopharma.2021.112221
Received 2 July 2021; Received in revised form 14 September 2021; Accepted 16 September 2021
Available online 21 September 2021
0753-3322/© 2021 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license
system responds to the infection, and a cytokine storm happens. Innate and adaptive immune responses result in the release of significant amounts of inflammatory cytokines, including interleukins-1β (IL-1β), 2 (IL-2), 6 (IL-6), 8 (IL-8), tumor necrosis factor-α (TNF-α), etc. [2,3]. Fever, dry cough, dyspnea, fatigue, nausea/vomiting or diarrhea [4], olfactory and/or gustatory dysfunctions [5] are the most common symptoms in patients. Excessive sputum is also produced in the patients [6]. Currently, the main treatment strategy is to use a combination of anti-viral drugs (such as Remdesivir), modulate the inflammatory response (such as Steroids), and supportive cares to control COVID-19. But still, there is no certain treatment, and studies are in progress to find a proper therapy with high efficacy and low side effects [7].

Due to the high cost and time consuming of new drugs discovery and the severity of this pandemic, the suggestion of simple, effective and accessible remedies to reduce the progression of the disease is valuable. It may have a significant impact on the control of the COVID-19 pandemic. Traditional medicines are reputable sources for the development of drugs against new diseases. It seems reasonable to pay attention to Traditional medicines and medicinal plants with prolonged use and beneficial effects [8,9]. Traditional Persian Medicine (TPM), due to its holistic view, along with other medical schools, can provide recommendations in the prevention and treatment of new diseases such as the COVID-19 pandemic [10–12]. Although this epidemic occurred in the 21st century, there are similarities between the manifestations of the corona disease and the pathological conditions described in Traditional Persian Medicine as obstruction. Several medicinal plants have been presented as anti-obstructive drugs in TPM textbooks. Combination of herbal medicine with modern medicine has represented the effectiveness of herbal medicine in COVID-19 management [13].

In public beliefs, Cinnamon (Darchini) has been known to be effective in corona disease as it is considered effective in traditional medicine for lung diseases [14,15]. This study aims to review and introduce Cinnamon which TPM mentions as an effective drug in lung obstruction similar to COVID-19 and present recent evidence on its various efficacies.

**Cinnamomum verum** J.Presl (Syn. Cinnamomum zeylanicum Blume), a popular universal spice belonging to the Lauraceae family, is commonly known as true Cinnamon, Ceylon cinnamon, and Darchini. Cinnamaldehyde, linalool, β-caryophyllene, and eugenol are the main components of Cinnamon and its essential oil. In addition, Methyl cinnamate, Cinnamyl acetate, and procyanidin-A are other important ingredients of Cinnamon [16]. Cinnamon is a valuable potent medicinal plant with several pharmacological activities including anti-inflammatory [17], antioxidant, and anti-proliferative [18], antibacterial [18,19], antifungal [20,21], antiviral [22], antioxidant [23], anti-hyperglycemia and anti-hyperlipidemic [24], antihypertensive [25], and Anti-Atherosclerotic [26] effects.

In this review, the potential effective functions of **Cinnamomum verum** from the viewpoint of TPM and its examined pharmacological effects contributed to SARS-CoV-2 infection treatment are presented. In this regard, valuable sources of Traditional Persian Medicine including “al-Havi fi al-Tibb” (Rhazes), “al-Qanun fi al-Tibb” (Avicenna), “al-Shamil fi al-Sana’a al-Tebbiya” (Ibn Nafis Qarashi), and “Makhzan-al-Adviah” (Aghili Khorasani) were used to investigate the effects of Darchini. The PubMed, Scopus, and Web of Science databases were also used to analyze clinical evidence on the anti-viral and anti-inflammatory effects of the Cinnamon. Research methodology is presented in Fig. 1.

### 2. Potential effects of Cinnamon in TPM against COVID-19

Accumulation of inflammatory cells leads to obstruction of respiratory tracts in asthma, chronic obstructive pulmonary disease (COPD), and COVID-19 [27]. In addition, increasing IL-1β and TNF-α in COVID-19 induce hyper mucin secretion. Studies reveal that genes, which involved in hyper mucin production and enhancing mucin viscosity, are upregulated in these patients. Also, SARS-CoV-2 infection results in ciliary structure and function disruption, leading to impairment in mucus excitation. Mucin hypersecretion and ciliary dysfunction can cause dysfunctional mucus gel accumulation in the respiratory tract. Elimination and removing these altered mucin macromolecules is
difficult, which would lead to acute lung injury and acute respiratory distress syndrome (ARDS) [28].

The muco-obstructive airway disease, which occurs in SARS-CoV-2, has similar features to “Sodde” or obstruction described in Traditional Persian Medicine. “Sodde” is the obstruction of the body’s ducts and vessels due to the accumulation of materials inside them, which prevents the movement of what should move in them. Based on the TPM humoral theory, imbalance in the quality and quantity of four natural humor (blood, phlegm, bile, and melancholy) can lead to different diseases. The most important cause of obstruction is the accumulation of abnormal thick “Ghalat” or viscose “Lazej” humor, which may occur in all parts of the body, including the lungs [29]. Accumulation of thick and viscous materials in the lungs causes obstruction and other complications, including cough and dyspnea [30]. Generally, to remove abnormal materials from the body, the physical properties of abnormal humor must be changed from a pathologic condition to optimum rheology. Therefore, the thick material must be diluted, and the viscous material must be separated into pieces [31]. In this way, the accumulated materials are easily removed, and the tract is opened. In the scientific language of TPM, these kinds of drugs that are used to move and eliminate the obstructing materials are named “Mofatethe” or opener [32,33]. Removing the macromolecular mucins at the early stages of the disease is essential and valuable in its treatment [28]. In this regard, Consumption of “Mofatethe” or opener drugs can be an approach for combatting COVID-19.

Cinnamon (Darchini), a well-known and valuable plant in TPM with hot and dry nature, as a potent anti-obstructive/opener drug, is effective in lung obstruction [15]. The essence of Darchini shows that it must be very thin, and therefore its effects should be powerful [15,33,34]. In TPM, “Latif”, or thin material, is defined as a substance that, after entering into the body, divides into small pieces and penetrates quickly in all parts of the body [35]. The taste of Cinnamon is a combination of spicy, astringent, sweet, umami, and bitter, which resemble its components outward to open the tracts. Therefore, they dilute and evaporate the thick humor by their dissolving effect or “Taghi” and divide the viscous humor from the attached surface into smaller pieces by its cutting effect or “Taghi” [32,33].

Different functions are attributed to the Darchini in TPM, and it has many benefits on various organs and various diseases. Table 1 represents the main functions of this medicine as an opener, diuretic, desiccant, and antidote in four primary textbooks of TPM written by four eminent scientists.

Cinnamon has a high penetration property into the chest, so it attenuates the material inside the chest, especially thick phlegm, cuts and clears it from the place it is attached to. In this way, it prepares the material for exit and opens the lung ducts [15,32]. Therefore, it cleans and warms the chest and lungs, facilitates the breath, opening its ducts, beneficial to asthma, shortness of breath, and cough, especially chronic cold ones. It is also helpful in fever and chills [15,32,33]. It can be said that due to cutting the thick and viscous phlegm, Darchini has mucolytic activity on pulmonary mucus. Mucolytic drugs reduce mucus viscosity by cutting disulfide bonds of gel mucins [37].

Since Cinnamon is a strong opener, it can also be a great diuretic. It heats the kidneys and softens the thick materials in them. It cleans the kidneys and relieves their pain [15]. Cinnamon can also open the obstruction of the liver, spleen, and gallbladder due to its great thin nature, enabling it to penetrate these organs. From TPM’s point of view, Cinnamon warms the stomach and liver, strengthens them for digestion, dries up the extra moisture from the stomach, attenuates and cuts phlegm, cleans it from waste materials, and digests thick foods [15,33,34]. Along with paying attention to respiratory and other complications in patients with pneumonia and respiratory failure in ICU, improving the gastrointestinal tract function is of great importance and useful in treatment [38].

Darchini prevents humor from infection and modifies infectious humor by drying excess moisture. In addition, it is a tonic drug for almost all organs, including the heart, liver, and stomach. It prevents pathogens entry into organs by its astringent effect and moderating organs’ properties, making them less prone to damage. Due to its strong aroma, Cinnamon is an exhilarating drug and causes happiness in the heart [15,32,33]. Iranian traditional medicine researchers have suggested that “Moghavvi” or tonic drugs mentioned in TPM can effectively manage the disease and protect main organs from SARS-CoV-2 damage [9].

3. Potential pharmacological effects of Cinnamon against COVID-19

3.1. Anti-viral effects

The pharmacological evidence of the anti-viral effects of Cinnamomum verum is summarized in Table 2. Cinnamon ingredients similar to curcumin can be effective on various proteins contributing to the virus proliferation process [44]. A molecular docking analysis on key protein targets of SARS-CoV-2 predicts interaction of C. zeylanicum essential oil components (eugenol, linalool, (E)-cinnamaldehyde, (E)-cinnamyl acetate, β-caryophyllene, eugenyl acetate, benzyl benzoate) with the virus targets in the body. Although the interactions were relatively weak, they may have synergistic effects inhibiting the coronavirus [45]. In silico analysis of 48 phytochemicals from different Cinnamon species showed that Tenfoilin and Pavetannin C1 had a higher binding affinity to the SARS-Cov-2 main protease enzyme and spike protein [46]. Ranjini et al. determined Angiotensin-converting enzyme inhibition by C. zeylanicum methanolic extract in sheep kidney, lung, and testis. Reducing ACE activity was almost near the standard drug (captopril) in the kidney [47]. Phenolic compounds, caffeic acid, cinnamic acid, gallic acid, and eugenol extracted from Cinnamomum zeylanicum exhibited an inhibitory effect of trypsin (a serine protease). Caffeic acid (IC50 = 84%) and cinnamic acid (IC50 = 53%) had the most enzyme inhibition potential [48]. Angiotensin-converting enzyme (ACE2) and type 2 transmembrane serine protease (TMPRSS2) are expressed in target cells participant in SARS-CoV-2 infection [49]. These findings (Fig. 2) may lead us to suggest Cinnamon as an anti-viral medicine for treating SARS-CoV-2 and similar diseases along with other drugs.

Table 1
main functions of cinnamon with promising beneficial effects in managing COVID-19.

| Textbook / Author | Mofatethe | Molattef | Mohallel | Moghatte | Juli | Monej | Moghavvi | Moder | Mofajefef | Monaghi | Mofarreh | Mosakhen | Teryagh |
|-------------------|-----------|---------|----------|----------|-----|------|---------|-------|---------|--------|--------|---------|--------|
| al-Havi           | +         | −       | −        | +        | +   | −    | +       | +     | −       | +      | −      | +       | +      |
| al-Qanun          | −         | +       | −        | +        | +   | +    | +       | −     | +       | +      | +      | +       | +      |
| al-Shamili        | +         | +       | +        | +        | +   | +    | +       | +     | +       | +      | +      | −       | +      |
| Mohzakh al-Adviah | +         | +       | +        | +        | +   | +    | +       | +     | +       | +      | +      | −       | +      |

Mofatethe (opener), Molattef (Attenuant), Mohallel (Dissolver), Moghatte (Cutting agent), Juli (Detersive), Monej (Maturative), Moghavvi (Tonic), Moder (Diuretic), Mofajefef (Desiccant), Monaghi (Abstergent), Mofarreh (Exhilarator), Teryagh (Antidote)
3.2. Anti-inflammatory effects

Inflammation plays a key role in the occurrence of complications and organ damages of the coronavirus. Even common coronary symptoms such as fever, fatigue, and diarrhea can be caused by elevated cytokines. Studies show that Cinnamon and its phytochemicals, including cinnamaldehyde, eugenol, cinnamic acid, and polyphenol fractions, have anti-inflammatory effects, reducing the expression of TNF-α, IL-1β, IL-6, and other cytokines in different ways significantly (Table 3). Cinnamon ethanolic extract shows an anti-inflammatory effect via interruption of toll-like receptors (TLR2 and TLR4) signaling pathways. It reduces proinflammatory cytokine production and inhibits NF-κB/AP-1 signaling, an essential step in the inflammation process. Trans-cinnamaldehyde (TCA) and p-cymene are active compounds that

Table 2
Pharmacological studies on antiviral effects of cinnamon.

| No | Extract /Main component | Part used | Model | Design | Dosage/Duration of treatment | Mechanism/outcome | Ref. |
|----|-------------------------|-----------|-------|--------|------------------------------|-------------------|------|
| 1  | water extract /cinnezeylanine | bark | in vitro and in vivo | By Vero cells and silkworm infection model | 0.5 m/ Once | Cinnzeylanine inhibits the proliferation of herpes simplex virus type 1 | [22] |
| 2  | NM | bark | in vitro | ? | – | 1. Pepsin enzymatic activity was inhibited. 2. The activity of HIV protease was also inhibited. | [39] |
| 3  | Type-A procyanidin polyphenol (IND02) | bark | in vitro | HIV-1 primary patient isolates | – | 1. HIV-1 Replication was blocked. 2. HIV-1 was inhibited, and T cell exhaustion markers, Tim-3, and PD-1 were down-modulated. | [40] |
| 4  | procyanidin type A (IND02) | NM | in vitro | Cell culture-derived HCV | – | 1. No effect on HCV replication 2. blockade of HCV entry, dose-dependently, occurring at a post binding step 3. Inhibiting HCV entry demonstrates the functional impact in the most physiological cell-based system for studying HCV-host interactions. | [41] |
| 5  | hydroalcoholic extract | wood | in vitro | HSV-1 | – | 1. Attachment of HSV-1 onto host cells was inhibited. 2. The viral titer of herpes simplex type 1 was reduced before, during, and after inoculation of herpes virus | [42] |
| 6  | essential oil | Bark and leaf | in vitro | cytopathic effect reduction method for anti-influenza (A/WS/33 virus) activity | – | No significant effect on influenza A/WS/33 virus activity | [43] |

NM: not mentioned, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HSV: hepatitis simplex virus, Tim-3: T cell immunoglobulin mucin domain 3, PD-1: programmed death-1

Fig. 2. Cinnamon ingredients inhibit virus proliferation through targeting essential proteins including SARS-CoV-2 spike protein (SARS-CoV-2 Spro), human angiotensin-converting enzyme (hACE2), SARS-CoV-2 main protease (SARS-CoV-2 Mpro), SARS-CoV-2 endoribonuclease (SARS-CoV-2 Nsp15), SARS-CoV-2 ADP-ribose-1’-phosphatase (SARS-CoV-2 ADRP), SARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp).
### Table 3
Pharmacological studies on anti-inflammation effects of cinnamon.

| No | Extract / Main component | Part used | Model | Design | Dosage/ duration of treatment | Mechanism/outcome | Ref |
|----|--------------------------|-----------|-------|--------|-------------------------------|-------------------|-----|
| 1  | Ethanolic and water extracts / E-cinnamaldehyde and o-methoxy cinnamaldehyde | bark | In vitro | LPS and IFN-γ activated RAW 264.7 macrophages | – | 1. LPS + IFN-γ induced NO, and TNF-α production was inhibited.  
2. Potency activity in regards to inhibition of TNF-α production was observed.  
3. Most of the inflammatory activity of cinnamon was caused by E-cinnamaldehyde and o-methoxy cinnamaldehyde. | [17] |
| 2  | polyphenol fraction | bark | In vivo/ in vitro | Male Wistar rats or Swiss albino mice/ ConA-stimulated lymphocytes | 50, 100, and 200 mg/kg/10 days | 1. Serum TNF-α concentration was reduced.  
2. Cytokines (IL-2, IL-4, and IFN-γ) release was inhibited.  
3. Prostaglandin was inhibited. | [51] |
| 3  | Polyphenol Extract | – | In vitro | Mouse 3T3-L1 preadipocytes | – | 1. TTP mRNA was induced  
2. VEGF mRNA was reduced  
3. The expression of multiple genes in adipocytes was regulated. | [52] |
| 4  | type-A procyanidin polyphenols | bark | In vivo | Adult male Wistar rats | 10, 30 and 100 mg/kg/7 days | The inflammatory cell infiltration was reduced in lung tissue. | [53] |
| 5  | type-A procyanidin polyphenols | bark | In vivo | Carrageenan-induced rat paw edema in Wistar rats | 4, 8 and 25 mg/kg/Single dose | 1. Serum C-reactive protein level was reduced.  
2. Serum turbidity was reduced.  
3. Anti-inflammatory and anti-arthritis effects in animal models without ulcerogenicity potential was exerted. | [54] |
| 6  | polyphenolic fraction | bark | In vivo | normal and cyclophosphamide-induced immune-compromised mice | 10, 25, and 50 mg/kg p.o./7 days | 1. Effect on body weights, HA titer, DTH responses, resident peritoneal macrophages, phagocytic activity, and resistance to E. coli induced abdominal sepsis was exerted.  
2. Immunomodulatory activity on multiple arms of immunity was exerted. | [55] |
| 7  | cinnamaldehyde | bark | In vitro | RBL-2H3 cells and human mast cells isolated from intestinal tissue | – | 1. Degranulation and mRNA expression was inhibited.  
2. Mediator release was reduced.  
3. Cytokine expression was reduced, but not the expression of proteases.  
4. Activation of ERK and PLCγ1 was inhibited.  
5. No apoptotic effect was observed.  
6. Release and expression of pro-inflammatory mast cell mediators were decreased. | [56] |
| 8  | hydroalcoholic extract/ type-A procyanidins polyphenols | bark | In vivo | in ovalbumin-induced experimental allergic rhinitis in BALB/c mice | 3, 10 and 20 μg/kg in nostril/ twice daily for 8 days | 1. The attachment of THP-1 cells or neutrophils to TNF-α-activated HUVECs or E-selectin/ICAM-1 was reduced.  
2. Anti-allergic efficacy in an animal model of allergic rhinitis was observed. | [57] |
| 9  | alcohol extract/ pentameric procyanidin type A polyphenol polymer (IND0) | bark | In vitro | Human leukemia monotypic THP-1 cells | – | 1. The binding of E-, L- and P-selectins with sialylated molecules was reduced.  
2. Interacting with sialosides and blocking the binding of selectins and leukocytes with sialic acids were observed. | [58] |
| 10 | Type-A procyanidin polyphenols | Bark | In vitro | isolated rat peritoneal mast cells | – | 1. The number of degranulated cells and levels of markers (histamine, β-HEX, and IL-4) was decreased in a dose-dependent manner.  
2. Mast cell was stabilized, and the allergic markers such as histamine, IL-4, and β-HEX in an IgE-mediated manner were inhibited. | [59] |
| 11 | ethyl alcohol and methyl alcohol extracts | bark | In vitro | collagen-induced arthritic BALB/c mice | 1,2 and 4 mg/Kg body weight/2 weeks | 1. Swelling in the spleen was reduced along with the generation of free radicals by lymphocytes.  
2. Nfatc3, TNF-a, Cai1, and mCalpain, all proteins involved in RA was inhibited. | [60] |
| 12 | essential oil blends | NM | In vitro | validated human cell cultures | – | 1. Effects on the levels of protein biomarkers that are critically involved in inflammation, immune modulation, and tissue remodeling processes were exhibited.  
2. Signaling pathways such as mitotic roles of the polo-like kinase canonical pathway were affected.  
3. The role of CHK proteins in the cell cycle checkpoint control pathway related to inflammation function was affected.  
4. BRCA1 was downregulated. | [61] |


| No | Extract /Main component | Part used | Model design | Dosage/ duration of treatment | Mechanism/outcome | Ref |
|----|--------------------------|-----------|--------------|-----------------------------|-------------------|-----|
| 13 | Essential Oil bark       | In vitro  | human dermal fibroblast system, a model of chronic inflammation and fibrosis | –                      | 5. Anti-inflammatory and immune-modulating properties were observed due to the inhibitory effect on protein biomarkers. | [62] |
| 14 | aqueous-alcoholic extraction/ polyphenol extract | NM In vivo | Hepatic transcription factors expressions including SREBP-1c and LXRx in rats fed a high-fat diet | 100 mg/kg body weight/ 12 weeks | 1. Bodyweight, visceral fat, liver weight, serum glucose, insulin concentrations, liver antioxidant enzymes, and lipid profile were decreased. 2. Reduction of serum and liver MDA 3. The hepatic SREBP-1c, LXR-α, ACLY, FAS, and NF-κB p65 expressions were suppressed 4. The PPARα, IRS-1, Nrf2, and HO-1 expressions were enhanced. 5. The reduction of hyperlipidemia, inflammation, and oxidative stress through activating transcription factors and antioxidant defense signaling pathways was reduced. | [63] |
| 15 | Ethanolic extracts bark   | In vitro  | THP-1 monocytes and HeLa- TLR4 transfected reporter cells | –                      | 1. TLR4 and TLR2 signaling pathways were mitigated. 2. NF-κB translocation was inhibited. 3. The highest anti-inflammatory potential, up to complete inhibition of pro-inflammatory cytokine production, was observed. | [64] |
| 16 | 70% aqueous ethanolic extract | bark In vitro | toll-like receptors TLR2 and TLR4 | –                      | 1. The phosphorylation of Akt and IκBα was mitigated. 2. The LPS-dependent IL-8 secretion in THP-1 monocytes was reduced dose-dependently. 3. Any toxic effects were excluded due to the High viability of the cells. | [65] |
| 17 | essential oil bark        | In vivo   | Acute pneumonitis mouse model | 6 oil drops (0.15 mL)/ 90 min | 1. The Vanilloid 1 or Ankyrin 1 ion channels were mediated. 2. Inflammatory airway hyperresponsiveness and certain cellular inflammatory parameters were reduced. | [66] |
| 18 | 70% aqueous ethanol bark  | In vitro/ in vivo | monocyte-derived dendritic cells /immunized-BALB/c mice with ovalbumin | 1 mL/kg body weight/every other day/ 23 days | 1. DC maturation and subsequent allergen-specific T cell proliferation and Th1 and Th2 cytokine production were inhibited. 2. Sulphidoleukotriene release and CDF63 expression by basophils were diminished. 3. The shift from OVA-specific IgE towards IgG2a production and to potent inhibition of OVA-specific proliferation was observed. 4. Calcipotriol-induced atopic dermatitis-like inflammation was prevented. | [67] |
| 19 | Cinnamic aldehyde NM      | In vitro  | Articular Chondrocyte and Human Osteoarthritis | –                      | 1. The expression levels of IL-1β, IL-6, TNF-α, MMP13, and ADAMTS-5 were decreased by inhibiting the NF-κB signaling pathway. 2. LPS-stimulated NF-κB activation was suppressed. | [68] |
| 20 | aqueous extracts and methanolic extracts | bark In vitro | mouse macrophage and human chondrosarcoma cell lines as well as in human primary chondrocytes | –                      | 1. NO, PGE2, LTβ4, and MMP production were suppressed. 2. Anti-inflammatory activity was observed more in C. zeylanicum compared to C. cassia. | [69] |
| 21 | polyphenol-rich standardized extract of cinnamon bark extract | bark Clinical trial | A randomized, double-blind placebo-controlled study | 200 µg/100 µL/ day/ 8 days | 1. The onset of allergic inflammation was modulated by acting directly on immune cells. 2. The severity of the symptoms of SAR was decreased. 3. General activity impairment was reduced along with a corresponding improvement in quality of life and work productivity. | [70] |

NM: not mentioned, LPS: Lipopolysaccharides, NF-kB: Nuclear factor- kappaB, TNF-a: tumor necrosis factor-a, IL: interleukin, PGE2: prostaglandin E2, HO: heme-oxygenase, NRF2: Nuclear factor erythroid 2-related factor 2, Th: T helper, IFN: Interferon, TTP: Tristetraprolin, VEGF: Vascular endothelial growth factor, ERK: extracellular signal-regulated kinases, NO: nitric oxide, IκBα: inhibitor of nuclear factor kappa B, MDA: Malondialdehyde, M-CSF: Macrophage-colony stimulating factors.
significant reduced the IL-8 secretion in lipopolysaccharides (LPS)-stimulated THP-1 monocytes. They have a synergistic anti-inflammatory effect in combination with other compounds of the herb [65]. Kim et al. indicated that Trans-cinnamaldehyde reduces the NO, IL-1β, IL-6, and TNF-α expression in LPS-activated RAW 264.7 macrophages via suppression of extracellular signal-regulated kinases (ERK), p38 mitogen-activated protein kinases (p38 MAPK), and Jun N-terminal kinases (JNK) phosphorylation [71]. Lipophilic and hydrophilic extracts of true Cinnamon have shown anti-inflammatory activity via inhibiting nitric oxide and TNF-α expression in LPS, and interferon-γ (IFN-γ) activated RAW 264.7 macrophages. E-cinnamaldehyde, α-methoxy cinnamaldehyde, eugenol, benzyl benzoate, and cinnamyl alcohol components have an anti-inflammatory effect in RAW 264.7 and J774A.1 macrophages [17]. In Covid-19 disease, several cytokines are involved in the systemic inflammatory response, and inhibiting a number of inflammatory cytokines together may be more effective than concentrating on one alone [72]. Therefore, consumption of Darchini can decrease cytokine storm of COVID-19 and may improve disease.

3.3. Antioxidant effects

COVID-19 is a viral disease with hyper inflammation and excessive reactive oxygen species (ROS) production, which play a critical role in cytokine release in inflammation diseases [3,73]. In vitro studies show that cinnamon essential oil exhibits a significant antioxidant effect compared to synthetic antioxidant butylated hydroxytoluene (BHT) and vitamin C [74]. Beji and Colleagues demonstrated that cinnamon powder could restore the activities of antioxidative enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) near normal in diabetic rat plasma [75]. Ethanolic extract of Cinnamon (EEC) improves antioxidant capacity by upregulating endogenous antioxidant enzymes, Gluthathione (GSH), gamma-glutamylcysteine synthetase (γ-GCS), NQO1, and NAD(P)H: quinone reductase (QR). Besides cinnamonaldehydes, two lignan and flavonoid compounds activated Nrf2 and its downstream genes, nqo1 and γ-gcs, in the normal human lung epithelial and As (III)-induced oxidative stress Beas-2B cell line [76]. TCA has protective effects against oxidative injury in V79-4 Chinese hamster lung fibroblasts via blocking the abnormal accumulation of ROS, suppressing mitochondrial dysfunction, and activation of the nuclear factor-erythroid-2-related factor 2 (Nrf2)/hemeoxygenase-1 (HO-1) signaling pathway [77]. In addition, water extracted polyphenols from Cinnamomum zeylanicum have in vitro antioxidant capacity [78].

3.4. Miscellaneous effects

Although COVID-19 is a respiratory infection, due to extrapulmonary distribution of the main viral entry receptor, ACE-2 in other tissues, and cytokine storm, causes a systemic disease in several various organs, including kidneys, heart, and small intestine, thyroid, liver, bladder, etc. These clinical manifestations complicate the condition and make its treatment more complex [79].

Patient autopsy shows epithelial exfoliation and hyperplasia, mucosal congestion, alveolar damage, edematous inflammation, and thrombosis in infected lungs [88]. Inhalation of Cinnamon essential oil (with cinnamaldehyde as the main ingredient) improves respiratory functions and inflammatory conditions in lipopolysaccharide-induced airway inflammation [60]. Type-A procyanidin polyphenols (TAPP) from Cinnamomum zeylanicum exhibited anti-asthmatic and anti-inflammatory effects in ovalbumin-induced airway hypersensitivity animal models. Hematologic parameters increased in rats treated with TAPP leading to improvement of oxygen supply. Treatment with TAPP dose-dependently decreases the lungs’ total protein, bronchoalveolar lavage (BAL) total protein, serum albumin, BALF albumin, and lung albumin. The histopathological examination of TAPP (30 and 100 mg/kg) treated rats showed reduced inflammatory cell infiltrates; therefore, it is pivotal to minimize pulmonary damage [53]. Cinnamon, with its various anti-inflammatory effects, can potentially reduce mucus obstruction. The mucolytic potential of type-A procyanidin polyphenols [53] and 1,8-cineole [81] ingredients of Cinnamon have previously been studied in obstructive diseases.

Acute myocardial injury, heart failure, myocarditis, arrhythmias, and cardiac arrest are cardiovascular complications, which SARS-CoV-2 may cause. The sign of myocardial damage is the increase in cardiac troponin levels [82]. Sedighi et al. reported in vivo cardioprotective effect of cinnamon extract that improved activity of antioxidant enzymes including serum CAT, SOD, GPx 5 days after reperfusion. In addition, the elevation of myocardial injury markers, cardiac troponin I, lactate dehydrogenase, and malondialdehyde (MDA) was prevented [83]. Cinnamaldehyde and cinnamic acid decrease serum creatine kinase-MB (CK-MB), Lactate Dehydrogenase (LDH), TNF-α and IL-6, and MDA content in myocardial tissue and increase serum NO activity and myocardial tissue SOD activity in acute myocardial infarction ischemia induced by isoproterenol in rats [84]. An in vivo study on pressure overload-induced mice demonstrated the protective effect of cinnamaldehyde on cardiac hypertrophy and cardiac fibrosis via the ERK signaling pathway [85].

Kidney and liver abnormalities have been observed in patients with severe COVID-19. Elevated serum creatinine and blood urea nitrogen (BUN), proteinuria and hematuria, mild reduction in serum albumin, and mild elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are reported in COVID – 19 patients [86, 87]. An autopsy study shows several kidney pathologic presentations, including acute tubule injury (ATI) and renal capillary obstruction by erythrocyte aggregation along with endothelial damage in SARS-CoV-2 infection [88]. In addition, moderate microvascular steatosis; has been seen in a liver autopsy of a patient by COVID-19. Liver injury may be related to inflammatory responses, direct viral cytotoxicity, anoxia, or drug-induced damage in SARS-CoV-2 [87].

The nephroprotective effect of Cinnamon was indicated by decreased serum creatinine, blood urea nitrogen, and glucose, and increased serum albumin and total protein. C. zeylanicum has represented protective effects against acetaminophen-induced apoptosis via downregulation of caspase-3 and proliferating cell nuclear antigen (PCNA), participants in apoptosis, in renal tissue [89]. Adding 3% cinnamon or 0.002% procyandin-B2 (PCB2) fraction in rat diet for 12 weeks was effective in preventing diabetic nephropathy. Expression of protein kinase Cα (PKC-α) and Monocyte chemoattractant protein-1 (MCP-1), an inflammatory cytokine, were stopped in treated rats. In addition, PCB2 decreases the expression of vascular cell adhesion molecule-1 (VCAM-1), which eases the infiltration of macrophages into renal tissue [90].

Hussain et al. demonstrated that Cinnamon bark aqueous extract (200 mg/kg/day) exhibited hepato-renal protective effect against acetaminophen-induced toxicity in Balb/c mice. Increasing total anti-oxidant ability and restoring complete oxidative status is essential in inhibiting oxidative damage by cinnamon pretreatment [91]. Similar results were observed by administrating C. verum essential oil to rats' carbon tetrachloride-induced hepatic and renal toxicity. Hepatic serum markers (ALT, AST, ALP, LDH, γ-GT), lipid profile (total cholesterol, triglyceride, low-density lipoprotein), kidney function markers (urea,
creatinine) were decreased, and high-density lipoprotein was increased. Theoretically, Cinnamon can be effective in SARS-CoV-2 through opener, diuretic, tonic, and antidote effects based on the TPM viewpoint. In addition, there are several Pharmacological evidence on anti-viral, anti-inflammatory, antioxidant, organ-o-protective and anti-depressant effects of Cinnamon involved in treating this disease.

Nevertheless, clinical trials in COVID-19 patients should reveal the efficacy of Cinnamon before the definitive recommendations. As the first step, this review provides basic information for future studies on the effectiveness of this drug in preventing and treating SARS-CoV-2 and other viral diseases, which may occur in the future. Due to the importance of lung involvement and obstruction of respiratory tracts in COVID-19 disease, among the potential effects of Cinnamon mentioned in traditional Persian medicine, its anti-obstructive/opener effect is prominent and considerable. However, based on our knowledge, no clinical research has been done on this issue so far, and further investigations are needed to distinguish its mechanisms in the future.

CRediT authorship contribution statement

Maryam Yakhchali and Zahra Taghipour drafted and wrote the manuscript. Maryam Yakhchali edited the final version of the manuscript. Mehran Mirazbadzed Ardakani, Mahdi Alizadeh Vaghlasoo, Mahdi Vazirian and Sima Sadrai contributed to supervise the study.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgment

The authors are grateful to thank prof Bagher Yakhchali, a scientific member of the National Institute of Genetic Engineering and Biotechnology, for his Excellent editing of the manuscript and valuable comments.

References

[1] M.M. Hosnain, S. Tasnim, A. Sultana, F. Faizah, H. Mazumder, L. Zou, E. McKyer, H.U. Ahmed, P. Ma, Epidemiology of mental health problems in COVID-19: a review, F1000Res 9 (2020) 636, https://doi.org/10.12688/ f1000research.24457.1.
[2] P. Pelaia, C. Tinello, A. Vatrella, G. De Sarro, G. Pelaia, Lung under attack by COVID-19 induced cytokine storm: pathogenic mechanisms and therapeutic implications, Ther. Adv. Respir. Dis. 14 (2020) 1–9, https://doi.org/10.1177/ 175346662093598.
[3] M. Soy, G. Keser, P. Atagündüz, F. Tabak, L. Atagündüz, S. Kayhan, Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment, Clin. Rheuma 39 (7) (2020) 2085–2094, https://doi.org/10.1007/ s10026-020-01905-1.
[4] Y. Yi, P.N.P. Lagnitson, S. Ye, E. Li, R.H. Xu, COVID-19: what has been learned and to be learned about the novel coronavirus disease, Int. J. Biol. Sci. 16 (10) (2020) 1753–1766, https://doi.org/10.7150/ijbs.45134.
[5] T.S. Ibekwe, A.J. Fasunla, A.E. Orimadegun, Systematic review and meta-analysis of smell and taste disorders in COVID-19, OTO Open 4 (3) (2020), https://doi. org/10.1177/2473974720959795.
[6] D.K. Rajendran, V. Rajagopal, S. Alagumaniyan, T. Sathossh Kumar, S.P. Sathiya Prabhakaran, D. Kautilingam, Systematic literature review on novel corona virus SARS-CoV-2: a threat to human era, Virusdisase 31 (2) (2020) 161–173, https://doi.org/10.1186/s13237-020-00604-z.
[7] A. Sabehnazagh, R. Avan, F. Saghafi, M. Moghadamzadeh, A. Sadremontaz, O. Arasteh, A. Tazafi, F. Faramarzi, M. Khataminia, H. Rezai Ghaleno, S. Habtemariam, A. Khoshi, Pharmacological treatments of COVID-19, Pharmacol. Rep. 72 (2020) 1446–1478, https://doi.org/10.1016/j.pr.2020.01.01252-9.
[8] K.C. Chinsemub, Coronaviruses and nature’s pharmacy for the relief of coronavirus disease 2019, Rev. Bras. Farm. 30 (5) (2020) 603–621, https://doi.org/10.1016/j.rbf.2020.01.014.
[9] R. Bahramosaltani, R. Rahimi, An evaluation of traditional persian medicine for the management of SARS-CoV-2, Front Pharmacol 11 (2020), 571434, https://doi.org/10.3389/fphar.2020.571434.
[10] M. Irandadzi, Y. Kartimi, F. Moudeli, M. Pasalar, Persian medicine recommendations for the prevention of pandemics related to the respiratory
human coronaviruses, Phytother. Res. 35 (3) (2021) 1237–1247, https://doi.org/10.1002/ptr.6888.

[100] Ghaderi H., Rafieian M., Rahmani Nezhad H. effect of hydroalcoholic Cinnamomum zeylanicum extract on reserpine-induced depression symptoms in mice Pharmacophore, 2018. 9(2): 35-44.

[101] E.S. Hwang, H.B. Kim, S. Lee, M.J. Kim, K.J. Kim, G. Han, S.Y. Han, E.A. Lee, J.H. Yoon, D.O. Kim, S. Maeng, J.H. Park, Antidepressant-like effects of β-caryophyllene on restraint plus stress-induced depression, Behav. Brain Res. 380 (2020), 112439, https://doi.org/10.1016/j.bbr.2019.112439.