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Biomedicine & Pharmacotherapy 143 (2021) 112221

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Cinnamon and its possible impact on COVID-19: The viewpoint of traditional and conventional medicine

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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 antidote effects. In addition, there is pharmacological evidence on anti-viral, anti-inflammatory, antioxidant, organ-o-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-CoV2 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 track 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, Coronavirus disease 2019; 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; ATI, 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; PCO, 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.

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https://doi.org/10.1016/j.biopha.2021.112221
Received 2 July 2021; Received in revised form 14 September 2021; Accepted 16 September 2021
Available online 21 September 2021

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], antidote [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 track. Elimination and removing these altered mucin macromolecules is

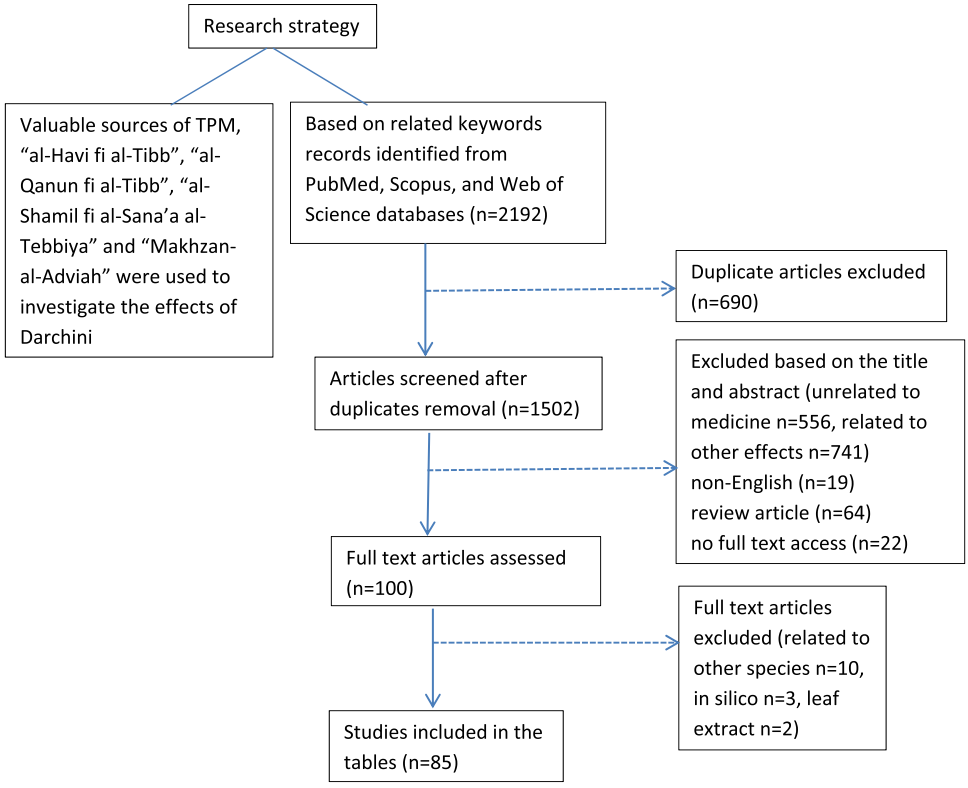

Fig. 1. Flowchart of the research methodology.

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 "*Ghaleez*" 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 track is opened. In the scientific language of TPM, these kinds of drugs that are used to move and eliminate the obstructing materials are named "*Mofatteh*" 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 "*Mofatteh*" 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 and functions [15]. Fiery and bitter ingredients are responsible for the strength opener or "*Mofatteh*" effect [36]. Opener drugs penetrate into dens or viscose humor by their thin property and move the accumulated materials outward to open the tracts. Therefore, they dilute and evaporate the thick humor by their dissolving effect or "*Tahlil*" and divide the viscose humor from the attached surface into smaller pieces by its cutting effect or "*Taghti*" [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 viscose phlegm, Darchini has mucolytic activity on pulmonary mucosa. Mucolytic drugs reduce mucin 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 Tenuifolin 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 (IC_{50} = 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	Mofatteh	Molattef	Mohallel	Moghatte	Jali	Monzej	Moghavvi	Moder	Mojaffef	Monaghi	Mofarreh	Mosakhen	Teryagh
al-Havi	+	–	–	–	+	+	–	+	+	–	–	+	+
al-Qanun	+	–	–	–	–	–	+	+	+	+	+	–	+
al-Shamil	+	+	+	+	+	+	+	+	+	+	+	+	+
Makhzan-al-Adviah	+	+	+	–	+	+	+	+	+	+	+	–	+

Mofatteh (opener), *Molattef* (Attenuant), *Mohallel* (Dissolver), *Moghatte* (Cutting agent), *Jali* (Detersive), *Monzej* (Maturative), *Moghavvi* (Tonic), *Moder* (Diuretic), *Mojaffef* (Desiccant), *Monaghi* (Abstergent), *Mofarreh* (Exhilarater), *Teryagh* (Antidote)

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 /cinnzeylanine	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

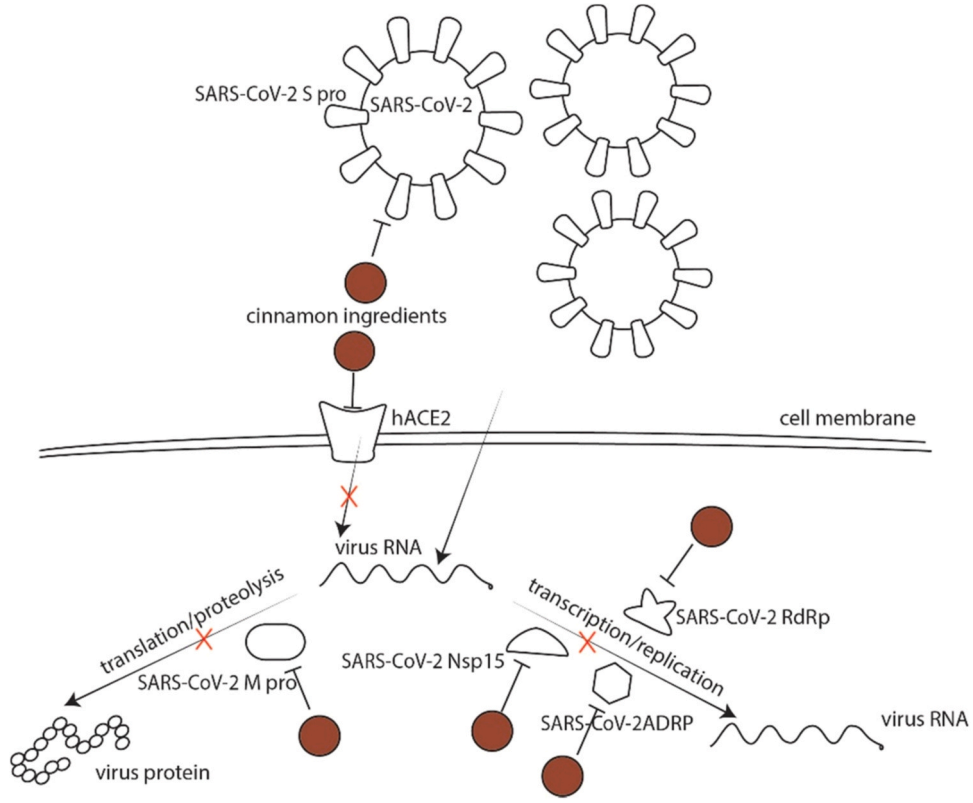

Fig. 2. Cinnamon ingredients inhibit virus proliferation through targeting essential proteins including SARS-CoV-2 spike protein (SARS-CoV-2 Spro), human angiotensin−converting enzyme (hACE2), SARS-CoV-2 main protease (SARS-CoV-2 Mpro), SARS-CoV-2 endoribonuclease (SARS-CoV-2 Nsp15), SARS-CoV-2 ADP-ribose-1″-phosphatase (SARS-CoV-2 ADRP), SARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp).

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 [50]. 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 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. Potent 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-arthritic 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 30 μg/ kg in nostril/ twice daily for 8 days	1. Alterations of the nasal, biochemical markers (serum IgE and histamine), hematological, morphological, and histopathological parameters were attenuated. 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 monocytic THP-1 cells	–	1. The attachment of THP-1 cells or neutrophils to TNF-α-activated HUVECs or E-selectin/ICAM-1 was reduced. 2. The binding of E-, L- and P-selectins with sialosides was reduced. 3. 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 vivo	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, CAII, 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]

(*continued on next page*)

Table 3 (*continued*)

No	Extract /Main component	Part used	Model	design	Dosage/ duration of treatment	Mechanism/outcome	Ref
						5. Anti-inflammatory and immune-modulating properties were observed due to the inhibitory effect on protein biomarkers. 6. Global gene expression was modulated.	
13	Essential Oil	bark	In vitro	human dermal fibroblast system, a model of chronic inflammation and fibrosis	–	1. Vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1, monocyte chemo-attractant protein-1, *IFN-γ* - induced protein 10, T-cell alpha chemoattractant, and monokine were decreased. 2. Epidermal growth factor receptors, MMP-1, and *PAI*-1 were decreased. 3. M-CSF was inhibited. 4. Global gene expression was modulated, and signaling pathways, which are essential in inflammation, were altered. 5. Anti-inflammatory effects were observed.	[62]
14	aqueous-alcoholic extraction/ polyphenol extract	NM	In vivo	Hepatic transcription factors expressions including SREBP-1c and LXR-a 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-a, ACLY, FAS, and NF-kB p65 expressions were suppressed 4. The PPARa, IRS-1, Nrf2, and HO-1 expressions were enhanced. 5. The reduction of hyperlipidemia, inflammation, and oxidative stress through activating transcription factors and antioxidative 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 cyto-kine 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 mature 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 CD63 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-1b, IL-6, TNF-a, MMP13, and ADAMTS-5 were decreased by inhibiting the NF-kB signaling pathway. 2. LPS-stimulated NF-kB 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, LTB4, 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

factor, HA: Haemagglutination, DTH: delayed-type hypersensitivity, PLCγ1: Phospholipase Cγ1, ConA: Concanavalin A, IgE: Immunoglobulin E, HUVECs: Human umbilical vein endothelial cells, ICAM-1: Intercellular Adhesion Molecule 1, β-HEX: Bet-hexosaminidase CAII: Carbonic anhydrase-II, BRCA1: breast cancer 1, PAI-1: Plasminogen activator inhibitor-1, SREBP-1: sterol regulatory element-binding protein 1, LXRs: liver X receptors, ACLY: ATP-citrate lyase, FAS: fatty acid synthase, PPARα: peroxisome proliferator-activated receptor α, DC: dendritic cells, OVA: ovalbumin, ADAMTS-5: A disintegrin and metalloproteinase with thrombospondin motifs 5, LTB4: Leukotriene B4, NFATc3: Nuclear Factor Of Activated T Cells 3, CHK: checkpoint kinase, MMPs: Matrix metalloproteinases, TLR: Toll-like receptor

significantly reduce 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 production in LPS, and interferon-γ (IFN-γ) activated RAW 264.7 macrophages. E-cinnamaldehyde, o-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, Glutathione (GSH), gamma-glutamylcysteine synthetase (γ-GCS), NQO1, and NAD(P)H: quinone reductase (QR). Besides cinnamaldehydes, two lignan and flavonol compounds activated Nrf2 and its downstream genes, *nqo*1 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 polysaccharides 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, mucosa congestion, alveolar damage, exudative inflammation, and thrombosis in infected lungs [80]. Inhalation of Cinnamon essential oil (with cinnamaldehyde as the main ingredient) improves respiratory functions and inflammatory conditions in lipopolysaccharide-induced airway inflammation [66]. Type-A procyanidin polyphenols (TAPP) from *Cinnamomum zeylanicum* exhibited anti-asthmatic and anti-inflammatory effects in ovalbumin-induced airway hyperresponsiveness 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-cineol [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% procyanidin-B2 (PCB2) fraction in rat diet for 12 weeks was effective in preventing diabetic nephropathy. Expression of protein kinase C-a (PKC-a) 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 antioxidant 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, ɣ-GT), lipid profile (total cholesterol, triglyceride, low-density lipoprotein), kidney function markers (urea,

creatinine) were decreased, and high-density lipoprotein was increased. It demonstrated significant antioxidant activity by reducing thiobarbituric acid reactive substances (TBARS) and protein carbonyl (PCO) levels, as oxidative damage markers, in liver and kidney tissues. In addition, reduction of CAT, SOD, GPx, and GSH (enzymatic and nonenzymatic antioxidants) levels was prevented dose-dependently. Moreover, histopathologic studies show inflammation in tissues along with other damages, and the anti-inflammatory and antioxidant effects of cinnamaldehyde are significant in this situation [92].

Pretreatment with alcoholic extract of cinnamon bark decreases hepatic lipid accumulation, plasminogen activator inhibitor1 mRNA expression, and thus 45% dampened liver steatosis in Acute Alcoholic Liver Disease in mice. In vivo and in vitro studies showed the hepatoprotective effect of cinnamon extract due to its anti-inflammatory effects on induced myeloid differentiation primary response gene (MyD88), nitric oxide synthase (iNOS), and TNF-α [93]. 1.5 g of cinnamon supplementation for 12 weeks has therapeutic effects on Non-alcoholic fatty liver disease (NAFLD) characteristics. Askari et al. showed that Homeostatic Model Assessment (HOMA) index, fasting blood glucose (FBS), Total Cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), ALT, AST, gamma glutamine transpeptidase (GGT), and high-sensitivity C-reactive protein were significantly decreased in patients with NAFLD [94]. The ethanolic extract of *C. zeylanicum* L. bark has exhibited hepatoprotective effect in (CCl4)-induced hepatotoxicity in male Wistar rats. In addition to reducing serum markers of liver damage, cinnamon extract consumption increased superoxide dismutase and catalase enzymes. Histopathological results indicate that tissue damage and necrosis were significantly improved [95]. These results were also reported by cinnamon essential oil administration against formaldehyde-induced hepatotoxicity in an animal model [96].

In another way, the patients with underlying diseases including hypertension, diabetes, obesity, cardiovascular disease, non-alcoholic fatty liver, chronic lung diseases, and kidney problems are more vulnerable to COVID-19 infection [97]. In addition to potential anti-coronavirus therapies, with its positive effects in treating underlying diseases, Cinnamon can reduce the risk of infection [24].

One of the major problems caused by the COVID-19 pandemic in patients, healthcare staff, and even healthy people is psychological symptoms, including anxiety, fear, distress, depression, and stress-related complication. Psychological, social interventions and the use of plants can help to improve mental health problems [98,99]. Cinnamon is a popular herbal tea, which TPM and pharmacological evidence point out its exhilarating and anti-depressant effects. In a reserpine-induced mouse model of depression, *C. zeylanicum* hydro-alcoholic extract exhibited an anti-depression effect equal to fluoxetine. This anti-depressant effect might be due to its potent antioxidant effect [100]. Furthermore, the elevation of proinflammatory cytokines including interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) are contributed in depression-like symptoms. β-Caryophyllene (BCP), a sesquiterpene in Cinnamon, decreases the expression of cyclooxygenase-2 (COX-2) and increases CB2 receptor expression in hippocampal tissue. In this way, it exerts anti-depressant effects via inflammatory responses suppression in a chronic restraint plus stress (CR+S) depression model [101].

4. Conclusion

COVID-19 is a complicated disease with several aspects. Therefore, in its treatment, it is better to use drugs that combat it in several ways. Cinnamon and its ingredients can be recommended in SARS-CoV-2 infection due to its multi-targeting properties. Several pharmacological studies confirm its effects mentioned in TPM, and its popularity among people makes it easy to use. In addition, treatment of this viral hyper inflammation disease with Cinnamon as a supplementary drug can decrease consumption of chemical drugs and their side effects. 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 Mirabzadeh Ardakani, Mahdi Alizadeh Vaghasloo, 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. Hossain, 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] C. 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/10.1177/1753466620933508.

[3] M. Soy, G. Keser, P. Atagündüz, F. Tabak, I. 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/s10067-020-05190-5.

[4] Y. Yi, P.N.P. Lagniton, 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/10.1177/2473974×20957975.

[6] D.K. Rajendran, V. Rajagopal, S. Alagumanian, T. Santhosh Kumar, S.P. Sathiya Prabhakaran, D. Kasilingam, Systematic literature review on novel corona virus SARS-CoV-2: a threat to human era, Virusdisease 31 (2) (2020) 161–173, https://doi.org/10.1007/s13337-020-00604-z.

[7] A. Sahebnasagh, R. Avan, F. Saghafi, M. Mojtahedzadeh, A. Sadremomtaz, O. Arasteh, A. Tanzifi, F. Faramarzi, R. Negarandeh, M. Safdari, M. Khataminia, H. Rezai Ghaleno, S. Habtemariam, A. Khoshi, Pharmacological treatments of COVID-19, Pharmacol. Rep. 72 (2020) 1446–1478, https://doi.org/10.1007/s43440-020-00152-9.

[8] K.C. Chinsembu, Coronaviruses and nature's pharmacy for the relief of coronavirus disease 2019, Rev. Bras. Farm. 30 (5) (2020) 603–621, https://doi.org/10.1007/s43450-020-00104-7.

[9] R. Bahramsoltani, 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. Iranzadasl, Y. Karimi, F. Moadeli, M. Pasalar, Persian medicine recommendations for the prevention of pandemics related to the respiratory

system: a narrative literature review, Integr. Med. Res. 10 (1) (2021), 100483, https://doi.org/10.1016/j.imr.2020.100483.
[11] M.B. Siahpoosh, How can persian medicine (traditional iranian medicine) be effective to control COVID-19? Trad. Integr. Med. 5 (2) (2020) 46–48, https://doi.org/10.18502/tim.v5i2.3624.
[12] S. Mahroozade, H. Mohammadi Kenari, F. Eghbalian, A. Ghobadi, B. S. Yousefsani, Avicenna's points of view in epidemics: some advice on coronavirus 2 (COVID-19), Complement. Med. Res. 28 (2021) 175–176, https://doi.org/10.1159/000509398.
[13] L. Ang, E. Song, H.W. Lee, M.S. Lee, Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of randomized controlled trials, J. Clin. Med. 9 (5) (2020) 1583, https://doi.org/10.3390/jcm9051583.
[14] F. Barati, M. Pouresmaieli, E. Ekrami, S. Asghari, F.R. Ziarani, M. Mamoudifard, Potential drugs and remedies for the treatment of COVID-19: a critical review, Biol. Proced. Online 22 (2020) 15, https://doi.org/10.1186/s12575-020-00129-1.
[15] A. Ibn Nafis Qarashi, Al-Shamil fi al-Sana'a al-Tebbiya Vol. 12, University of Medical Sciences, Tehran, Iran, 2008.
[16] N. Singh, A.S. Rao, A. Nandal, S. Kumar, S.S. Yadav, S.A. Ganaie, B. Narasimhan, Phytochemical and pharmacological review of Cinnamomum verum J. Presl-a versatile spice used in food and nutrition, Food Chem. 338 (2021), 127773, https://doi.org/10.1016/j.foodchem.2020.127773.
[17] D. Gunawardena, N. Karunaweera, S. Lee, F. Van Der Kooy, D.G. Harman, R. Raju, L. Bennett, E. Gyengesi, N.J. Sucher, G. Münch, Anti-inflammatory activity of Cinnamon (C. zeylanicum and C. cassia) extracts - identification of E-cinnamaldehyde and o-methoxy cinnamaldehyde as the most potent bioactive compounds, Food Funct. 6 (3) (2015) 910–919, https://doi.org/10.1039/c4fo00680a.
[18] B. Alizadeh Behbahani, F. Falah, F. Lavi Arab, M. Vasiee, F. Tabatabaee Yazdi, Chemical composition and antioxidant, antimicrobial, and antiproliferative activities of cinnamomum zeylanicum bark essential oil, Evid. Based Complement. Altern. Med. eCAM 2020 (2020), 5190603, https://doi.org/10.1155/2020/5190603.
[19] A. Urbaniak, A. Głowacka, E. Kowalczyk, M. Lysakowska, M. Sienkiewicz, The antibacterial activity of cinnamon oil on the selected gram-positive and gram-negative bacteria, Med Dosw Mikrobiol. 66 (2) (2014) 131–141.
[20] J. Ahmed, E. Altun, M.O. Aydogdu, O. Gunduz, L. Kerai, G. Ren, M. Edirisinghe, Anti-fungal bandages containing cinnamon extract, Int. Wound J. 16 (3) (2019) 730–736, https://doi.org/10.1111/iwj.13090.
[21] H.N.H. Tran, L. Graham, E.C. Adukwu, In vitro antifungal activity of Cinnamomum zeylanicum bark and leaf essential oils against Candida albicans and Candida auris, Appl. Microbiol. Biotechnol. 104 (20) (2020) 8911–8924, https://doi.org/10.1007/s00253-020-10829-z.
[22] Y. Orihara, H. Hamamoto, H. Kasuga, T. Shimada, Y. Kawaguchi, K. Sekimizu, A silkworm-baculovirus model for assessing the therapeutic effects of anti-viral compounds: characterization and application to the isolation of anti-virals from traditional medicines, J. Gen. Virol. 89 (1) (2008) 188–194, https://doi.org/10.1099/vir.0.83208-0.
[23] M. Dorri, S. Hashemitabar, H. Hosseinzadeh, Cinnamon (Cinnamomum zeylanicum) as an antidote or a protective agent against natural or chemical toxicities: a review, Drug Chem. Toxicol. 41 (3) (2018) 338–351, https://doi.org/10.1080/01480545.2017.1417995.
[24] H. Mollazadeh, H. Hosseinzadeh, Cinnamon effects on metabolic syndrome: a review based on its mechanisms, Iran. J. Basic Med. Sci. 19 (12) (2016) 1258–1270, https://doi.org/10.22038/ijbms.2016.7906.
[25] P. Nyadjeu, E.P. Nguelefack-Mbuyo, A.D. Atsamo, T.B. Nguelefack, A.B. Dongmo, A. Kamanyi, Acute and chronic antihypertensive effects of Cinnamomum zeylanicum stem bark methanol extract in L-NAME-induced hypertensive rats, BMC Complement. Alter. Med. 13 (2013) 27, https://doi.org/10.1186/1472-6882-13-27.
[26] I.N. Nayak, R. Chinta, R. Jetti, Anti-atherosclerotic potential of aqueous extract of cinnamomum zeylanicum bark against glucocorticoid induced atherosclerosis in wistar rats, J. Clin. Diagn. Res. 11 (5) (2017) Fc19–fc23, https://doi.org/10.7860/JCDR/2017/23910.9864.
[27] L. Zuo, K. Lucas, T.M. Best, C.A. Fortuna, C.C. Chuang, Molecular regulation of toll-like receptors in asthma and COPD, Front. Physiol. 6 (2015) 312, https://doi.org/10.3389/fphys.2015.00312.
[28] J. He, S. Cai, H. Feng, B. Cai, L. Lin, Single-cell analysis reveals bronchoalveolar epithelial dysfunction in COVID-19 patients, Protein Cell 11 (9) (2020) 680–687, https://doi.org/10.1007/s13238-020-00752-4.
[29] M. Yakhchali, M. Alizadeh Vaghasloo, M. Mirabzadeh Ardakani, M. Vazirian, S. Sadra, Targeting atherosclerotic plaque in avicenna's view, J. Integr. Cardiol. Open Access 3 (4) (2020) 1–11, https://doi.org/10.31487/j.JICOA.2020.04.14.
[30] M. Yakhchali, M. Mirabzadeh Ardakani, M. Alizadeh Vaghasloo, The effect of tastes in treating atherosclerosis, Trad. Integr. Med. 4 (2) (2019) 56–57, https://doi.org/10.18502/tim.v4i2.1669.
[31] M. Alizadeh Vaghasloo, M.A. Zareian, S.M.A. Soroushzadeh, The Concept of Nozj, Trad. Integr. Med. 1 (2016) 133–135.
[32] M.H. Aghili Khorasani, Makhzan-al-Adviah, Tehran University of Medical Sciences, Tehran, 2008.
[33] H. Avicenna, in: A. Masoudi (Ed.), Al-Qanun fi al Tibb [The Canon of medicine] Vol. 2, Al-Mai, Tehran, 2013.
[34] M.I.Z. Rhazes, in: S. afsharipour (Ed.), Al-havi fi al-Tibb Vol. 20, Iranian Academy of Medical Sciences, Tehran, 2006.
[35] A. Ibn Nafis Qarashi, Al-Shamil fi al-Sana'a al-Tebbiya (Part One of The Third Section), University of Medical Sciences, Research Institute for Islamic and Complementary Medicine, Tehran, Iran, 2010.
[36] M. Chashti, Exir-e Azam, Research Institute for Islamic & Complementary Medicine, Tehran, 2004.
[37] A. Yuta, J.N. Baraniuk, Therapeutic approaches to mucus hypersecretion, Curr. Allergy Asthma Rep. 5 (2005) 243–251, https://doi.org/10.1007/s11882-005-0044-6.
[38] H. Mohammadi Kenari, G. Kordafshari, M. Kamalinejad, S. Aghighi, M. Moghimi, Treatment of hospital acquired pneumonia (HAP) with persian medicine (PM): a case report, Trad. Integr. Med. 3 (2) (2018) 69–77.
[39] S.M. Gopinath, G.M. Vidya, K.S. Dayananda, T.P. Narasimha Murthy, Ashalatha. Isolation, characterization and purification of bio-active compounds from andrographis paniculata and cinnamon verum for anti-hiv activity, Int J. Innov. Res Sci. Eng. Technol. 6 (3) (2014) 13777–13783.
[40] B.J. Connell, S.Y. Chang, E. Prakash, R. Yousfi, V. Mohan, W. Posch, D. Wilflingseder, C. Moog, E.N. Kodama, P. Clayette, H. Lortat-Jacob, A cinnamon-derived procyanidin compound displays Anti-HIV-1 activity by blocking heparan sulfate- and co-receptor- binding sites on gp120 and reverses T cell exhaustion via impeding Tim-3 and PD-1 upregulation, PLoS One 11 (10) (2016), 0165386, https://doi.org/10.1371/journal.pone.0165386.
[41] C. Fauvelle, M. Lambotin, L. Heydmann, E. Prakash, S. Bhaskaran, M. Vishwaraman, T.F. Baumert, C. Moog, A cinnamon-derived procyanidin type A compound inhibits hepatitis C virus cell entry, Hepatol. Int. 11 (5) (2017) 440–445, https://doi.org/10.1007/s12072-017-9809-y.
[42] M. Moshaverinia, M. Rastegarfar, A. Moattari, F. Lavaee, Evaluation of the effect of hydro alcoholic extract of Cinnamon on herpes simplex virus-1, Dent. Res J. 17 (2) (2020) 114–119.
[43] H.J. Choi, Chemical constituents of essential oils possessing anti-influenza A/WS/33 virus activity, Osong Public Health Res. Perspect. 9 (6) (2018) 348–353, https://doi.org/10.24171/j.phrp.2018.9.6.09.
[44] D. Dourado, D.T. Freire, D.T. Pereira, L. Amaral-Machado, E.E. Alencar, Will curcumin nanosystems be the next promising antiviral alternatives in COVID-19 treatment trials? Biomed. Pharmacother. = Biomed. Pharmacother. 139 (2021), 111578 https://doi.org/10.1016/j.biopha.2021.111578.
[45] J.K.R. Da Silva, P.L.B. Figueiredo, K.G. Byler, W.N. Setzer, Essential oils as anti-viral agents, potential of essential oils to treat SARS-CoV-2 infection: an in-silico investigation, Int. J. Mol. Sci. 21 (10) (2020), https://doi.org/10.3390/ijms21103426.
[46] Murahari M. Prasanth DSNBK, In silico identification of potential inhibitors from Cinnamon against main protease and spike glycoprotein of SARS CoV-2, J. Biomol. Struct. Dyn. 39 (2021) 4618–4632, https://doi.org/10.1080/07391102.2020.1779129.
[47] H.S. Ranjini, E.G. Padmanabha Udupa, S.U. Kamath, M. Setty, B. Hadapad, A. Kamath, An in vitro study of Cinnamomum zeylanicum as natural inhibitor of angiotensin-converting enzyme (ACE) on sheep (Ovis aries) tissues, Asian J. Pharm. Clin. Res. 9 (5) (2016) 249–252, https://doi.org/10.22159/ajpcr.2016.v9i5.13424.
[48] D. Shahwar, M.A. Raza, S.H. Rehman, M.A. Abbasi, A. Rahman, An investigation of phenolic compounds from plant sources as trypsin inhibitors, Nat. Prod. Res. 26 (12) (2012) 1087–1093, https://doi.org/10.1080/14786419.2011.559637.
[49] H. Amawi, G.I. Abu Deiab, A.A.A. Aljabali, K. Dua, M.M. Tambuwala, COVID-19 pandemic: an overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics, Ther. Deliv. 11 (4) (2020) 245–268, https://doi.org/10.4155/tde-2020-0035.
[50] C.H. Luo, L.L. Ma, H.M. Liu, W. Liao, R.C. Xu, Z.M. Ci, J.Z. Lin, L. Han, D. K. Zhang, Research progress on main symptoms of novel coronavirus pneumonia improved by traditional Chinese medicine, Front. Pharmacol. 11 (2020), 556885, https://doi.org/10.3389/fphar.2020.556885.
[51] B. Rathi, S. Bodhankar, V. Mohan, P. Thakurdesai, Ameliorative effects of a polyphenolic fraction of cinnamomum zeylanicum L. bark in animal models of inflammation and arthritis, Sci. Pharm. 81 (2) (2013) 567–589, https://doi.org/10.3797/scipharm.1301-16.
[52] H. Cao, R.A. Anderson, Cinnamon polyphenol extract regulates tristetraprolin and related gene expression in mouse adipocytes, J. Agric. Food Chem. 59 (6) (2011) 2739–2744, https://doi.org/10.1021/jf103527x.
[53] A.D. Kandhare, S.L. Bodhankar, V. Singh, V. Mohan, P.A. Thakurdesai, Anti-asthmatic effects of type-A procyanidine polyphenols from cinnamon bark in ovalbumin-induced airway hyperresponsiveness in laboratory animals, Biomed. Aging Pathol. 3 (1) (2013) 23–30, https://doi.org/10.1016/j.biomag.2013.01.003.
[54] S. Vetal, S.L. Bodhankar, V. Mohan, P.A. Thakurdesai, Anti-inflammatory and anti-arthritic activity of type-A procyanidine polyphenols from bark of Cinnamomum zeylanicum in rats, Food Sci. Hum. Wellness 2 (2) (2013) 59–67, https://doi.org/10.1016/j.fshw.2013.03.003.
[55] N. Balekar, S. Bodhankar, V. Mohan, P.A. Thakurdesai, Modulatory activity of a polyphenolic fraction of Cinnamomum zeylanicum L. bark on multiple arms of immunity in normal and immunocompromised mice, J. Appl. Pharm. Sci. 4 (7) (2014) 114–122, https://doi.org/10.7324/JAPS.2014.40720.
[56] Y. Hagenlocher, K. Kießling, M. Schäffer, S.C. Bischoff, A. Lorentz, Cinnamaldehyde is the main mediator of cinnamon extract in mast cell inhibition, Eur. J. Nutr. 54 (8) (2015) 1297–1309, https://doi.org/10.1007/s00394-014-0810-0.
[57] U.M. Aswar, A.D. Kandhare, V. Mohan, P.A. Thakurdesai, Anti-allergic effect of intranasal administration of type-A procyanidin polyphenols based standardized

extract of cinnamon bark in ovalbumin sensitized BALB/c mice, Phytother. Res. 29 (3) (2015) 423–433, https://doi.org/10.1002/ptr.5269.
[58] W.L. Lin, S.Y. Guu, C.C. Tsai, E. Prakash, M. Viswaraman, H.B. Chen, C.F. Chang, Derivation of cinnamon blocks leukocyte attachment by interacting with sialosides, PLoS One 10 (6) (2015), 0130389, https://doi.org/10.1371/journal.pone.0130389.
[59] A.D. Kandhare, U.M. Aswar, V. Mohan, P.A. Thakurdesai, Ameliorative effects of type-A procyanidins polyphenols from cinnamon bark in compound 48/80-induced mast cell degranulation, Anat. Cell Biol. 50 (4) (2017) 275–283, https://doi.org/10.5115/acb.2017.50.4.275.
[60] M.M.F. Qadir, A. Bhatti, M.U. Ashraf, M.A. Sandhu, S. Anjum, P. John, Immunomodulatory and therapeutic role of Cinnamomum verum extracts in collagen-induced arthritic BALB/c mice, Inflammopharmacology 26 (1) (2018) 157–170, https://doi.org/10.1007/s10787-017-0349-9.
[61] X.S. Han, T.L. Parker, J. Dorsett, An essential oil blend significantly modulates immune responses and the cell cycle in human cell cultures, Cogent Biol. 3 (1) (2017), 1340112, https://doi.org/10.1080/23312025.2017.1340112.
[62] X.S. Han, T.L. Parker, Anti-inflammatory activity of Cinnamon (Cinnamomum zeylanicum) bark essential oil in a human skin disease model, Phytother. Res. 31 (7) (2017) 1034–1038, https://doi.org/10.1002/ptr.5822.
[63] Z. Tuzcu, C. Orhan, N. Sahin, V. Juturu, K. Sahin, Cinnamon polyphenol extract inhibits hyperlipidemia and inflammation by modulation of transcription factors in high-fat diet-fed rats, Oxid. Med. Cell. Longev. 2017 (2017), 1583098, https://doi.org/10.1155/2017/1583098.
[64] A. Schink, J. Neumann, A.L. Leifke, K. Ziegler, J. Fröhlich-Nowoisky, C. Cremer, E. Thines, B. Weber, U. Pöschl, D. Schuppan, K. Lucas, Screening of herbal extracts for TLR2- and TLR4-dependent anti-inflammatory effects, PLoS One 13 (10) (2018), 0203907, https://doi.org/10.1371/journal.pone.0203907.
[65] A. Schink, K. Naumoska, Z. Kitanovski, C.J. Kampf, J. Fröhlich-Nowoisky, E. Thines, U. Pöschl, D. Schuppan, K. Lucas, Anti-inflammatory effects of cinnamon extract and identification of active compounds influencing the TLR2 and TLR4 signaling pathways, Food Funct. 9 (11) (2018) 5950–5964, https://doi.org/10.1039/c8fo01286e.
[66] E. Csikós, K. Csekő, A.R. Ashraf, Á. Kemény, L. Kereskai, B. Kocsis, A. Böszörményi, Z. Helyes, G. Horváth, Effects of Thymus vulgaris L., Cinnamomum verum J. Presl and Cymbopogon nardus(L.) rendle essential oils in the endotoxin-induced acute airway inflammation mouse model, Molecules 25 (15) (2020), https://doi.org/10.3390/molecules25153553.
[67] R. Ose, J. Tu, A. Schink, J. Maxeiner, P. Schuster, K. Lucas, J. Saloga, I. Bellinghausen, Cinnamon extract inhibits allergen-specific immune responses in human and murine allergy models, Clin. Exp. Allergy 50 (1) (2020) 41–50, https://doi.org/10.1111/cea.13507.
[68] P. Chen, A. Ruan, J. Zhou, L. Huang, X. Zhang, Y. Ma, Q. Wang, Cinnamic aldehyde inhibits lipopolysaccharide-induced chondrocyte inflammation and reduces cartilage degeneration by blocking the nuclear factor-kappa B signaling pathway, Front. Pharmacol. 11 (2020) 949, https://doi.org/10.3389/fphar.2020.00949.
[69] P. Raina, C.V. Chandrasekaran, A. Aggarwal, N. Wagh, R. Kaul-Ghanekar, Comparative analysis of anti-inflammatory activity of aqueous and methanolic extracts of C. cassia and C. zeylanicum in RAW264.7, SW1353 and primary chondrocytes, Int. J. Pharm. Pharm. Sci. 7 (11) (2015) 392–396.
[70] E. Steels, E. Steels, P. Deshpande, P. Thakurdesai, S. Dighe, T. Collet, A randomized, double-blind placebo-controlled study of intranasal standardized cinnamon bark extract for seasonal allergic rhinitis, Complement. Ther. Med. 47 (2019), 102198, https://doi.org/10.1016/j.ctim.2019.102198.
[71] M.E. Kim, J.Y. Na, J.S. Lee, Anti-inflammatory effects of trans-cinnamaldehyde on lipopolysaccharide-stimulated macrophage activation via MAPKs pathway regulation, Immunopharmacol. Immunotoxicol. 40 (3) (2018) 219–224, https://doi.org/10.1080/08923973.2018.1424902.
[72] S.M. Sending, J.S. Yakisich, Use of vagus nerve stimulation and vagal maneuvers as adjuvant therapy for COVID-19 patients, SciMedicine J. 3 (Special Issue "COVID-19") (2021) 10–15, https://doi.org/10.28991/SciMedJ-2021-03-SI-2.
[73] L. Zuo, K. Lucas, T.M. Best, C.A. Fortuna, C.C. Chuang, Molecular regulation of toll-like receptors in asthma and COPD, Front. Physiol. 6 (2015) 312, https://doi.org/10.3389/fphys.2015.00312.
[74] I. Kallel, B. Hadrich, B. Gargouri, A. Chaabane, S. Lassoued, R. Gdoura, A. Bayoudh, E. Ben Messaoud, Optimization of cinnamon (cinnamomum zeylanicum blume) essential oil extraction: evaluation of antioxidant and antiproliferative effects, Evid. Based Complement. Altern. Med. 2019 (2019), 6498347, https://doi.org/10.1155/2019/6498347.
[75] R.S. Beji, S. Khemir, W.A. Wannes, K. Ayari, Antidiabetic, antihyperlipidemic and antioxidant influences of the spice cinnamon (Cinnamomum zeylanicumon) in experimental rats, Braz. J. Pharm. Sci. 54 (2) (2018), https://doi.org/10.1590/s2175-97902018000217576.
[76] A.L. Li, G.H. Li, Y.R. Li, X.Y. Wu, D.M. Ren, H.X. Lou, X.N. Wang, T. Shen, Lignan and flavonoid support the prevention of Cinnamon against oxidative stress related diseases, Phytomedicine 53 (2019) 143–153, https://doi.org/10.1016/j.phymed.2018.09.022.
[77] Y.H. Choi, trans-cinnamaldehyde prevents oxidative stress-induced apoptosis in V79-4 Chinese hamster lung fibroblasts through the Nrf2-mediated HO-1 activation, Biol. Pharm. Bull. 43 (11) (2020) 1707–1714, https://doi.org/10.1248/bpb.b20-00407.
[78] T. Ghosh, A. Basu, D. Adhikari, D. Roy, A.K. Pal, Antioxidant activity and structural features of Cinnamomum zeylanicum, 3 Biotech 5 (6) (2015) 939–947, https://doi.org/10.1007/s13205-015-0296-3.
[79] Y. Zhang, X. Geng, Y. Tan, Q. Li, C. Xu, J. Xu, L. Hao, Z. Zeng, X. Luo, F. Liu, H. Wang, New understanding of the damage of SARS-CoV-2 infection outside the respiratory system, Biomed. Pharm. 127 (2020), 110195, https://doi.org/10.1016/j.biopha.2020.110195.
[80] X.W. Bian, Autopsy of COVID-19 patients in China, Natl. Sci. Rev. 7 (9) (2020) 1414–1418, https://doi.org/10.1093/nsr/nwaa123.
[81] L.J. Juergens, J. Worth, U.R. Juergens, New perspectives for mucolytic, anti-inflammatory and adjunctive therapy with 1,8-Cineole in COPD and asthma: review on the new therapeutic approach, Adv. Ther. 37 (2020) 1737–1753, https://doi.org/10.1007/s12325-020-01279-0.
[82] S. Ganatra, S.S. Dani, S. Shah, A. Asnani, T.G. Neilan, D. Lenihan, B. Ky, A. Barac, S.S. Hayek, M. Leja, J. Herrmann, P. Thavendiranathan, M. Fradley, V. Bang, K. Shreyder, R. Parikh, R. Patel, A. Singh, S. Brar, A. Guha, D. Gupta, P. Mascari, R.D. Patten, D.M. Venesy, A. Nohria, F.S. Resnic, Management of cardiovascular disease during coronavirus disease (COVID-19) pandemic, Trends Cardiovasc. Med. 30 (6) (2020) 315–325, https://doi.org/10.1016/j.tcm.2020.05.004.
[83] M. Sedighi, A. Nazari, M. Faghihi, M. Rafieian-Kopaei, A. Karimi, M. Moghimian, S.A. Mozaffarpur, M. Rashidipour, M. Namdari, M. Cheraghi, B. Rasoulian, Protective effects of cinnamon bark extract against ischemia-reperfusion injury and arrhythmias in rat, Phytother. Res. 32 (10) (2018) 1983–1991, https://doi.org/10.1002/ptr.6127.
[84] F. Song, H. Li, J. Sun, S. Wang, Protective effects of cinnamic acid and cinnamic aldehyde on isoproterenol-induced acute myocardial ischemia in rats, J. Ethnopharmacol. 150 (1) (2013) 125–130, https://doi.org/10.1016/j.jep.2013.08.019.
[85] L. Yang, Q.Q. Wu, Y. Liu, Z.F. Hu, Z.Y. Bian, Q.Z. Tang, Cinnamaldehyde attenuates pressure overload-induced cardiac hypertrophy, Int. J. Clin. Exp. Pathol. 8 (11) (2015) 14345–14354.
[86] S. Adapa, A. Chenna, M. Balla, G.P. Merugu, N.M. Koduri, S.R. Daggubati, V. Gayam, S. Naramala, V.M. Konala, COVID-19 pandemic causing acute kidney injury and impact on patients with chronic kidney disease and renal transplantation, J. Clin. Med. Res. 12 (6) (2020) 352–361, https://doi.org/10.14740/jocmr4200.
[87] S.A. Alqahtani, J.M. Schattenberg, Liver injury in COVID-19: the current evidence. United European, Gastroenterol. J. 8 (5) (2020) 509–519, https://doi.org/10.1177/2050640620924157.
[88] H. Su, M. Yang, C. Wan, L.X. Yi, F. Tang, H.Y. Zhu, F. Yi, H.C. Yang, A.B. Fogo, X. Nie, C. Zhang, Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, Kidney Int. 98 (2020) 219–227, https://doi.org/10.1016/j.kint.2020.04.003.
[89] A. Abdeen, A. Abdelkader, M. Abdo, G. Wareth, M. Aboubakr, L. Aleya, M. Abdel-Daim, Protective effect of Cinnamon against acetaminophen-mediated cellular damage and apoptosis in renal tissue, Environ. Sci. Pollut. Res. Int. 26 (1) (2019) 240–249, https://doi.org/10.1007/s11356-018-3553-2.
[90] P. Muthenna, G. Raghu, P.A. Kumar, M.V. Surekha, G.B. Reddy, Effect of Cinnamon and its procyanidin-B2 enriched fraction on diabetic nephropathy in rats, Chem. Biol. Interact. 222 (2014) 68–76, https://doi.org/10.1016/j.cbi.2014.08.013.
[91] Z. Hussain, J.A. Khan, A. Arshad, P. Asif, H. Rashid, M.I. Arshad, Protective effects of Cinnamomum zeylanicum L. (Darchini) in acetaminophen-induced oxidative stress, hepatotoxicity and nephrotoxicity in mouse model, Biomed. Pharm. 109 (2019) 2285–2292, https://doi.org/10.1016/j.biopha.2018.11.123.
[92] K. Bellassoued, F. Ghrab, H. Hamed, R. Kallel, J. van Pelt, A. Lahyani, F.M. Ayadi, A. El Feki, Protective effect of essential oil of Cinnamomum verum bark on hepatic and renal toxicity induced by carbon tetrachloride in rats, Appl. Physiol. Nutr. Metab. 44 (6) (2019) 606–618, https://doi.org/10.1139/apnm-2018-0246.
[93] G. Kanuri, S. Weber, V. Volynet, A. Spruss, S.C. Bischoff, I. Bergheim, Cinnamon extract protects against acute alcohol-induced liver steatosis in mice, J. Nutr. 139 (3) (2009) 482–487, https://doi.org/10.3945/jn.108.100495.
[94] F. Askari, B. Rashidkhani, A. Hekmatdoost, Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in non-alcoholic fatty liver disease patients, Nutr. Res. 34 (2) (2014) 143–148, https://doi.org/10.1016/j.nutres.2013.11.005.
[95] A. Eidi, P. Mortazavi, M. Bazargan, J. Zaringhalam, Hepatoprotective activity of Cinnamon ethanolic extract against CCI4-induced liver injury in rats, Excli J. 11 (2012) 495–507.
[96] F. Niknezhad, S. Sayad-Fathi, A. Karimzadeh, M. Ghorbani-Anarkooli, F. Yousefbeyk, E. Nasiri, Improvement in histology, enzymatic activity, and redox state of the liver following administration of Cinnamomum zeylanicum bark oil in rats with established hepatotoxicity, Anat. Cell Biol. 52 (3) (2019) 302–311, https://doi.org/10.5115/acb.18.180.
[97] P. Portincasa, M. Krawczyk, W. Smyk, F. Lammert, A.D. Ciaula, COVID-19 and non-alcoholic fatty liver disease: two intersecting pandemics, Eur. J. Clin. Investig. 50 (10) (2020) 13338, https://doi.org/10.1111/eci.13338.
[98] K.M. Chow, B.M.H. Law, M.S.N. Ng, D.N.S. Chan, W.K.W. So, C.L. Wong, C. Chan, A Review of psychological issues among patients and healthcare staff during two major coronavirus disease outbreaks in china: contributory factors and management strategies, Int. J. Environ. Res. Public Health 17 (18) (2020), https://doi.org/10.3390/ijerph17186673.
[99] M.H. Shahrajabian, W. Sun, A. Soleymani, Q. Cheng, Traditional herbal medicines to overcome stress, anxiety and improve mental health in outbreaks of

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 stressinduced depression, Behav. Brain Res. 380 (2020), 112439, https://doi.org/10.1016/j.bbr.2019.112439.