Int. J. Plant Bas. Pharm. (2023) 3(2), 191-199

INTERNATIONAL JOURNAL OF PLANT BASED PHARMACEUTICALS
https://ijpbp.com

REVIEW

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Bioactive compounds, and bio-activities common to three natural products expected to boost the treatment of the comorbidities of COVID-19: A review

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ARTICLE INFO

Article History:

Received: 22 April 2023
Revised: 18 July 2023
Accepted: 15 August 2023
Available online: 21 August 2023

Edited by: B. Tepe

Keywords:

Nigella sativa
Curcuma longa
Honey
SARS-CoV-2
Bio-activity
Synergy

ABSTRACT

COVID-19, with many variants of its causative virus, has been and is still causing ravages and claiming many lives all over the globe. Currently, there are no therapeutic agents against the disease except for a few already existing ones that are used to manage the symptoms and comorbidities associated with the disease. Even some currently developed vaccines cannot efficiently handle various variants of the causative agent for COVID-19. This review is aimed at utilizing the possible synergy that might exist in the combination therapy of *Nigella sativa*, *Curcuma longa*, and honey for better management of COVID-19 and the associated comorbidities. The literature search was performed by inputting some relevant keywords into important search engines and websites such as Google, Google Advanced Search, PubMed, and so on. In vitro studies on some bioactive compounds isolated from *N. sativa* and *C. longa* have demonstrated activity against SARS-CoV-2. The three natural products, *N. sativa*, *C. longa*, and honey have exhibited wonderful activities against some of the health conditions associated with COVID-19; such include; antiviral, immunomodulatory, antioxidant, anti-inflammatory, bronchodilatory, antihistamine, antitussive, antimicrobial and other activities. Some of the major active compounds responsible for the bioactivities of these products and their mechanisms of action have been highlighted. The products individually have exhibited strong biological activities against conditions associated with COVID-19 and so are expected to exert a synergistic effect when combined in the treatment of the disease even with many variants of the causative organism.

1. Introduction

Single-stranded positive sense, enveloped RNA viruses with a non-segmented genome belonging to the family Coronaviridae and the order Nidovirales named Coronaviruses, have been implicated in varying severe respiratory illnesses in humans and animals (Aleebrahim-Dehkordi et al., 2021). From the 1960s to date, seven human coronaviruses (HCoVs) have been identified (Cui et al., 2019; Lau et al., 2021; Pourrajab et al., 2020); they include OC43 HKU1, HCoV-229E, MERS-CoV, NL63, SARS-CoV and SARS-CoV-2.

SARS-CoV-2 is the third novel coronavirus to emerge in this century. It causes COVID-19 infection which appeared in Wuhan, China in 2019. It was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. Within a few months, SARS-CoV-2 has spread to hundreds of countries around the world. It is dangerous because it is transmitted easily from person to person, whether or not the person is exhibiting symptoms (Cui et al., 2019). Symptoms of COVID-19 include; chills, fatigue, sore throat, dry cough, chest pain, muscu-

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e-ISSN: 2791-7509
doi: https://doi.org/10.29228/ijpbp.32

lar and joint pain, abdominal pain, vomiting, headache, fever, and other symptoms (Romero et al., 2022).

Nigella sativa, a medicinal plant found throughout many regions of the world, is being used ethnomedicinally in the treatment of various diseases and disorders. It has been shown to possess antioxidant, anti-inflammatory, anti-ulcer, and other properties. One of the major bioactive compounds, thymoquinone, isolated from *N. sativa*, has demonstrated activity against SARS-CoV-2 (Badary et al., 2021).

Curcuma longa is used for culinary and medicinal purposes. Curcuminoids, the bioactive compounds isolated from *C. longa*, have demonstrated activities against a wide range of diseases. These compounds have shown antiviral, anti-inflammatory, bronchodilatory, antihistaminic, antitussive, immunomodulatory, and antimicrobial activities (Rattis et al., 2021). Among the curcuminoids, curcumin was identified to be the most abundant and is potent against viruses such as HIV, herpes simplex virus, hepatitis C virus, and others (Tung et al., 2019).

Honey, a naturally occurring sweet agent produced by *Apis mellifera* (honeybee), has always been utilized as an antimicrobial and also in the treatment of inflammatory conditions such as cough, asthma, etc. It is made up of a wide range of compounds such as sugars, enzymes, amino acids, vitamins, and minerals as well as secondary metabolites such as phenolics and flavonoids (Abedi et al., 2021; Machado De-Melo et al., 2018).

Among the natural products that have potential in the management of COVID-19, are the pumpkins. Pumpkins have been found to possess pharmacological activities such as antiviral, antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, and antihypertensive activities. Important phytoconstituents such as phenolics, flavonoids, and terpenoids, vitamins such as vitamins A, C, and E, and minerals such as selenium, zinc, and iron have been identified and isolated from the seeds and peels of pumpkins. Due to these pharmacological activities, and the mineral and vitamin contents of pumpkins, they can be used as medicines and foods to boost the body's immunity against COVID-19 and other debilitating ailments of humans (Hussain et al., 2021; Hussain et al., 2023a; Hussain et al., 2023b).

As the rate by which COVID-19 disease affects people has risen globally, the search for how various coronaviruses relate to each other intensifies. Currently, variants for SARS-CoV-2 by WHO are alpha, beta, gamma, delta, eta, iota, kappa, lambda, and mu which are classified either as variants of interest or concern (Lauring & Malani, 2021).

The alpha variant is the major variant that drove the second wave of the disease in the United Kingdom in the fall of 2020. It possesses different mutations that affect the spike proteins that make the variant more virulent. In October 2020, the beta variant was first identified in South Africa and has spread to other countries. Research has shown that this variant has spectacular mutations that escape the antibodies isolated from patients who had COVID-19 disease previously, predisposing people with coronavirus earlier to contract this variant despite their existing immunity (Mahase, 2021).

The gamma variant was first detected in Brazil and then in the USA but has remained the dominant variant in South America. The delta variant was detected in India in October 2020. The emergence of the delta variant with a mutation on the K417N spike protein is another development that has given this variant a second name "delta plus''. It was reported that antibodies from the vaccinated people were still effective against this variant (Mahase, 2021).

The Eta variant was initially detected in December 2020 in the UK through genome sequencing. Its potential to reduce the neutralizing ability of some monoclonal antibody treatments and convalescent plasma has been pronounced by the CDC. In November 2020, the Iota variant was first identified in New York City, USA, and has so far been reported in 53 countries. The kappa variant appeared first in India in October 2020 and has been reported in 55 countries. The lambda variant accounted for 80% of the pandemic when it was first discovered in Peru in December 2020 (Lauring & Malani, 2021).

The Mu variant, discovered in Colombia in January 2021, has also been reported in other countries in South America, North America, Asia, and Europe. This variant has mutations that might make the immune systems susceptible to COVID-19 while decreasing the effectiveness of vaccines as reported by WHO (Álvarez-Díaz et al., 2020; Xie et al., 2021). The Omicron variant was first reported from South Africa and Botswana on 24 November 2021 (Petersen et al., 2022).

The three products *N. sativa*, *C. longa*, and honey have been separately used in the treatment of COVID-19 but have not been used in their combined state. Thus, this review looks at the synergy that will possibly exist in the combination of the three for better management of the comorbidities associated with COVID-19.

2. Materials and methods

The literature search for this review was carried out using Google, Google Advanced Search, PubMed, and Scopus. The original articles retrieved from the search were relevant and related to the topic of the review. Searching was conducted before June 2022 using varied keywords which include antiviral, anti-inflammatory, and anti-SARS-CoV-2 properties of *N. sativa*, *C. longa*, and honey.

3. Pharmacological properties of *N. sativa*, *C. longa*, and honey for prevention and therapy of COVID-19

COVID-19 is accompanied by comorbidities and multiorgan dysfunction which contribute immensely to the severity of the disease and mortality among patients (Badary et al., 2021). Some of the clinical features are; fever, coughing, sore throat, headaches, fatigue, myalgia (muscle pain), and breathlessness which later progress into pneumonia, respiratory failure, and death.

The major contributing factors to the fatality of COVID-19 are an imbalance in the production of some inflammatory mediators and pro-oxidants and an exaggerated immune response in the sufferers leading to Acute Respiratory Distress Syndrome (ARDS) (Maideen, 2020; Mohammed et al., 2019).

N. sativa, *C. longa*, and honey (Figure 1) are very effective in combating the conditions associated with COVID-19, hence, they exhibited antiviral, antioxidant, anti-inflammatory, immunomodulatory, bronchodilatory, antihistaminic and antitussive and antibacterial effects both in animal models and some clinical trials (Cheng et al., 2018; Hossain et al., 2020; Maideen, 2020; Rattis et al., 2021).

4. *N. sativa*

N. sativa (family, Ranunculaceae) popularly known as “Black Cumin” is native to many regions of the world including the Mediterranean, North Africa, the Indian subcontinent, Greece, Syria, Albania, Turkey, Southwest Asia, India, Saudi Arabia, Egypt, Iran and Pakistan (Hannan et al., 2021; Salehi et al., 2021) where it is used for culinary and medicinal purposes. Its seed has been traditionally employed in the treatment of ailments such as cough, dizziness, bronchitis, asthma, chest congestion, paralysis, infertility, inflammation, chronic headache, and gastrointestinal disorders such as diarrhea, flatulence, etc. (Ahmad et al., 2021). The seed oil is used as a remedy for eczema, abscess, orchitis, nasal ulcer, and swollen joint. It is also usually combined with honey in the treatment of asthmatic problems including chest congestion and bronchospasm. *N. sativa* possesses antiviral, immunomodulatory, antioxidant, anti-inflammatory, and other properties, and can also cure COVID-19 symptoms which include; chills, fatigue, sore throat, dry cough, chest pain, muscular and joint pain, abdominal pain, vomiting, headache, fever, and other symptoms.

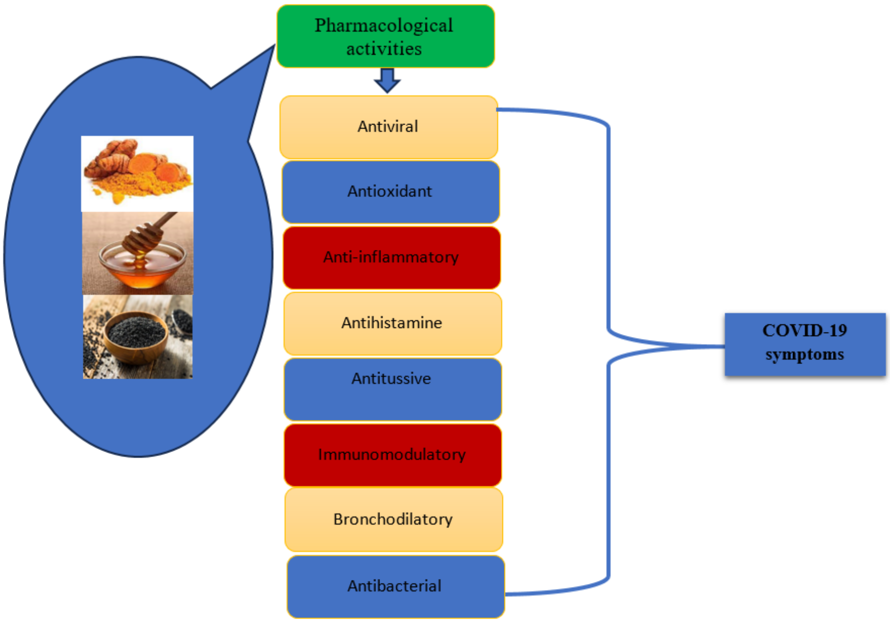

Figure 1. The synergy of biological activities of *N. sativa*, *C. longa*, and honey can fight all severe and mild symptoms of COVID-19

4.1 Antiviral activity of N. sativa

N. sativa has been reported to have activities against viruses such as Infectious Laryngotracheitis Virus, Murine Cytomegalovirus, Hepatitis C Virus, Avian Influenza Virus, Peste Des Petits Ruminants, Human Immune-deficiency Virus among other viruses (Abdel-Moneim et al., 2013; Onifade et al., 2013; Sohail & Umar, 2017; Umar et al., 2016). When administered intraperitoneally, black seed (*N. sativa*) oil reduced murine cytomegalovirus titer in the spleen and liver of infected mice after a few days of treatment and after 10 days of treatment, the virus titer was undetectable (Salem & Hossain, 2000).

In human subjects infected with the hepatitis C virus, alcohol extract of black seed significantly decreased the viral load. The patients were administered 500 mg/kg of the extract daily for one month (Abdel-Moneim et al., 2013). Non-vaccinated turkeys (birds) were infected with the H9N2 strain of avian influenza virus and subsequently fed with formulated feeds containing different percentages (2%, 4%, and 6%) of powdered seeds of *N. sativa* (Acner, 2020). There were significant reductions in viral shedding in the treated groups compared to the group infected but not treated.

Black cumin seeds exhibited both prophylactic and curative effects on goats infected with peste des ruminants (Sohail & Umar, 2017). Onifade et al. (2013) reported that treatment with 10 ml of *N. sativa* twice a day for six months, led to sero-reversion and complete recovery of HIV patients. The fever, diarrhea, and multiple pruritic lesions accompanying the sickness disappeared after twenty days of treatment.

4.2 Anti-SARS-CoV-2 activity of N. sativa

Thymoquinone (TQ) (Figure 2, Table 1), the major alkaloid constituent of *N. sativa*, has demonstrated activity against clinical isolates of SARS-CoV-2. In silico studies have shown that there is a possibility of TQ inhibiting the growth of COVID-19-causing organisms by binding to domains on the spike as well as envelope proteins of the virus and hindering virus entry into the host cell. Also, TQ is proposed to inhibit the viral protease and thus diminish the replication of the virus (Badary et al., 2021).

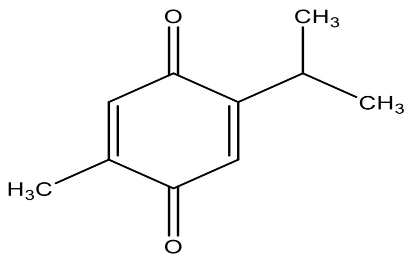

Figure 2. Chemical structure of thymoquinone (2-Isopropyl-5-methylybenzo-1,4-quinone)

4.3 Antioxidant properties of N. sativa

In the 1,1-diphenyl-2-picryhydrazyl (DPPH) free radical scavenging capacity model, methanol seed extract of *N. sativa* exhibited good antioxidant activity. Comparatively, the extract showed an antioxidant activity (IC_{50} of 12.256 mg/ml), higher than ascorbic acid

(IC_{50} of 0.097 mg/ml) (Mammad et al., 2017). TQ increases the synthesis and activities of antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, and glutathione-S-transferase, thereby offering the body system protection against reactive oxygen species (Mahmoud & Abdelrazek, 2019).

4.4 Anti-inflammatory properties of N. sativa

Acute and sub-acute anti-inflammatory studies on *N. sativa* oil were conducted using Carrageenan-induced and Complete Freund's Adjuvant-induced models respectively (Pop et al., 2020). In the acute phase, 1.5 h after administration of the oil, 2 and 4 ml/kg body weight of the oil exhibited an anti-inflammatory effect that was comparable to diclofenac at 5 mg/kg. However, in the sub-acute phase, the oil exhibited no anti-inflammatory effect. Synthetic thymoquinone was able to significantly reduce the levels of pro-inflammatory mediators, Il-1β, Il-6, TNF-α, IFN-γ, and PGE_2.

Table 1. The pharmacological properties of *N. sativa*, *C. longa*, and honey which can prevent or fight COVID symptoms

S/N	Pharmacological activities	Bioactive compound			Experimental model		
		N. sativa	*C. longa*	Honey	*N. sativa*	*C. longa*	Honey
1	Antiviral	-	Curcumin	Methylglyoxal	In vitro	In vivo (Tung et al., 2019)	In vivo (Hossain et al., 2020)
2	Anti-SARS-CoV-2	Thymoquinone	Curcumin	-	In silico (Badary et al., 2021)	In silico (Bormann et al., 2021)	In silico & in vitro
3	Antioxidant	Thymoquinone	Curcumin	-	In vivo & in vitro (Mahmoud & Abdelrazek, 2019)	In vivo (Wang et al., 2018)	In vitro
4	Anti-inflammatory	Thymoquinone	Curcumin	-	In vivo (Pop et al., 2020)	In vivo (Bhatt et al., 2021)	In vivo
5	Anti-histaminic	Nigellone & Thymoquinone	Curcumin	-	In vivo (Ikhsan et al., 2018; Mahboubi, 2018)	In vivo (Lee et al., 2018)	In vivo
6	Antitussive	Thymoquinone	-	-	In vivo (Hossain et al., 2020)	In vivo	In vivo
7	Immunomodulatory	Thymoquinone	Hydrazino-curcumin	-	In vivo (Shaterzadeh-Yazdi et al., 2018)	In vivo (Noor et al., 2022)	In vitro & in vivo
8	Bronchodilatory	-	-	-	In vivo	In vivo	In vivo
9	Antibacterial	Thymoquinone	Curcumin	Defensin-1 and hydrogen peroxide	In vitro (Mohammed et al., 2019)	In vivo & in vitro (Zheng et al., 2020)	In vitro (Almasaudi, 2020)

4.5 Anti-histaminic properties of N. sativa

Nigellone and TQ were identified as the major constituents of *N. sativa* responsible for its anti-histaminic effect. They inhibited the formation of 5-lipoxygenase products and 5-hydro-eicosa-tetra-enoic acid from polymorphonuclear leukocytes as well as the release of histamine from mast cells (Ikhsan et al., 2018; Mahboubi, 2018).

4.6 Antitussive properties of N. sativa

Extracts of *N. sativa* demonstrated antitussive properties in guinea pigs by reducing the number of coughs produced induced by citric acid aerosol. The TQ constituent exerted an antitussive effect in guinea pigs probably through binding to the opioid receptors (Hossain et al., 2020).

4.7 Immunomodulatory properties of N. sativa

Six different polar solvent extracts of black cumin and four varied commercial products of its seed oil were investigated for their immunomodulatory effect on some asthma-related mediators of inflammation (Koshak et al., 2018). They were able to suppress IL-2, IL-6, and PGE_2 in T-lymphocytes and monocytes. Most of the preparations increased the release of IL-1β-induced PGE_2 while a few of them showed a slight tendency to inhibit IL-6 release in IL-1β-induced A549 lung epithelial cells.

TQ modulated the immune system by preventing the biosynthesis of mediators such as 5-LO, COX, PGD2, and LTS. It also reduced LPS-induced proinflammatory cytokines, e.g., interleukins, and TNF-α (Shaterzadeh-Yazdi et al., 2018).

4.8 Bronchodilatory properties of N. sativa

Boiled extract of *N. sativa* exerted a bronchodilatory effect on asthmatic subjects by significantly increasing all the measured PFTs which were comparable to that of the standard drug (Boskabady et al., 2010).

4.9 Antibacterial activity of N. sativa

Bacterial infection associated with COVID-19 lead to impairment of the immune system, an increase in the bacterial colonization of the nasopharynx, and damage to the respiratory tract mucosa (Grinbaum & Kiffer, 2021). Though there is a high rate of administration of antibiotics during the treatment of COVID-19, studies have revealed that there is a low rate of bacterial infection compared to viral diseases such as influenza.

n-Hexane and chloroform fractions of *N. sativa* had appreciable activities against *Escerichia coli*, *Klebsiella pneumoniae*, and *Enterobacter aerogenes* but weak activity against *Staphylcoccus aureus*. Ethanol fraction exhibited a high inhibition against *S. aureus* whereas acetone, ethyl acetate, and water fractions did not show any activity against the bacteria (Al-Ameedy & Omran, 2019).

Oil components of black cumin exhibited antibacterial activity against *S. aureus*, *Bacillus subtilis*, and *B. cereus* with the highest zones of inhibition found in *B. subtilis* (Mohammed et al., 2019). It was proposed that TQ is chiefly responsible for its antibacterial activity but the precise mechanism of action is not yet fully elucidated.

5. C. longa

C. longa (family, Zingiberaceaa) possesses rhizomes underneath the ground. It has been used for many years in the Indian traditional medicine practice for the cure of illnesses such as infectious diseases, inflammation, gastric, hepatic, and blood disorders. In modern medical practice, it has a wide range of pharmacological effects such as antioxidant, anti-inflammatory, antimicrobial, antitumor, and hepatoprotective effects (Tung et al., 2019). *C. longa* also possesses antiviral properties, and can also cure COVID-19 symptoms which include; chills, fatigue, sore throat, dry cough, chest pain, muscular and joint pain, abdominal pain, vomiting, headache, fever, and other symptoms.

5.1 Anti-viral activity of C. longa

Curcumin (Figure 3, Table 1), the major active component of *C. longa*, is potent against viruses such as HIV, Herpes Simplex Virus (HSV), Zika Virus, Hepatitis C virus (HCV), influenza A virus and human papillomavirus (HPV). Curcumin made into carbon quantum dots has also been found to be active against the human coronavirus (HCoV) by blocking its entry into the host (Tung et al., 2019).

5.2 Anti-SARS-CoV-2 activity of C. longa

Curcumin exerts antiviral activity by hindering the cellular-virus attachment. Both in silico and docking analysis have shown that curcumin has a high affinity for S glycoprotein and ACE2 by forming six and two hydrogen bonds respectively thereby preventing the attachment of the virus to the host cell (Maurya et al., 2020). Recently, curcumin has been reported to significantly reduce SARS-CoV-2 RNA levels in human Calu-3 and Vero E6 cell cultures (Bormann et al., 2021).

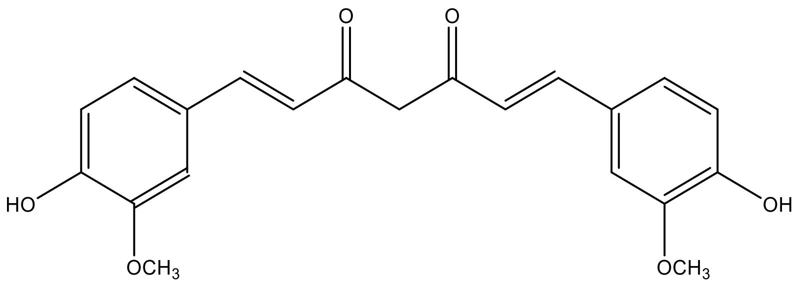

Figure 3. Chemical structure of curcumin (1,7-bis(4-hydroxyl-3-methoxylphenyl)-1,6-heptadiene-3,5-dione)

5.3 Antioxidant properties of C. longa

Curcumin increased the activity of SOD, reduced the level of MDA, and improved the activity of xanthine oxidase in oxidative stress-induced rats (Wang et al., 2018).

Curcumin is eight times more effective in preventing lipid peroxidation and oxidation of hemoglobin than vitamin E. Curcuminoids are generally utilized to improve the shelf life in food systems due to their good antioxidant properties (Wang et al., 2018).

5.4 Anti-inflammatory properties of C. longa

Curcumin has been shown to possess strong anti-inflammatory properties. Its anti-inflammatory effect occurs due to the suppression of pro-inflammatory cytokines, increase in the metabolism of xenobiotics, decrease in neutrophil migration, and reduced immune reaction (Bhatt et al., 2021).

5.5 Antihistaminic properties of C. longa

Curcumin exerts both antihistaminic and immunomodulatory properties by activating T-cells and other mediators in patients with COVID-19. It can also suppress the expression of CD80, CD86, and class-II antigens by dendritic cells and blocks the release of inflammatory cytokines like IL1β, IL6, and TNFα from LPS-stimulated dendritic cells (Lee et al., 2018).

5.6 Antitussive properties of C. longa

The most common symptom prevalent in patients with COVID-19 is dry cough which is of the major modes of viral transmission. Fatty acids in turmeric act as mucoprotective agents. Volatile oils from turmeric are also effective against respiratory tract disorders such as cough relieving, removal of sputum, prevention of asthma, etc., and may be efficacious adjuvants in the management and treatment of respiratory diseases (Li & Ma, 2020; Wiersinga et al., 2020).

5.7 Immunomodulatory properties of C. longa

Hydrazinocurcumin (Table 1) exerts its immunomodulatory effect by targeting COVID-19 immunological human host receptors such as angiotensin-converting enzyme-2 (ACE2), tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and protease-activated receptor to hinder viral infection and multiplication (Noor et al., 2022).

5.8 Bronchodilatory properties of C. longa

Currently, physicians use some bronchodilator spices herbs such as turmeric, garlic, clove, and ginger to prevent and manage coronavirus infection. These natural substances dilate the respiratory airway, allowing more volume of atmospheric air to enter the lungs. Thus, more oxygen molecules go into the lungs and get dissolved in the blood, and respiratory membrane, and are carried to the main organs of the body (Vadivelan et al., 2021).

5.9 Antibacterial activity of C. longa

Curcumin is a polyphenolic active substance with broad-spectrum antibacterial properties. It can inhibit bacterial virulence, inhibit bacterial biofilm formation, and prevent bacterial adhesion to host receptors. Curcumin affects DNA by downregulating bacterial gene expression, inhibiting bacterial responses, or interacting with DNA molecules to achieve bacteriostatic effects. It also inhibits bacterial cell division by binding to tubulin, thereby acting as a bacteriostatic agent, disrupting RNA to interrupt protein synthesis, and directly interacting with enzymes (Zheng et al., 2020).

6. Honey

Honey is a sweet natural product mainly produced by *A. mellifera* after sucking and secreting the nectar of the plant (Arawwawala & Hewageegana, 2017; Stagos et al., 2018). Based on the floral source, monofloral and multi-floral kinds of honey are obtainable. Monofloral kinds of honey, e.g. Manuka honey, are more in abundance than multifloral honey and are so named according to the plant species. Honey is also classified according to components of the flower sources, e.g. Pasture honey, Manuka honey, Jelly bush honey, and Jungle honey (Al-Hatamleh et al., 2020; Fukuda et al., 2011).

Due to the various plants on which honey is produced and the different nectars that the producers feed on, honey contains considerable amounts of both primary and secondary metabolite compounds which include water, sugars, enzymes, amino acids, flavonoids, organic acids, phenolic acids, minerals, vitamins, and volatile compounds. Small amounts of enzymes such as diastase, invertase, glucose-oxidase, acid phosphatase, catalase, and β-glucosidase are also found to be present in honey (Abedi et al., 2021; Machado De-Melo et al., 2018). Honey possesses antiviral, immunomodulatory, antioxidant, anti-inflammatory, and other properties, and can also cure COVID-19 symptoms which include; chills, fatigue, sore throat, dry cough, chest pain, muscular and joint pain, abdominal pain, vomiting, headache, fever, and other symptoms.

6.1 Antiviral activity of honey

Honey has been proven potent against viruses such as influenza virus, varicella-zoster virus, rubella, herpes simplex virus, etc. Some of the important antiviral compounds in honey responsible for its antiviral activity include methylglyoxal, copper, ascorbic acid, flavonoids, nitric oxide, and hydrogen peroxide. These compounds carry out their function by inhibiting viral replication and/or virucidal activity (Hossain et al., 2020). A study showed that the consumption of honey in HIV-positive subjects increased CD4 T lymphocytes and decreased the viral load. Methylglyoxal affects the late stage of HIV infection by blocking virion assembly and maturation (Al-Hatamleh et al., 2020).

6.2 Anti-SARS-CoV-2 activity of honey

Honey and its major components are capable of inhibiting the growth of viruses including SARS-CoV-2. The mechanism of the anti-viral activity of honey is vast; one of them is the structure of the virus by the interaction of honey and its components with proteins in the virus or by binding to target receptors on the virus (Abedi et al., 2021). The major compounds in honey responsible for its anti-viral properties are phenolics and flavonoids.

A few studies have been carried out on the effects of honey against COVID-19. In silico studies proved the flavonoid content of honey effective against COVID-19 by targeting S protein cleavage of host-cell receptors, and other targets to hamper viral replication. An in vitro experiment on the anti-SARS-CoV-2 effects of a flavonoid (naringin) on Vero E6 cells infected with SARS-CoV-2 proved the potency of the compound. A study on the use of a combination of honey, *N. sativa*, and *Anthemis hyalina* as an adjuvant in the treatment of some COVID-19 patients greatly improved the condition of the patients (Ali & Kunugi, 2021).

6.3 Antioxidant properties of honey

The antioxidant properties of different types of honey samples from Western Paraná, Southern Brazil, were investigated. The honey samples which were very rich in total phenol and flavonoid contents exhibited very good antioxidant properties by reducing the levels of free radicals generated by the ferric reducing antioxidant potential (FRAP), DPPH and 2,2-azinobis (3-etilbenzotiazoline-6-sulfonic acid (ABTS) models (Galhardo et al., 2020).

In a similar study by Pena Júnior et al. (2022), 15 monofloral honey samples obtained from Minas Gerais, Brazil, exhibited antioxidant properties by quenching the free radicals released from DPPH. Analysis of the total phenolics and flavonoids showed that the samples were rich in bioactive compounds.

6.4 Anti-inflammatory properties of honey

Honey is reported to have inhibited inflammatory biomarkers such as mitogen-activated protein kinase and nuclear factor kappa. These markers in turn induce the other inflammatory factors such as IL-1β, IL-6, IL-10, lipoxygenase 2 (LOX-2), cyclooxygenase-2 (COX-2), C-reactive protein, and TNF-α (Hossain et al., 2020). A combination of different kinds of commercial honey inhibited respiratory bust induced by thrombin in neutrophils of humans as well in the peritoneal macrophages of rodents. At 400 mg/mL, Manuka honey inhibited the neutrophil synthesis of TNF-α. The reactive oxygen species quenching capacity of Manuka honey was attributed to the methyl syringate content of it (Masad et al., 2021).

6.5 Antihistaminic properties of honey

Treatment with honey before the injection of histamine dihydrochloride in rats caused a significant inhibition of wheal. The antihistamine property of honey was not as effective as that obtained with the standard drug chlorpheniramine (Weerakoon et al., 2014).

6.6 Antitussive properties of honey

In children under 2-18 years with upper respiratory tract infections, the effect of honey and dextromethorphan on nocturnal cough and sleep quality was assessed. In a comparison of honey, dextromethorphan, and no treatment, honey was rated most favorably for symptomatic relief by the parents of the children under study (Paul et al., 2007).

The effect of doses of a mixture of milk and honey, given for three consecutive days to children suffering from non-specific acute cough, was compared to those of over-the-counter antitussive, dextromethorphan (DM) and levodropropizine (LDP). From the answers provided by the parents of the children in a cough questionnaire, the milk and honey mixture was as effective as DM and LDP (Sopo et al., 2015).

6.7 Immunomodulatory properties of honey

Exposure of a cell line to different types of honey caused a substantial reduction in the release of ROS which was followed by a meaningful increase in the manufacturing of tumor necrosis factor (Masad et al., 2021).

Honey is believed to activate T-lymphocytes, B-lymphocytes, and neutrophils which ultimately produce cytokines such as IL-1, IL-6, and TNF-α. It equally increases the serum levels of interferon-gamma (IFN-γ), and interferon-gamma receptor 1 (IFNGR1) in breast cancer in rats (Ahmad et al., 2021).

6.8 Bronchodilatory effect of honey

Bee honey when co-administered with seeds of *N. sativa* proved to have bronchodilatory effects on asthmatic patients. There was a significant increase in the forced vital capacity (FVC) in the asthmatics administered with the mixture. Honey was also able to improve significantly the pulmonary function tests, forced expiratory volume (FEV1), peak expiratory flow rate (PEFR), and FVC in individuals diagnosed with bronchial asthma (Abbas et al., 2019).

6.9 Antibacterial activity of honey

A combination of honey and lemon juice gave a better activity than honey alone. When used singly against *K. pneumoniae* and *Streptococcus* spp., the antibiotics tetracycline and ampicillin showed very negligible effects but mixing them with honey gave appreciable zones of inhibition. Other bacteria proven to be susceptible to honey are *E. erogens*, *S. aureus*, *Salmonella typhimurium*, *E. coli*, etc. Phenolic compounds, peptide defensin-1, and hydrogen peroxide (Table 1) are some of the compounds in honey that contribute to its antibacterial properties (Almasaudi, 2020; Gowramma et al., 2021).

7. Conclusions

Individually, *N. sativa*, *C. longa*, and honey have exerted antiviral, antioxidant, anti-inflammatory, antihistaminic, antitussive, immunomodulatory, bronchodilatory, and antibacterial activities, and were also able to clear the symptoms due to COVID-19. Some isolated phytocompounds from these natural products were responsible for the said activities. When administered singly, these products proved effective, and it is expected that when combined, there would be a synergistic effect that will give a boost to the desired effects. Formulations from these products can be incorporated into the diet for consumption or their decoctions made and taken orally for either the treatment or prevention of COVID-19.

Further studies should focus on carrying out in vivo experiments using these products to validate these claims. Also, synthetic chemists could leverage the isolated compounds to synthesize chemotherapeutic agents for the treatment of COVID-19.

Acknowledgments

None.

Conflict of interest

The authors confirm that there are no known conflicts of interest.

Statement of ethics

In this study, no method requiring the permission of the "Ethics Committee" was used.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

The authors declare that the study did not receive any financial support/grant from any public or private organization.

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Supplementary File

None.

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