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Promising roles of *Zingiber officinale* roscoe, *Curcuma longa* L., and *Momordica charantia* L. as immunity modulators against COVID-19: A bibliometric analysis

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ABSTRACT

Zingiber officinale, Curcuma longa, and *Momordica charantia* are medicinal plants that are commonly used in the form of herbal tea, which is formulated to strengthen the immune system, especially against COVID-19 infection. Excellent antioxidant, anti-inflammatory, and immunostimulatory properties have been reported for their bioactive compounds, which have been shown to aid in stimulating immune systems as well as lowering the risk of severe COVID-19 such as lung injury. Yet, no bibliometric study on the subject is available. Hence, the purpose of this study is to quantitatively examine the existing articles related to the therapeutic potential of these three herbs, as well as their mechanisms of action in combating the SARS-CoV-2 virus. A total of 121 papers were retrieved from Scopus database up to 14th March 2023. The bibliometric analysis was conducted using VOSviewer software. Based on the literature search, *Z. officinale* was the most researched plant. India appeared as the most prolific country, with the highest number of articles contributed by two authors from India (Rathi, R. and Gayatri Devi, R.). In terms of keywords, the plants were associated with immune modulation, management of symptoms, antioxidant, anti-inflammatory and antiviral activities. Several important bioactive compounds were responsible for these effects such as gingerol, paradol, shogaol, curcumin, calebin A, momordicoside, karaviloside and cucurbitadienol. These compounds were hypothesized to prevent and cure COVID-19 by regulating inflammatory response, downregulating oxidative stress and modulating immunostimulatory activity. This review paper therefore supports the potential of *Z. officinale, C. longa*, and *M. charantia* to be formulated as a herbal blend for treating and preventing COVID-19 infection.

1. Introduction

Coronavirus disease (COVID-19) is an infectious viral respiratory syndrome that is caused by SARS-CoV-2 virus. This disease begins to emerge in December 2019 and remains increasing day by day with cumulative cases of 762,201,169 up to 6 April 2023 reported by World Health Organization (WHO) [1]. Based on Centers for Disease Control and Prevention (CDC), patients infected with COVID-19 may experience mild to severe symptoms 2–14 days after being exposed to the virus. The symptoms include cough, sore throat, loss of taste or smell, nasal congestion, muscle aches, shortness of breath, fever and headache [2]. Remdesivir and hydrochloroquine are two examples of small compounds that are used by the clinicians to treat this illness. These molecules may be successful at inhibiting SARS-CoV-2, but with more doses, undesirable side effects such as gastrointestinal issues and cardiovascular toxicity have been observed [2]. Thus, it is crucial to provide more alternative treatments derived from plants because they are more affordable, safe and natural.

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In this study, *Zingiber officinale, Curcuma longa* and *Momordica charantia* were chosen to be reviewed and analysed as a combined herbal extract using bibliometric tool. It is hypothesized that polyherbal extract-based formulation is associated with improved efficacy of the herbal supplement. It capable to enhance the bioavailability of active constituents, amplifying therapeutic effects, and diminishing their toxicity [3]. *Z. officinale* (Zingiberaceae) or ginger, is a herbaceous perennial plant that is extensively used as traditional herbal medicines and also in cooking as spices. This plant originated from South-East Asia, Southern China and India [3]. A ginger plant can reach a height of 90 cm. The rhizome is characterized as thick lobed with light brown colour and a pungent aromatic smell. Ginger is commonly added as an ingredient in tea along with cinnamon. A previous study highlighted the anti-infective activities of cinnamon which can be attributed to its phytochemicals [4]. Similarly, ginger was reported to consist of numerous phytochemicals associated with its bioactivities including polyphenols (gingerol), phenolic compounds (zingerone, gingerenone-A, quercetin, and 6-dehydrogingerdione) and terpene compounds (α-farnesene, and β-sesquiphellandrene, β-bisabolene, α-curcumene and zingiberene) [3,5].

C. longa or turmeric is classified as a rhizomatous herbaceous perennial plant that belongs to the family Zingiberaceae. Turmeric is widely used in cooking, cosmetics, tea, as well as colorants. This plant is native to tropical South Asia and widely cultivated in India, Indonesia, Thailand, Cambodia, Malaysia, Cambodia, Bangladesh, Nepal, West Bengal, Madagascar, and the Philippines [6]. Turmeric plants can grow up to 100 cm in height. The rhizome is tuberous with a segmented and rough skin texture and yellowish-brown colour with orange interior. Turmeric contains many phytochemicals including volatile oils such as sesquiterpenes (turmerone, zingiberene and curcumenol) and curcuminoids (curcumin, demethoxycurcumin, 5′-methoxycurcumin, and dihydrocurcumin) [7].

M. charantia or bitter gourd belongs to the Cucurbitaceae family and is commonly grown in subtropical and tropical regions [8]. Currently, bitter gourd is mainly cultivated in South East Asia, India, and China. The height of the plant can reach up to 2–4 m. The fruits are green, elongated and oval in shape with a pointy surface. Bitter gourd contains numerous bioactive compounds including carotenoids (β-cryptoxanthin, lycopene, lutein, α-carotene, β-carotene and zeaxanthin), cucurbitane triterpenoids (charantin, kuguacins A – S, momordicine I, II and III, saponins and sapogenins) and phytosterols (ergosterol peroxide, stigmasterol, campesterol, β-sitosterol and decortinone) [9].

Medicinal herbs have been used to treat SARS-CoV-2 and other viral infections. It has been advised to treat COVID-19 utilising natural treatment in addition to pharmaceutical drugs since there are numerous of evidences to support the claim that herbal remedies may help lower and manage the risk of the disease [10,11]. Several studies have documented the benefit of ginger, turmeric and bitter gourd as immune boosters and antioxidants, suggesting a potential treatment for managing COVID-19 disease. Administration of ginger, turmeric and bitter gourd extracts in preclinical studies have shown to reduce inflammation in the body, improve oxidative status as well as improve the body's antibody responses toward infections [5,6,12,13].

According to ethnomedical research, ginger has been employed by Traditional Chinese Medicine (TCM) for more than 200 years to cure a variety of ailments, including constipation, colds, indigestion, nausea, pain and infectious disorders [5]. Turmeric has been used in Ayurvedic medicines for hundreds of years and is the most researched Ayurvedic herb. Due to its major antioxidant and calming properties, it supports the Ayurveda recommendation of turmeric extract for a balanced inflammatory response [7]. While bitter gourd is mostly used in African folk medicine to treat fever, worm infestations, inflammation, syphilis, menorrhagia, skin disorders, and rheumatism [8].

Although each of these herbs is well known for its potential as an immune booster, their combined effects have not been explored. Therefore, this present review aims to highlights the research gaps and explore the research opportunities based on the global trends and the influential aspects of the author, country, organization and journal in prevention and treatment of COVID-19 disease using *Z. officinale, C. longa* and *M. charantia*. In addition, this review provides a comprehensive information on the phytochemical compounds that were associated with anti-inflammatory, antioxidant and immnostimulatory properties, their mechanism of actions and safety data.

2. Research methodology

2.1. Data collection

The articles published from the year 2019–2023 related to *Z. officinale*, *C. longa* and *M. charantia* plants for prevention and treatment of Covid-19 were retrieved from the Scopus database up to 14th March 2023. The decision to select Scopus as the sole database was based on the fact that it already covers 99% of the journals found in the Web of Science database [14]. Original and English articles of *Z. officinale*, *C. longa* and *M. charantia* tea related to COVID-19, particularly in the improvement of immunity were included. While, review paper, book chapter, letter and note were excluded from the screening process [15]. The main keywords used to identify relevant articles were presented as in Table 1 and the PRISMA flowchart of the search strategy is described as in Fig. 1. Full texts that met the eligibility criteria from the inclusion and exclusion requirements were analysed based on the title, abstract, and introduction.

2.2. Data analysis and visualization

The selected articles were retrieved in CSV format and imported to Microsoft Excel. The articles were analysed and visualized by using VOSviewer 1.6.19 (Leiden University, Netherlands) using co-occurrence, co-authorship analysis and citation analysis, applying full counting method [16]. Then, the data on author keyword, country, organization, author, publication source and document were presented in network and overlay visualization, represented by different colour and size of nodes. The species names were confirmed using The World Flora Online (WFO) and the chemical structures of the compounds were drawn using ChemSketch software (ACD/labs, Canada).

3. Results

3.1. Analysis of keywords, author, country, organization and journal of *Z. officinale*

Bibliometric analysis for author keywords found 172 items. "Covid-19" was the most occurrence term with the highest total link strength (142), followed by "immune system" (53) and "zinc" (53) (Table 2). Fig. 2 presents the network visualization of the author keyword analysis, which comprised of 19 clusters. While Fig. 3 presents the overlay visualization based on average publication year. The time trend is represented by different colours of nodes while the size of the nodes represents the occurrence numbers of keywords. The yellow node is represented by the keywords related to the latest publication such as ayurvedic medicine, anti-viral, adaptogens, herbal supplement,

Table 1
The list of keywords used and number of documents retrieved from Scopus database.

Keyword	Number of documents
Zingiber officinale OR ginger AND immune AND COVID-19	79
Curcuma longa OR turmeric OR curcumin AND immune AND COVID-19	196
Momordica charantia OR bitter gourd OR AND immunity AND COVID-19	6

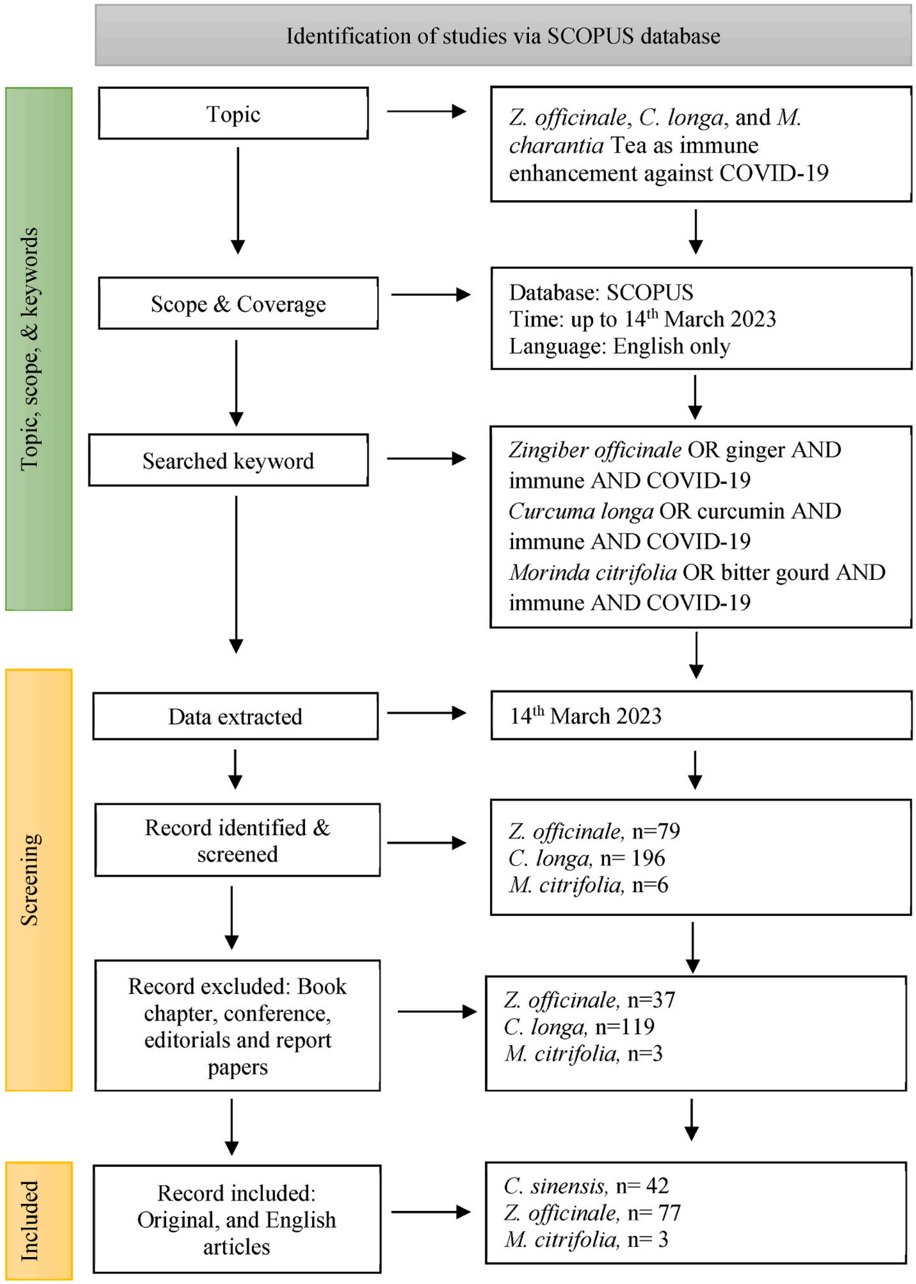


Fig. 1. The PRISMA flowchart of the search strategy.

Table 2
The most productive author keywords.

Keyword	Occurrence	Total link strength
Covid-19	25	142
Immune system	5	53
Zinc	4	53
Coronavirus	5	50
Ginger	3	42
Immunity	10	39
Sars-cov-2	2	38
Garlic	2	36
Honey	2	36
Nutrition	2	36

pandemic and protein-ligand interactions.

As shown in Table 3, Rathi, R. and Gayatri Devi R. from India, published two articles that were the highest among the authors. Meanwhile, Aishwarya, T.S., Dey, Y. N., Francis, T. V., and Avula, B. were among the authors who recently published their articles in 2022 (Supplementary 1a). India showed the biggest node as in Supplementary 1b, indicating the highest number of documents published which was 15 articles. All organizations had one document published with Warsaw University of Life Sciences, Poland had the highest citation. It is worth noting that a significant majority of the organizations in the top 10 list are situated in India. The nodes were of equal size, indicating an equal number of documents contributed by each organization (Supplementary 1c). International Journal of Research in Pharmaceutical Sciences produced the highest document which was three articles, while Pharmaceuticals received the highest citation (8) as shown in Table 4. The International Journal of Research in Pharmaceutical Sciences was one of the pioneering journals to publish on this particular topic. (Supplementary 1d).

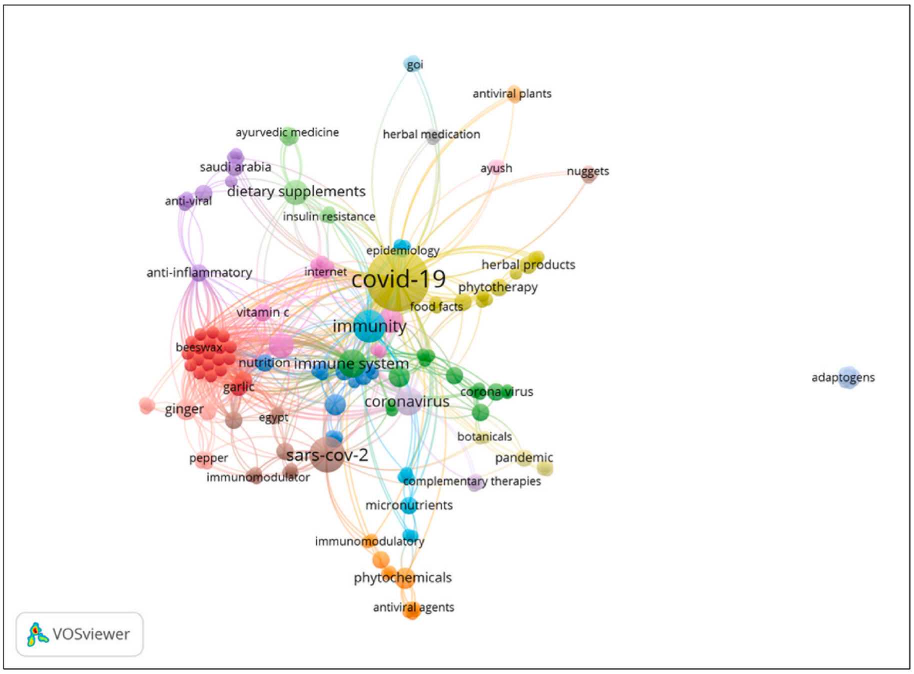


Fig. 2. Network visualization of author keywords analysis for *Z. officinale*.

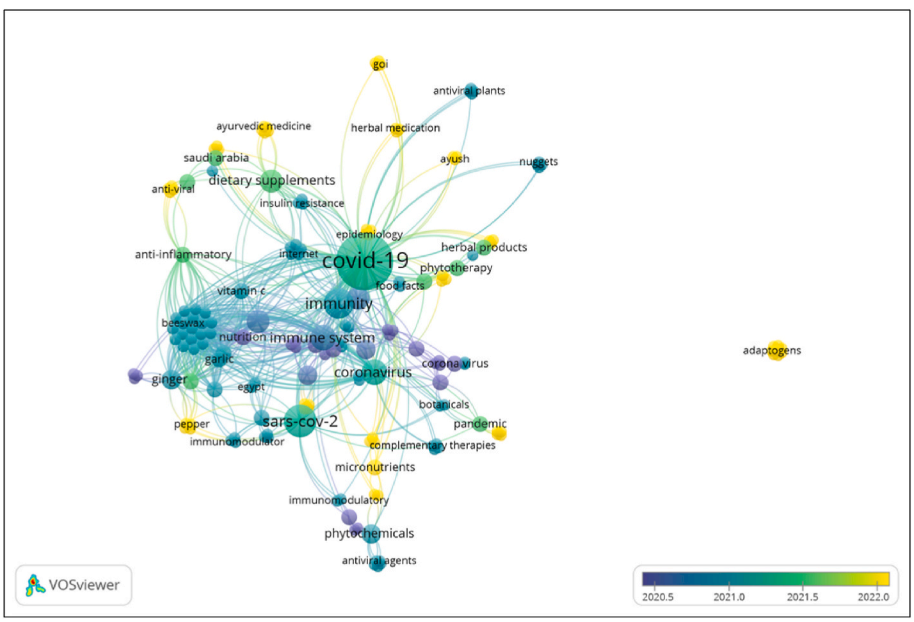


Fig. 3. Overlay visualization of author keywords analysis of *Z. officinale*.

3.2. Analysis of keywords, author, country, organization, and journal of C. longa

There was a total of 308 author keyword found with the top 3 keywords (the most occurrences) were, "Covid-19", "Sars-cov-2" and "Curcumin" (Table 5). The network map in Fig. 4 showed a total of 31 clusters with "Covid-19" having the largest node. The terms such as "lung injury", "cytokine storm in covid-19" and "curcuma longa" were among the keywords found in the recent publication as shown in the yellow nodes (Fig. 5).

A total of 307 authors were found with all the top 10 authors published two articles. Ahmadi, Roshangar, Tahmasebi and Valizadeh were among the top cited authors (Table 6). Based on the overlay visualization (Supplementary 2a), the authors were grouped into 50 clusters. Datta S., Anand I., and Bhavani K. were among the authors who published recently. The nodes were of equal size, indicating an equal number of documents published by each author. For country analysis, a total of 39 countries were found with India having the highest number of publications (36), number of articles (515) and total link strength (12), followed by the United States and Iran. Armenia, South Korea and Pakistan were observed to have recent publications on *C. longa* (Supplementary 2b). For organization, a total of 228 were found with Tabriz of University Medical Sciences producing four articles from two different centers, Immunology Research Centre and Stem Cell Research Centre (Supplementary 2c). This university also received the highest citation (48) and total link strength (17). For publication sources,

Table 3
The most productive authors, countries and organizations.

Author	TP	Country	TP	Organization	TP
Rathi R.	2	India	15	Warsaw University of Life Sciences, Poland	1
Gayatri Devi R.	2	United States	4	Goa University, India	1
Ak G.	1	Turkey	3	KLE College of Pharmacy Belagavi, India	1
Arora S.	1	Jordan	3	Asmara University, India	1
Behl T.	1	Saudi Arabia	3	Regional Ayurveda Research Institute for drug development, India	1
Bungau S.	1	Australia	2	Adamas University, India	1
Chadha S.	1	Bangladesh	2	Chitkara University, India	1
Gallo M.	1	Iran	2	University Cattolica Del Sacro Cuore, Italy	1
Khullar G.	1	Eqypt	2	Selcuk University, Turkiye	1
Kumar A.	1			University North, Croatia	1

TP = Total of publication.

Table 4
The most productive journals.

Journal	Document	Citation
International Journal of Research in Pharmaceutical Sciences	3	1
Journal of Ayurveda and Integrative Medicine	2	1
Medicinal Plants	2	4
Pharmaceuticals	2	8
Tropical Journal of Pharmaceutical Research	2	1
Clinical Nutrition Open Science	1	1
Nutrients	1	2
Advances in Integrative Medicine	1	7
Healthcare (Switzerland)	1	7
Heliyon	1	1

Table 5
The most productive keywords.

Keyword	Occurrences	Total link strength
Covid-19	47	254
Sars-cov-2	17	85
Curcumin	9	68
Immunity	9	62
Coronavirus	8	66
Ayurveda	7	35
Immune system	6	60
Zinc	5	57
Molecular docking	5	24
Nutrition	4	45

International Journal of Research in Pharmaceutical Science published the highest document with six articles and Nutrient received the highest citation (131) (Table 7). While, recent articles were observed to have published in the Journal of Ayurveda and Integrative Medicine, Gene Reports and Journal of Herbal Medicine (Supplementary 2d).

3.3. Analysis of keywords, author, country, organization, and journals of M. charantia

A total of 15 author keyword were found and with covid-19 had 2 occurrences and 9 total link strength (Table 8). Three clusters were generated based on the network map (Fig. 6) and covid-19 had the biggest node, indicating the highest occurrence. While overlay map showed that the term "Chinese medicine" and "Southern benin" were among the keywords published in the recent articles (Fig. 7).

Table 9 showed the top 3 authors, publishing one article each. Zhang, H. and Zhou, Q. were among the authors who published recently (Supplementary 3a). In terms of country, only three countries contributed to the publication of *M. charantia* with Brazil receiving the highest number of citations (8). Based on the overlay visualization (Supplementary 3b), China was observed to have recent publications on *M. charantia*. For organization, Universidade do vale do Taquari–Univates, Brazil, and Tianjin University of Traditional Chinese Medicine, China produced two articles and received the highest citation which was eight citations. Tianjin University of Traditional Chinese Medicine also contributed to the recent publication (Supplementary 3c). For document analysis, the article written by Marmitt D.J. received the highest citation which was eight. The article is entitled, "Compounds of plants with activity against SARS-CoV-2 targets", published by Expert Review of Clinical Pharmacology in 2021 which was also the most cited journal for this research (Table 10). Expert Review of Clinical Pharmacology was one of the earliest journals to publish on *M. charantia* research related to COVID-19 (Supplementary 3d).

4. Discussion

4.1. Bibliometric analysis

Bibliometric analysis has significantly improved scientific understanding in uncovering the global trend on a specific topic [17]. The number of papers on traditional herbal therapy increases every year due to its safety, ease of availability, low cost, and potential efficacy. However, in the case of bitter gourd, the full potential of this plant in the management of COVID-19 is not been fully discovered. Only three documents of *M. charantia* related to COVID-19 natural remedies were retrieved after the exclusion process. On the other hand, 77 publications relating to the use of turmeric were discovered, indicating a significant potential for this plant in the treatment of COVID-19. According to country analysis, India dominated the study trend on the application of ginger, turmeric, and bitter gourd in the alternative therapy for COVID-19. India is renowned for its richness in biodiversity, distinctive culture, and ancient medical practises including Ayurveda, Unani, Siddha, and Homeopathy [18]. While the research trend for turmeric was led by Iranian institutes. Thus, it is crucial for these countries to engage in this research collaboration.

The keyword analysis revealed extensive preclinical trial studies using ginger, turmeric and bitter gourd, starting with evaluating the plant's potential antiviral and other related properties (such as antioxidant and anti-inflammatory). The molecular mechanisms, bioactive compounds or their combinations were also determined in rats, indicated by the keywords such as "active ingredient", "molecular docking", and "phytochemical". There is still lacking research activities relating to herbal drug development and clinical trial on these plants for COVID-19. The term "COVID-19" was identified as the most productive keyword, suggesting the important role of these plants in improving conditions related to this disease.

4.2. Ginger, turmeric and bitter gourd's compounds interacted with SARS-CoV-2 protein via computational analysis

Anti-SARS-CoV-2 drugs inhibit virus replication and survival by targeting SARS-CoV-2-related papain-like protease (PLpro) [19]. Numerous ginger compounds, including 8-gingerol, 10-gingerol, and 6-gingerol, were studied for their ability to inhibit PLpro via molecular docking. It was found that 6-gingerol exhibited a high binding affinity with the main protease, SARS-CoV3C like molecule and cathepsin K which are essential for SARS-CoV-2 replication [17]. Another docking analysis found that 4-gingerol, had the lowest binding energy against SARS-CoV-2 Mpro which could serve as a viral inhibitor for COVID-19 infection [20]. Sesquiphellandrene, a ginger-derived terpene, has been reported to bind to S protein and hence interfere with the S protein-ACE2 interaction [21].

Moreover, a computational analysis demonstrated curcumin as

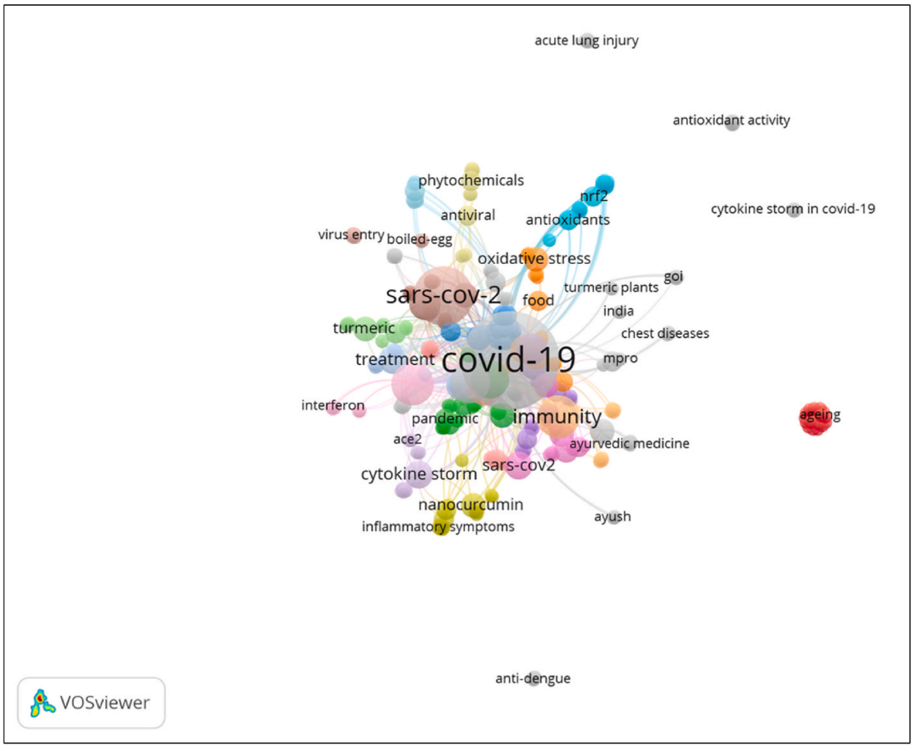


Fig. 4. Network visualization of author keywords analysis for *C. longa*.

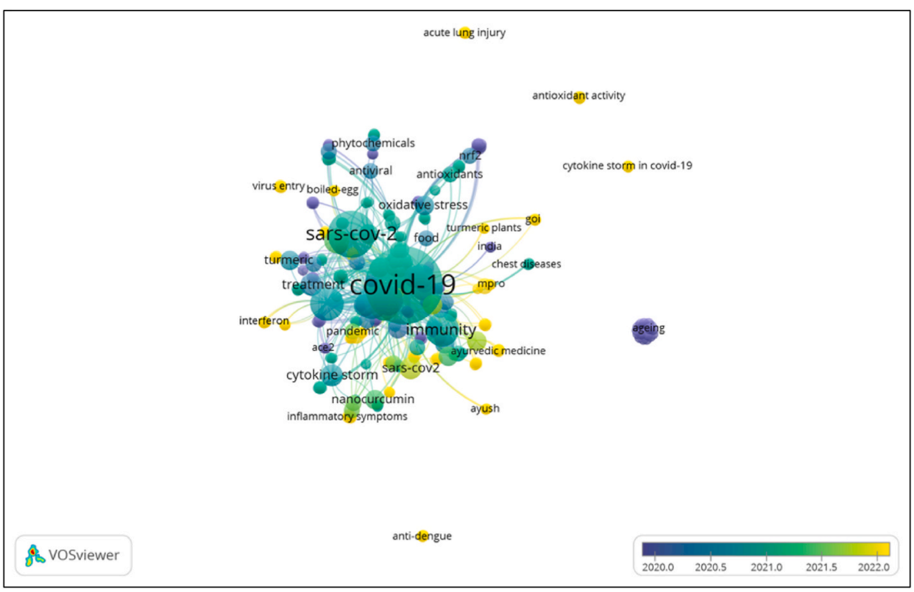


Fig. 5. Overlay visualization of author keywords analysis for *C. longa*.

potent antiviral agent [22]. It binds with the S glycoprotein with high affinity by forming six hydrogen bonds [23]. Network pharmacology was used to explore the mechanism of several compounds in *C. longa* rhizome. This study discovered that ten compounds (curcumin, turmeronol A, turmeronol B, cyclocurcumin, calebin A, 4-Hydroxycinnamic acid, ar-turmerone, caffeic acid, demetoxycurcumin, and quercetin) were linked to four major target proteins (EGFR, TLR4, IFNG, and AGTR2) [24].

The inhibitory effects of *M. charantia* compounds were also evaluated against the SARS-CoV-2 virus, and the results revealed that karaviloside III had a stronger inhibitory activity than FDA drugs [25]. Inhibitory actions against the target proteins were also demonstrated by momordicoside B, kuguaglycoside A, and cucurbitadienol, suggesting that these compounds could be employed to prevent further transmission of the SARS-CoV-2 virus [26]. The summary of phytochemical compounds that have the potential in inhibiting the replication of the SARS-CoV-2 virus is presented in Table 11.

4.3. Ginger, turmeric and bitter gourd downregulate the oxidative stress

Oxidative stress results from the excessive production of free radicals in the cells and tissues. Migration of leukocytes into the infection site

Table 6
The most productive authors, countries and organizations.

Author	TP	Country	TP	Organization	TP
Ahmadi M.	2	India	36	Tabriz of University Medical Sciences, Iran	4
Roshangar I.	2	United States	7	Allameh Tabataba'i University, Iran	1
Tahmasebi S.	2	Iran	6	Bangkok Thonburi University, Thailand	1
Valizadeh H.	2	Italy	4	Coastal Carolina University, USA	1
Kumar A.	2	Russia	4	Islamic Azad University, Iran	1
Behl T.	2	Australia	2	Kharazmi University, Iran	1
Mehta V.	2	Bangladesh	1	Kowsar University, Iran	1
Ganguly A.	2	Canada	1	Payame Noor University, Iran	1
Jubie S.	2	Croatia	1	Razi University, Iran	1
Latha S.	2	French	1	Shahid Beheshti University, Iran	1

TP = Total of publication.

Table 7
The most productive journals.

Journal	Document	Citation
International Journal of Research in Pharmaceutical Science	6	9
European Journal of Pharmacology	2	10
Nutrients	2	131
Current Pharmaceutical Biotechnology	2	26
Indian Journal of Traditional Knowledge	2	3
International Journal of Pharmaceutical Research	2	1
Medical Hypotheses	2	61
Medicinal Plants	2	1
Pharmaceuticals	2	16
Clinical Nutrition Open Science	1	1

Table 8
The most productive author keywords.

Keyword	Occurrence	Total link strength
Covid-19	2	9
Active ingredients	1	5
Chinese medicine	1	5
Medicinal plants	1	5
Southern benin	1	5
Traditional treatment	1	5
Compound	1	4
Goi	1	4
Herbals	1	4

causes pulmonary viral infections to enhance the formation of reactive oxygen species (ROS). ROS accumulation disrupts the cell's biological activities by causing cellular damage through lipid peroxidation [32]. Antioxidants can reduce oxidative damage directly by interacting with free radicals or indirectly by reducing the activity or expression of free radical-producing enzymes or increasing the activity or expression of intracellular antioxidant enzymes [33].

Ginger has been shown to exert an antioxidative effect by various phenolic compounds such as shogaol (6-gingerdione, 10-gingerdione and 1-dehydrogingerdione) and gingerol (8-gingerol, 10-gingerol, and 12-gingerol) through several mechanisms [27]. In one study, 6-gingerol inhibited lipid peroxidation by increasing the Beclin1 expression to promote autophagy in endothelial cells and inhibit PI3K/AKT/mTOR pathway signaling without affecting the cell cycle [34]. Earlier research using animal models suggested that ginger supplementation may prevent oxidative stress by elevating superoxide dismutase (SOD), catalase, glutathione peroxidase, and blood glutathione activities, while also drastically lowering oxidative stress markers including malondialdehyde (MDA) and nitric oxide [35].

C. longaor turmeric also acts as an antioxidative agent via inhibition of ROS-generating enzymes like xanthine hydrogenase/oxidase and lipoxygenase/cyclooxygenase. This mechanism is devoted to the action of its main compound, curcumin [36]. Curcumin protects cells in the body from free radical damage by lowering their oxygen content. Another mechanism is through the elevation of serum concentration of GSH and SOD [37]. Antioxidant compounds present in bitter gourd also have been proven in numerous studies to increase the activity of antioxidant enzymes such as GSH, SOD, glutathione-*s*-transferase, catalase, glutathione, and peroxidase [38,39].

4.4. Ginger, turmeric, and bitter gourd activate the inflammatory response

Inflammation and hemorrhagic lesions in the pulmonary system can result from neutrophil activation and degranulation following COVID-19 infection. Calprotectin, a neutrophil activation marker, was found in high concentrations in the blood of COVID-19 patients, and its levels were higher in those who had advanced to the disease's severe stage. Acute respiratory distress syndrome (ARDS) is exacerbated by lung damage caused by NETosis, autophagy, and ROS production in activated neutrophils [40]. One of the mechanisms involved in inflammation is the suppression of nuclear factor erythroid 2–related factor 2 (Nrf2) pathways and/or activation of nuclear factor-κB (NF-κB) related signaling [41].

Ginger aqueous extract was reported to exert the anti-inflammatory pathway by reducing neutrophil infiltration and activation in an inflammatory model, as determined by myeloperoxidase (MPO) activity

Fig. 6. Network visualization of author keywords analysis for *M. charantia*.

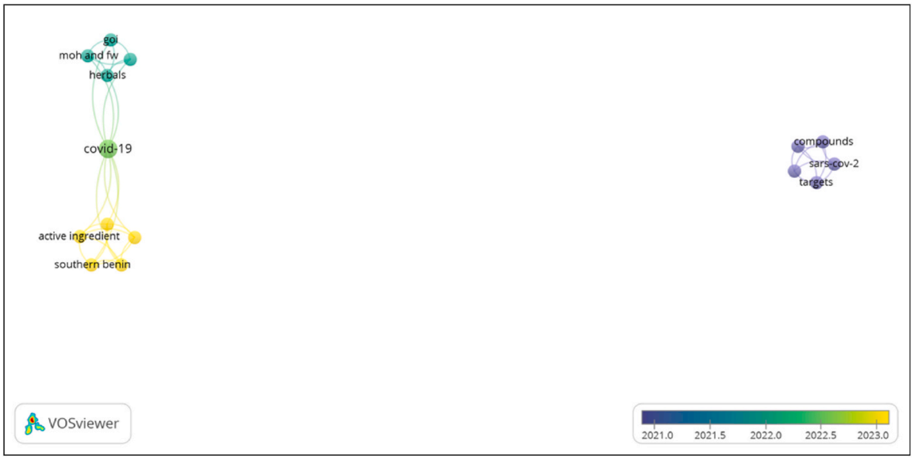


Fig. 7. Overlay visualization of author keywords analysis for *M. charantia*.

Table 9
The most productive authors, countries and organizations for *M. charantia*.

Author	TP	Country	TP	Organization	TP
Goettert M.I.	1	Brazil	1	Universidade do vale do taquari–univates, Brazil	2
Marmitt D. J.	1	China	1	Tianjin University of Traditional Chinese Medicine, China	2
Rempel C.	1	India	1	Ratibha Niketan College, India	1

TP = Total of publication.

Table 10
The most common journals.

Journal	Citation
Expert Review of Clinical Pharmacology	8
International Journal of Applied Pharmaceutics	0
Journal of Ethnopharmacology	0

[42]. In an animal model of allergic asthma, ginger aqueous extract lowered leukocyte infiltration [43]. Pre-treatment with zingerone, on the other hand, reduced lung histopathologic changes, alveolar hemorrhage, neutrophil build-up, and MPO activity in a mouse model of acute lung damage [44]. Two major subsets of macrophages, including M1-and M2 macrophages, generated large amounts of pro-inflammatory mediators (such as TNF-α, IFN-γ, IL-6, IL-12, nitric oxide (NO), and ROS) and anti-inflammatory cytokines (IL-10, TGF-β and IL-1 receptor antagonist), respectively [45]. Shogaols (6-shogaol, 8-shogaol and 10-shogaol) and gingerols (8-gingerol and 10-gingerol, 1-dehydro-10-gingerdione, and 6-Dehydrogingerdione) reduced the production of TNF-α, IL-1β, IL-6, IL-12, MCP-1, COX-2, iNOS, and NO in LPS-induced mouse macrophages [46].

The major target of SARS-CoV-2 infection is alveolar type II (ATII) cells, which leads to the apoptotic death of target cells and the subsequent infection of adjacent ATII alveolar cells [47]. The inflammatory process generates diffuse alveolar damage that can develop into ARDS by causing cellular damage, multinucleated giant cells, and a fibrin-rich hyaline membrane. Curcumin reduced the death of ATII cells and the levels of pro-inflammatory cytokines (TNF-β, IL-6, and C-reactive protein) in serum in a model of lung damage induced by benzo (a) pyrene (BaP) [48]. Another mechanism involves the inhibition of cyclooxygenase activity. By inhibiting cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes, the production of prostaglandin (PG) E2 could be impeded. In vitro studies have demonstrated curcumin's capacity to reduce COX-2 expression and prostanoid production in human cells. In the mouse macrophage cell line induced by lipopolysaccharide (LPS), curcumin was also found to reduce the expression of COX-2 [49].

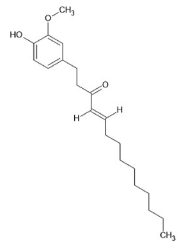
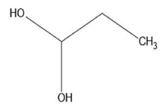
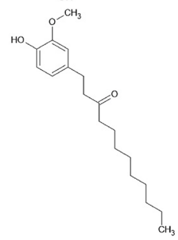
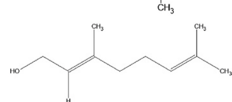
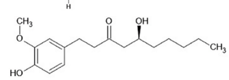
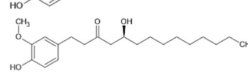
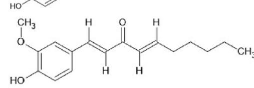
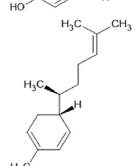
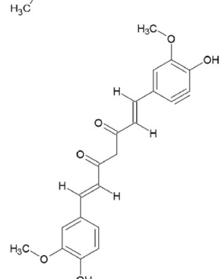
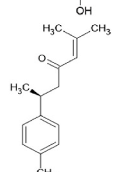
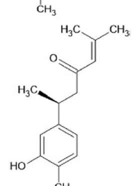
In the previous study, bitter gourd extract decreased IL-6 and TNF-expression in EAT and restored cytokine levels in serum, pointing to the possible anti-inflammatory role of bitter gourd in obese rats [50]. The inhibitory effect may be due to the suppression of prostaglandin, thus reducing both the concentration of COX-2 enzyme and inflammatory cytokines. Its activity may be attributed to flavonoid and triterpenoid plant compounds, such as momordicoside, kuguaglycoside, karavilagenin, goyaglycosides, and Kuguacin J, which have been widely reported in the fruits [51]. Moreover, the inflammatory activity of bitter gourd is also modulated via a reduction in COX-2 protein expression, inducible nitric oxide synthase (iNOS), and NF-κB. A study by Chao et al. (2014), revealed that 10% wild bitter gourd diet was able to significantly inhibit the iNOS protein's expression, hence decreasing the generation of inflammatory mediator NO [52].

4.5. Ginger, turmeric, and bitter gourd modulate the immunostimulatory activity

Modulation of the immune response is essential in the management of inflammatory and immune-related diseases like COVID-19. Phytochemicals of ginger such as gingerols, shogaols, paradols, and volatile compounds are known as effective mediators of the immune system. The phenolic compound, 8-gingerol has been studied as an immunosuppressant, and it has been found to suppress splenocyte proliferation induced by LPS and concanavalin A (ConA) in vitro [53]. Additionally, it reduced the concentration of $CD19^{+}$ B cells, $CD3^{+}$ T cells, IgG, IgG1, and IgG2b in mice, demonstrating the immunosuppressive potential of ovalbumin (OVA). In the comparison study of ginger compounds, the COX-2 inhibitory effects of 6-, 8-, 10-, and 12-gingerols, 8-gingerdiol, shogaols, and paradols were examined. Among the compounds, 10-gingerol had the strongest inhibitory activity on COX-2, whereas the other gingerol derivatives with shorter and longer unbranched alkyl side chains had moderately weaker inhibitory effects [54].

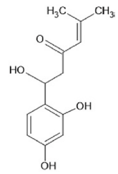
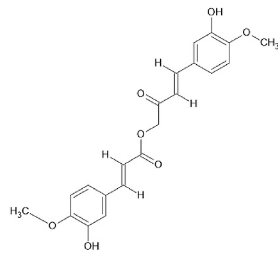
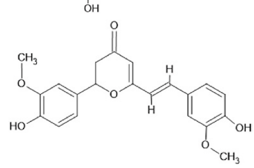
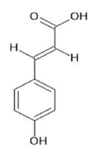
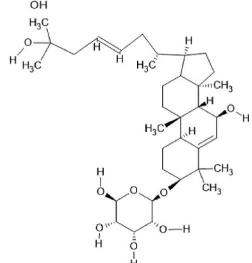
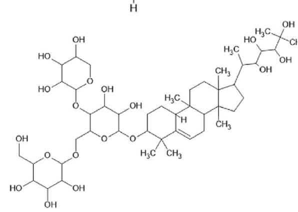
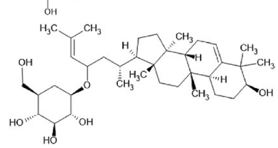
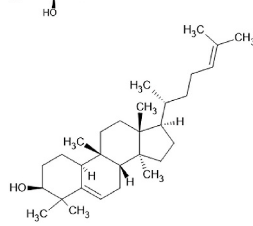
Turmeric also has been shown to boost the immune system with its main compound, curcumin. The immunomodulatory properties of curcumin were associated with various immunomodulators, including macrophages, and both B and T lymphocytes. Cytokines and other transcription factors, as well as their downstream signaling pathways, are also involved in this mechanism [55]. An earlier study demonstrated that turmeric can regulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells as well as improve the body's antibody responses to the infection [56]. Other bioactive compounds besides curcumin such as α-turmerone and ar-turmerone have also been researched for their capacities to regulate the immune system. They were found to stimulate the proliferation and cytokine

Table 11
Phytochemical compounds that have potentials against COVID-19.

Compound	Class	Structure	Bioactivity	**Reference**
Z. officinale 10-shogaol	Phenolic		Inhibited the expression of TNF-a, IL-1b, IL-6, IL-12. Modulated the production of Th1 cell cytokines. Decreased calcification by reducing the formation of ROS.	[27]
Propanediol	Primary alcohol		Possessed antiviral properties.	[28]
8-paradol	Phenolic		Exhibited strong stimulatory effects on the proteins that reduce oxidative stress	[27]
Geraniol	Terpene		Prevented DNA oxidation. Enhanced endogenous antioxidants.	[27]
6-gingerol	Phenolic		Downregulated IL-6, IL-8, PGE2, and iNOS. Reduced H_2O_2, MPO, NO, and MDA levels. Suppressed Th1 cell development.	[27]
10-gingerol	Phenolic		Suppressed the M1 macrophage- related inflammatory parameters.	[27]
6-dehydroshogaol	Phenolic		Have anti-inflammatory and antioxidant effects.	[27]
Zingiberene	Terpene		Reduced the production of TNF-a, IL-1b, IL-6 and ROS. Stimulated GPx, SOD, and CAT activities.	[27]
C. longa Curcumin	Curcuminoid		Inhibited the production of ROS-generating enzymes. Inhibited the NF-κB signaling pathways	[29]
Ar-turmerone	Sesquiterpenoid		Blocked the action of cyclooxygenase and lipoxygenase.	[30]
Turmeronol A	Sesquiterpenoid		Inhibited LPS-induced upregulation of TNF-a, IL-1β and IL-6 at the mRNA and protein levels.	[30]

(*continued on next page*)

Table 11 (*continued*)

Compound	Class	Structure	Bioactivity	**Reference**
Turmeronol B	Sesquiterpenoid		Suppressed NF-κB activation, which in turn prevented the synthesis of inflammatory mediators and the activation of macrophages.	[30]
Calebin A	Coumaric acid		Inhibited NF-κB activation through the suppression of direct binding of NF-κB/p65 to the DNA.	[30]
Cyclocurcumin	Curcuminoid		Inhibited TNF-α release from lipopolysaccharide (LPS)-stimulated human macrophages	[30]
4-Hydroxycinnamic acid	Phenolic		Elevated the concentration of antioxidative enzymes (GSH, SOD and CAT)	[30]
M. charantia Karaviloside III	Cucurbitane triterpenoid glycosides		Downregulated the protein expression of COX-2, iNOS, and NF-κB.	[31]
Momordicoside B	Cucurbitane triterpenoid glycosides		Increased the level of GSH, SOD, glutathione-*s*-transferase, catalase, glutathione and peroxidase.	[31]
Kuguaglycoside A	Cucurbitane triterpenoid glycosides		Neutralized the free radicals which attenuate the inflammation.	[31]
Cucurbitadienol	Cucurbitane triterpenoid glycosides		Increased the phagocytic mechanism stimulation.	[31]

production of human peripheral blood mononuclear cells [30].

Lymphocyte cells have a critical role in the fabrication of immunomodulatory cytokines and antibodies. In a past study, bitter gourd juice induced interferon-gamma (IFN) gamma production and showed its promising activity in immunostimulatory therapy specific for Th1 cells and IFN-gamma production [57]. Bitter gourd also increased the phagocytic mechanism stimulation by carbon clearance assay in mice and it showed a significant increase in the phagocytic index [58]. Momordicins have been shown to have an immunomodulatory effect by reducing lymphocyte activity or altering the kinetics of immunological responses. Mitogenic responses in mice spleen cells were inhibited due to the lectin, concanavalin A, and lipopolysaccharides. Momordicins increased the expression of the cell activation target point (CD86) on B cell subsets, which is a key component of humoral immunity, and induced surface membrane immunoglobulin activity, hence activating B cell proliferation [59]. After 96 h of co-culture, it stimulated the spleen cells to generate a significant amount of non-specific immunoglobulin IgM, which can regulate the immune system [60]. Fig. 8 shows the schematic presentation of the mechanisms involving the down-regulation of oxidative stress, regulation of inflammatory response and modulation of immunostimulatory activities of ginger, turmeric and gingers's compounds.

4.6. The effective dose and toxicological data

In vivo studies revealed that the effective dosage for anti-inflammatory and antioxidant effects of ginger extract was found to be in the range of 200–500 mg/kg/day. Meanwhile, for the immunostimulatory effects, the recommended dose was between 28 and 720 mg/kg/day. In addition, doses up to 4000 mg/day were reported to be safe [61]. Similarly, based on US Food and Drug Administration (FDA), the approved daily intake of ginger is up to 4 g. Generally, a recommended dose of ginger is between 250 and 1000 mg/day for daily intake. It is rare to be associated with side effects but in high doses, a previous study found that at a dose of above 6 g intake, ginger can cause gastrointestinal problems including diarrhea, heartburn, and gastrointestinal reflux [62].

According to US FDA, curcuminoids have been approved for daily use at doses between 4000 and 8000 mg/day and doses up to 12,000 mg/day of 95% concentration content of curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin. In addition, several studies proved that turmeric was safe up to 12 g/day [63]. It is quite difficult to determine the optimal dosage for curcumin due to paucity and variability in current available data, but curcumin is considered relatively safe and well tolerated at doses up to 8000 mg/day. The effective dose of bitter gourd specifically for the purpose of immune enhancement is unclear due to limited available data, however, the safe dose of the dried fruit is 3–15 g/day. Based on a study by Husna et al. (2013), the LD_{50} of the ethanolic extract of bitter gourd was revealed to be safe at a dose of 2000 mg/kg and below. Higher doses may be associated with toxic effects on the tissue, blood as well as a vital organ like the liver. Pre-clinical studies showed that the aqueous extract of bitter gourd significantly decreased the hemoglobin concentration of albino rats [64].

In the aspect of herb-herb interaction, there is no reported incidence between ginger, turmeric and bitter gourd. Similarly, there is also no interaction found between these herbs with other herbs making them promising candidates for formulation in a polyherbal form. Moreover, a recent study on acute and subacute oral toxicity has shown that a polyherbal formulation, comprising five herbs, demonstrated potential anti-inflammatory activity without any observed toxicity effects [65]. Concerning drug-herbs interaction, it was reported that ginger may cause toxicity by interacting with metronidazole, a nitroimidazole antibiotic. Ginger was found to increase the bioavailability and half-life of metronidazole [66]. Besides, ginger reduced the clearance and elimination rate constant of this drug for oral administration. Ginger also may interact with blood-thinning and antiplatelet agents such as warfarin and clopidogrel. The use of these medications in combination with ginger, which is also known to be a natural blood thinner, can increase the risk of bleeding. Similarly, turmeric and bitter gourd also interacted with warfarin which may further induce bleeding [67].

The consumption of bitter gourd among pregnant mothers should follow the safety and recommended guidelines. This is because there were several reports on the reproductive toxicity of bitter gourd. In one study, aqueous leaf extracts of bitter gourd were found to decrease plasma progesterone and estrogen levels in a dose-dependent manner in female Wistar rats [68]. The ethanolic extract of bitter gourd seed also has a greater impact on spermatogenesis and induced histological changes in both testis and accessory reproductive organs of albino mice [69].

5. Conclusion

The research questions for this review have been answered, enabling us to identify the direction of the study, notable authors, their affiliations, and the countries where the majority of the research has been carried out. The authors acknowledge certain limitations in this study. The limitation pertains to the utilization of a single database, Scopus, the restriction to the widely-used keyword "COVID-19" and the publication type which focused exclusively on "articles". Despite these limitations, we have discovered clear evidence that ginger, turmeric and bitter gourd can affect key fundamental processes involved in COVID-19

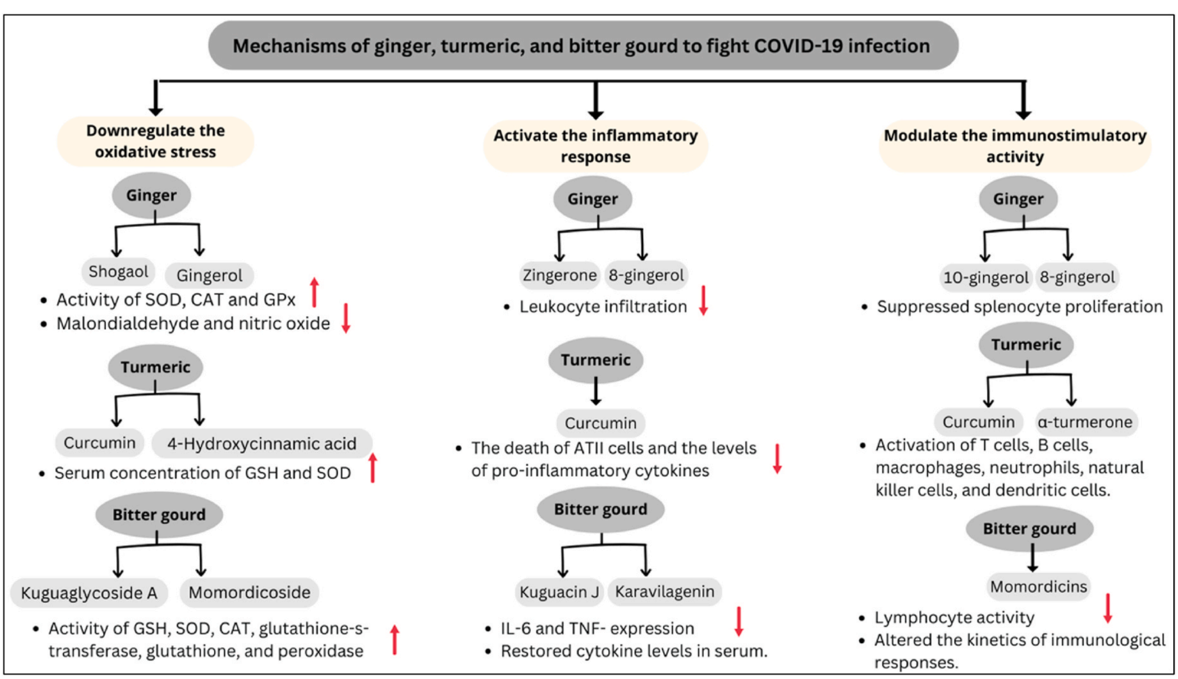


Fig. 8. Schematic diagram presenting the mechanisms of ginger, turmeric and bitter gourd in preventing and treating COVID-19 infection.

pathogenesis due to their antioxidant, anti-inflammatory, and immunomodulatory activities. These plants were discovered to suppress oxidative reactions by preventing radical species formation. They may also help to reduce disease severity by lowering pro-inflammatory cytokines, decreasing lymphocyte activity, and modulating the kinetics of immunological responses. The ability of ginger, turmeric, and bitter gourd to prevent and treat COVID-19 was attributed to its significant chemical constituents, including shogaols, gingerols, momordicoside, kuguaglycoside, karavilagenin, curcumin, α-turmerone and ar-turmerone. Based on these accumulated benefits of ginger, turmeric and bitter gourd, it is worthwhile to explore further research in this particular area. Based on these accumulated benefits of ginger, turmeric and bitter gourd, it is worthy to conduct a further research on this specific topic, combining these plants into herbal tea extract, namely Imbang Tea ("equilibrium" or "balance" tea). A comprehensive efficacy study should also be performed so that it may be given safely alongside standard of care to boost its therapeutic action in patients with mild to severe COVID-19 illness for lowering viral load, cytokine storm, and clinical recovery.

Authorship contribution statement

FAAM and HIS designed and supervised the study. FH performed the literature search and drafted the manuscript and NHZ critically edited the manuscript. AF and MASH revised the manuscript. All authors approved the final version to be submitted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jafr.2023.100680.

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