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A Mini Review on the Phytochemistry, Toxicology and Antiviral Activity of Some Medically Interesting Zingiberaceae Species

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Authors' contributions

This work was carried out in collaboration among all authors. Authors CMM, KNN and PTM wrote the first draft of the manuscript, Authors BZG, JTK, DSTT, CLI, EML, DTM and CMF collected information on plants bioactivity. Authors AM,ENM and DDT collected information on plant phytochemistry. All authors read and approved the final manuscript.

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ABSTRACT

Background: Plants of the Zingiberaceae family namely *Curcuma longa, Aframomum melegu*eta and *Zingiber officinale* are known for their many biological activities such as the antiviral activity.
Aim: To provide an updated knowledge on the phytochemistry, toxicology and antiviral activity of some medically interesting Zingiberaceae species.

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Study Design: Multidisciplinary advanced bibliographic surveys and dissemination of the resulted knowledge.

Results: The literature review shows that these edible plants have antiviral properties on different types of viruses (Rhinovirus, hepatitis B and C viruses, Herpes simplex viruses type 1 and 2, Human immunodeficiency viruse, Enterovirus 71, Ebola Virus, Human cytomegalovirus, Chikungunya virus, Epstein-Barr Virus, Japanese Encephalitis Virus, Respiratory syncytial virus, Fish viral hemorrhagic septicemia virus, Influenza A virus, Epstein-Barr virus, Coronavirus SARS-CoV-1, etc.). In addition, the literature indicated that these plants are a significant source of nutrients, which can boost the immune system and are safe according to the existing toxicological data.

Conclusion: The present mini-review can therefore help to inform future scientific research towards the development of antiCovid-19 herbal drugs of relevance as well as nutraceuticals from these three plants species for the improvement of human health and wellbeing using reverse pharmacology approach. Molecular docking of some naturally occurring isolate compounds against SARS-CoV-2 proteases is in progress.

Keywords: Curcuma longa; Aframomum melegueta; Zingiber officinale; antiviral activity; Covid-19.

1. INTRODUCTION

Plants are known as inexhaustible sources of substances responsible of various biological activities, including those with antiviral properties [1,2]. Several studies have shown that extracts from certain plants traditionally used for the management of viral infections have a real action against viruses responsible of these diseases [1]. Among these plants are quoted species of the Zingiberaceae family, namely: *Curcuma longa, Aframomum melegue*ta and *Zingiber officinale*. These three species [3] have the advantage of being edible [4] and therefore less dangerous for their use for antiviral properties[5]. The aim of this review article was to list the phytochemicals that have shown the antiviral activity of *C. longa*, *Z. officinale* and *A. melegueta* extracts. It also focuses on toxicological studies in order to reassure the use of these plants by the population of developing countries who, in most cases, resort to medicinal plants for the treatment of numerous pathologies including novel emerging viruses like SARS-CoV-2. Covid-19 is an emerging infectious disease with highly variable clinical expression. This pathology is characterized by a decrease in hemoglobin (anemia) and neutrophil levels while serum ferritin, albumin and lactate dehydrogenase levels increase significantly in many affected patients [6]. Thus, it has been demonstrated *in silico* that viral proteins, notably the ORF8 protein and the envelope glycoprotein, bind to the beta chain of haemoglobin to form a complex necessary for the attack of ferriporphyrin IX by other viral proteins such as ORF 10 and ORF 3a in order to dissociate it in heme and release free iron in solution. This drastically reduces the oxygenation capacity of the organism by inhibiting the biochemical route of the heme synthesis. The accumulation of iron in the blood plasma of affected individuals can cause inflammation and an increase in the level of C-reactive protein and albumin [7]. In response to this inflammation stress, the human body reacts by producing ferritin to bind to free iron to reduce damage [7]. Biochemically, inflammation is characterized by the production of reactive oxygen species (ROS) such as singlet oxygen, superoxide anion, hydrogen peroxide, hydroxyl radical and many other free radicals [8]. To this end, in addition to hygiene measures, the consumption of foods rich in antioxidants or those with effects on hemoglobin is recommended as an alternative means to support the antiCovid-19 response; this, in order to strengthen the immune system and ensure the oxygenation of cells.

However, current clinical data indicate that SARS CoV-2 attacks both the immune system [7,8] (T-cell infection such as HIV does) and hemoglobin (such as *Plasmodium spp*) [9]. The physiological role of plants and their constituents (secondary metabolites and micronutrients) with antioxidant properties in strengthening the immune system and hematopoiesis [10] as well as their virucidal [11] effects are well documented. The use of functional foods (drugs) with immunostimulant, virucidal, antioxidant and red blood cells boosting properties is a better therapeutic option in the time of this pandemic.

2. METHODOLOGY

A literature search was conducted to obtain updated information about the phytochemistry and virucidal activity of three plants of the zingiberaceae family namely *C. longa, A. melegueta* and *Z. officinale* from various electronic databases like Pub Med, Pub Med Central, Science Direct, Scileo, DOAJ and Google scholar. The scientific name of this plant species was used as a keyword for the search, along with the terms phytochemistry, toxicology and virucidal/antiviral activity.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Phytochemical data

Data on the phytochemistry of *C. longa*, *Z. officinale* and *A. melegueta* are given in the Table 1.

The analysis of data from the studies of different authors mentioned above, indicated that the chemical composition of the zingiberaceae species investigated varies according to several factors [12]: part of the plant used, origin of the sample, post-harvest treatment, solvent used, etc [13]. It should be noted that previous studies have identified several active ingredients with antiviral properties of which curcumin, demethoxycurcumin, zingerol, gingerol, etc. [14].

3.1.2 Antiviral activity

3.1.2.1 Curcuma longa

Several reports[15,16] indicated that *C. longa* extracts have a broad spectrum of activity against viruses. Among the viral species that have been shown to be sensitive to extracts [2] from this plant are : HIV-1 and 2, Parainfluenza Virus Type 3 (PIV-3), Feline Infectious Peritonitis Virus (FIPV), vesicular Stomatitis Virus (VSV), Herpes Simplex Virus type 1 (HSV-1), coxsackieviruses, hepatitis B and C virus (HCV, HBV), Human Papillomavirus (HPV) [5], Japanese Encephalitis Virus (JEV), HTLV-1, Dengue virus [17], (DENV), HCMV (Human cytomegalovirus), Epstein-Barr virus, BHV 1 (Bovine herpesvirus 1), Chikungunya virus, Ebola virus [18], Enterovirus 71 (EV71), RVFV (Rift Valley fever virus), HuNoV (Human Norovirus), RSV (Respiratory syncytial virus), VHSV (Fish viral hemorrhagic septicemia virus), IAV (Influenza A virus), SARS-Covid 1 [14], etc.

3.1.2.2 Aframomum melegueta

The literature reports [19] that extracts of *A. melegueta* [20] have an activity against HIV, avian pox virus (FPV), Fowl pox virus (FPV) and the viral species of the following diseases: yellow fever, smallpox and measles (smallpox viruses), Newcastle disease (NDV) [21].

3.1.2.3 Zingiber officinale

Studies on *Z. officinale* [22,23] indicate that extracts from this plant have an action against: rotavirus, H1N1 virus or influenza virus H5N1, Herpes virus (or HSV) type 1 and 2, cold virus (rhinovirus), seasonal influenza virus or Human Syncytial Virus (HRSV), Hepatitis C virus, HIV-1 [24,25,26] and SARS-Covid 1 [14].

3.1.3 Toxicity studies

The various plants mentioned above have been used in food and/or traditional medicine for hundreds of years and inspire great confidence. Few toxic elements have been reported on *C. longa*, especially the rhizome, which is considered as the most widely used part [3].

Investigations of the acute toxicity study of the curcuminoid-essential oil complex (CEC) in rats and mice at the maximum recommended dose level of 5,000 mg/kg bw for 14 days revealed no signs and symptoms or toxicity or mortality in any of the tested animals. The repeated administration of CEC for 90 days in Wistar rats at a dose of 1,000 mg/kg BW did not induce any observable toxic effects [27]. A similar study also showed no toxicity in rats [28].

Although Chainani-Wu et al. [29] have revealed some gastric irritations in humans or the hepatotoxic effect in mice or rats due to high doses of Turmeric extracts and especially curcuminoids. Meanwhile, Roshan et al. [30] asserted that the consumption of high doses of Curcuma can be at the origin of uterine contractions in pregnant women or reduce testosterone levels or sperm motility.

The study on Grains of Paradise extract (rich in 6-gingerol, 6-shogaol and 6-paradol) has demonstrated its capacity of decreasing blood glucose, but at higher doses may cause liver toxicity [31]. Akpanabiatu et al. [32] indicated that the LD_{50} of *A. melegueta* seed oil on Wistar albino rats is 273.83 mg/kg body weight and conclude that this low LD_{50} value is an indication of a possibility of this plant being toxic.

A patented ginger extract EV.EXT 33 administered by oral gavage in concentrations of 100, 333, and 1000 mg/kg, to three groups of 22

Table 1. Chemical composition of some plants of the family Zingiberaceae

Plant species	Chemical compounds	References
	Constituents of essential oils	
Curcuma longa	α- and β-turmerones, ar-turmerone, zingiberene, ar-curcumene, atlantone, cineole, d-phallandrene, α-phellandrene, curlone, , d-sabinene, borneol, terpinolene, 1, 8-cineole, undecanol, p-cymene, etc.	[3], [5], [33], [34], [35], [36], [37]
	Macro and micronutrients	
	Micronutrients: Calcium, Magnesium, Phosphorus, Zinc, Copper, Iron, Manganese, Potassium, Vitamins A, B1 (Thiamine), B2 (Riboflavin), B3 (Niacin), B5, B6, B9, Folate, C (Ascorbic Acid), E, K, Macronutrients: Fibre, carbohydrates, lipids (omega 3, omega 6 and omega 9) and proteins	[2], [5], [33], [38], [39]
	Other Compounds	
	Curcumin, demethoxycurcumin, bis-demethoxycurcumin and cyclo-curcumin, alkaloids, flavonoids, tannins, cardiac glycosides, terpenes, steroids, saponins, anthocyans, leucoanthocyans, anthraquinones, saponins, quinones etc.	[3], [5], [34], [36], [37], [40]
Zingiber officinale	**Constituents of essential oils**	
	Zingiberene, curcumene, farrnesene, gingerols, shogaols, paradols, zingerone, car-3-ene, α-terpinene, α-terpineol, neurol, 1, 8-cineole, neral, geranial, geraniol et geranyl acetate, isovaleraldehyde, nonanol, ethyl-pinene, α-Pinene, β-pinene, camphene, sabinene, β-bisabolene myrecene, β-sesquiphellandrene, α-sesquiphellandrene, sequithujene, cis-sequisabinene hydrate, zingiberol, citral (geranial et neral),gingerone, citronellal, linalool, borneol, 10-dehydrogingerdione, 6- et 4,6, 8 ou 10-gingerdione , limonene ; [6]-methyl gingediol, le [4]-gingediacetate, le [6]- gingediacetate, le [6]-methyl-gingediacetate, etc.	[12], [13], [22], [23], [41], [42], [43], [44], [45]
	Micro and macronutrients	
	Macronutrients: fibre, carbohydrates, lipids (with omega 3, 6 and 9 fatty acids), and proteins (with the following amino acids: histidine, isoleucine, leucine, lysine, methionine, cystine, phenylalanine, tyrosine, threonine, tryptophan, valine). Micronutrients: sodium, magnesium, phosphorus, potassium, calcium, magnesium, manganese, phosphorus, potassium, sodium, selenium, iron, copper, zinc, selenium, iodine, vitamins A (thiamine), B1 (thiamine), B2 (Riboflavin), B3 or PP or niacin, B5, B6 (pyridoxine), B9 (folic acid), C, D, E, K1, K2	[2], [13], [39], [43], [46]
	Other Compounds	
	Flavonoids (Flavan-3-ol, flavone, flavonol, flavanone, tannins, quercetin, rutin, fisetin, morine, gallic acid, ferulic acid, vanillic acid, hexahydrocurcumin and desmethylhexahydrocurcumin, 3S,5S)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl), allicin, alliin, ajoene, galanolactone, gingerenones, gingediones, etc., and a mixture of these compounds.	[12], [13], [23] [39], [41]
Aframomum	**Constituents of essential oils**	

Plant species	Chemical compounds	References
	Constituents of essential oils	
melegueta	2-octyl acetate, α-humulene, α-caryophyllene, β-caryophyllene, caryophyllene oxide, myrtenyl acetate, linalyl acetate isolimonene, β-eudesmene, pinocarvyl acetate, 6-paradol, 6- shogaol, 6-gingerdione, [6]-gingerol, eugenol, α et β-pinene, zingiberone, β-bisabolene, α-guaiene, aromadendrene, *trans*-β-farnesene , diarylheptanoids, β-selinene, γ- selinene, (*E*)-nerolidol, , caryophylladienol, oxide de α-humulène, zingerone, p-cymène, Z-β-ocymène, E-β-ocymène, acétate de 2-heptyle, oxyde de linalol, linalol, terpinen-4-ol, acétate de bomyle, acetate de pinyle, t-sabinol, lilacin, myrtenol, myrtenol, ∂-elemene, copaene, cyperene, α-gurjunene, γ-gurjunene, β-patchoulene, β-cubebene, germacrene-D, β-chamigrene, elixene, α-muurolene, γ-element, γ-cadiinene, β-cadinene , γ-cadinene , γ-muurolene, edene, elemol, humulene epoxide, humulane -1,6-dien-3-ol, spiro-[4.4]nonan-2-one, β-maalinene, spathulenol, muurolol, viridiflorol, longiborneol, α-cadinol, isoaromadendrene epoxide, isopetasan, octadec-9-enoic acid, etc.	[47], [48], [49], [50]
	Macro and micronutrients	
	Macronutrients: carbohydrates, fibre, protein Micronutrients: Magnesium, Calcium, Potassium, Phosphorous, Sodium, Iron, Zinc, Manganese, Copper Vitamins B1, C	[51], [52], [53]
	Other Compounds	
	Benzaldehyde-3-hydroxy-4-methoxy, butan-2-one-4-(3-hydroxy-2-methoxyphenyl), flavonoids (quercetin, kaempferol and its derivatives), triterpenoids ; labdane diterpenoids, labdane diterpenes G3 and G5, zerumin A and (E)-labda 8(17),12-diene-15,16-dial saponins, tannins, alkaloids, steroids, cardioglycosides.	[1], [20], [50], [52], [54], [55]

pregnant female rats between days 6 and 15 of gestation caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight [55]. Plengsuriyakarn et al. [4] reported no toxic effects (5000 mg/kg bw) with the crude ethanolic extract on the Syrian golden hamsters.

Conversely, some adverse effects of ginger have been reported. The *in utero* exposure to ginger tea results in increased early embryo loss with increased growth in surviving fetuses [56]. Ginger may cause heartburn, and in doses higher than 6 g may act as a gastric irritant and inhalation of dust from ginger may produce IGE-mediated allergy [57]. Fixed oil of *Z. officinale* have the inherent ability to induce an array of toxicities [58] such as organs' toxicities (hypertrophy of the liver, kidneys, lungs and spleen), cellular toxicity and oxidative stress [59].

3.2 Discussion

3.2.1 Phytochemistry

Analyzing the phytochemical data presented above, It can be noticed that *C. longa* [36] oils are mainly made up of α- and β-turmerones, ar-turmerone, zingiberene, ar-curcumene; while those of *Z. officinalis* [12] are mainly made up of Zingiberene, curcumene, farrnesene, gingerols, shogaols, paradols. In addition, the oils of *A. meleguet*a *are* composed mainly of 2-octyl acetate, α-humulene, α-caryophyllene, β-caryophyllene, caryophyllene oxide and myrtenyl acetate. Several sources [13] reported that the biological properties of these plants are linked to the presence of essential oils and/or other compounds including polyphenolic compounds. The antiviral activity of some constituents of the essential oils of *C. longa*, *Z. officinale* and *A. meleguet*a (ar-curcumene, β-sesquiphellandrene, α-zingiberene, zingerone, gingerols, etc.) have been reported in the literature [12,22]. The same is true for certain polyphenolic compounds from these plants [13], [14] (curcumin, desmethylhexahydrocurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, gallic acid, ferulic acid, morine, etc.) [16].

In addition, the data analysis from the phytochemical studies presented above showed that *C. longa*, *Z. officinale* and *A. meleguet*a, are a good source of macronutrients (carbohydrates, fats and proteins) and micronutrients (sodium, magnesium, phosphorus, potassium, calcium, magnesium, manganese, phosphorus, potassium, sodium, selenium, iron, copper, zinc, selenium, iodine, vitamins A , B_1 , B_2 , B_3 or PP or niacin, B_5, B_6, B_9, C, D, E, K1, K2). This predicts that these zingiberaeae species would be good candidates for the management of Covid-19, given the roles of these different nutrients in the immune response [60,61].. According to the literature, deficiencies in these nutrients disrupt natural and acquired immune responses. Although also involved in other biochemical processes: substrate biosynthesis for the synthesis of purine or pyrimidine nucleotides for the synthesis of DNA, mRNA, or the maintenance of various other metabolic pathways involved in the activation of the immune system (synthesis of immune proteins: antibodies or immunoglobulins, cytokines, etc.) In fact, the effects of trace elements on the immune system are mainly related to the presence of zinc and selenium [61]; although other micronutrients are also involved (magnesium, iron, copper, iodine, etc.) [62].

These nutrients intervene by contributing to the maintenance of the integrity of physical barriers (epithelial barriers) or by participating in the migration of immune cells (neutrophils, phagocytes) through chemotactism, or in the differentiation or proliferation of T lymphocytes, or by modulating the activity of immune cells or the production of immunoglobulins [61,62]. Selenium's involvement in phagocyte cell recruitment is via thioredoxine reductase, which affects the nuclear transcription factor kappa B (NFκB), involved in the transcription of adhesion molecules and cytokines. The modulation of the action of immune cells is achieved either by their intervention in the reactions involved in the elimination of pathogens or in the generation of the oxidizing molecules of the respiratory explosion. This is the case of iron, which is essential to the functioning of myeloperoxidase, an enzyme involved in the elimination of bacteria by neutrophils [62,63]. Concerning the roles of trace elements in the differentiation and proliferation of lymphocytes, Malosse [62] showed that zinc deficiency is associated with thymic atrophy and a decrease in the number of T cell precursors in this organ. The decrease in cytotoxic T cell precursors (CD8+ T cells) associated with zinc deficiency or the effect of selenium bioavailability on cytotoxic cell activity has also been reported in the literature [61,62]. Zinc deficiency also intervenes by modifying the nature of the cytokines secreted. With regard to the production of immunoglobulins, it is modulated mainly by the intake of magnesium, selenium and zinc. Some, such as zinc, act as a cofactor in the synthesis of immunoglobulins, although excessive zinc intake has negative effects.

On the other hand, certain micronutrients (selenium, copper and zinc) act as co-factors of the enzymes (glutathione peroxidase, superoxide dismutase and thioredoxine reductase) involved in the protection against free radicals. Indeed, the accumulation of free radicals is responsible for the deterioration of body cells including immune cells by oxidation of lipids constituting their membranes [61,62]. Malosse [62] had reported that the deficiency in certain trace elements decreases the activity of phagocytic or neutrophil cells and that this loss of activity would be related to the decrease in the activity of certain enzymes including glutathione peroxidase. In addition to trace elements, other antioxidants of dietary origin, such as vitamins C (ascorbic acid) and E (tocopherol), also contribute to the protection of immune cells against attacks by endogenous free radicals [60-62]. Indeed, during an immune response, the cells of the immune system produce a large quantity of oxygenated metabolites that can cause significant damage at the site of infection.

Tocopherol, which is the active form of vitamin E, reacts with free radicals or their derivatives (hyperoxide lipids), keeping it at low physiological concentrations. This prevents oxidative reactions from taking radicals on excessive proportions. Tocopherol can also influence the production of molecules involved in inflammatory reactions [60]. Malosse [62], has also shown that alpha-tocopherol, which is the most biologically active form of vitamin E, acts on the release of cytokines by macrophages and monocytes, and decreases the secretion of pro-inflammatory cytokines like Interleukins (IL-1, IL-6) and Tumor Necrosis Factor α (TNF-α) . Furthermore, It acts on the chemotaxis and immune cell adhesion by modulating the expression of vascular and intercellular adhesion molecules and certain chemokines. He also reported on several studies showing that vitamin E supplementation in phagocytic cells improves phagocyte cell function, including the bactericidal action of neutrophils.

As for vitamin C, the literature also indicated that vitamin C plays an important role in immune response processes including: increased chemotaxis, phagocytosis, production of reactive oxygen derivatives by leukocytes and elimination of microorganisms, proliferation and differentiation of lymphocytes, production of cytokines and immunoglobulins. Vitamin C is involved in the maintenance of redox potential or in the recycling of vitamin E or beta-carotene, which also contribute to the elimination of free radicals [62].

Immuno-modulating properties of vitamins A and D have also been reported in the literature. These nutrients are believed to act mainly in cell division and differentiation of immune system cells [60]. According to Malosse [62], vitamins A and D are involved in the immune system by acting at the level of physico-chemical barriers: maintenance of the integrity of mucosal epithelia, production of mucin within the intestine, effect on intestinal microbiota, etc.). He added that a deficiency of retinoic acid, which is an active metabolite of vitamin A, can be the cause of several immunological events. In view of the multiple roles of this acid in the immune response, particularly during the: (i) presentation of the antigen by acting in the presence of inflammatory stimuli such as Tumor Necrosis Factor alpha (TNFα), (ii) maturation and proliferation of Th2 lymphocytes by inducing the expression of genes responsible for the production of IL-4 and Th2 lymphocyte-promoting transcription factors, and blocking the expression of the T-bet transcription factor of Th1 cells, (iii) modulating the differentiation of regulatory T cells or other T cells, stimulating the expression of the transcription factor FOXP3 (for Forkhead box P3) and the growth factor TGF-β, or positively regulating the expression of receptors on the surface of Treg lymphocytes, (iv) production of immunoglobulins by B-lymphocytes, by acting via the above spread mechanisms (modulation of CD4 LT differentiation, and modulation of dendritic cell activity) or by activating the inducible nitric oxide synthase (iNOS), the presence of which together with IL-5 and nitric oxide is essential for IgA secretion, (v) recruitment and migration of immune cells by regulating the expression of proteins involved in migration, (vi) induction of the expression of integrins and molecules, such as the adhesion molecule ICAM-1 (Inter-Cellular Adhesion Molecule-1) and α4β7-integrin, involved in the adhesion of immune cells to endothelial cells, etc., (vii) induction of the expression of integrins and molecules, such as the adhesion molecule ICAM-1 (Inter-Cellular Adhesion Molecule-1) and α4β7-integrin, involved in the adhesion of immune cells to endothelial cells, etc., (viii) induction of the expression of integrins and molecules, such as the adhesion molecule ICAM-1 (Inter-Cellular Adhesion Molecule-1) and α4β7-integrin, involved in the adhesion of immune cells to endothelial cells.

Malosse [62] argued on studies that have shown that a deficiency in vitamin D can inhibit: the proliferation of memory B or LT lymphocytes or other immune cells, the expression of certain cytokines (IL-2, interferon IFN-gamma, or the cytotoxic action mediated by the LCD8 or the regulation of adhesion molecules, such as E-selectin or chemokine synthesis.

With respect to B vitamins, particularly vitamins B6 and B9 (folic acid) and B12 (cobalamin), their roles in the immune response have also been reported in the literature. Indeed, vitamin B6 is involved in the synthesis of nucleic acids and other pathways involved in the production of antibodies and cytokines as coenzymes, or in the proliferation of lymphocytes or in the action of NK cells or helper lymphocytes. Vitamin B9 acts alone or in combination with vitamins B6 and B12, increasing the proportion of circulating T-lymphocytes or promoting the action of NK cells [62].

In addition, the results of the phytochemical studies outlined above revealed that *C. longa* and *Z. officinale* also represent a source of amino acids including essential amino acids (histidine, isoleucine, leucine, lysine, methionine, cystine, phenylalanine, tyrosine, threonine, tryptophan, valine) and essential fatty acids (omega 3, omega 6 and omega 9 fatty acids). Like trace elements, these nutrients also contribute directly or indirectly to the body's defense system [62]. Indeed, amino acids are involved in: the stimulation or regulation of lymphocyte proliferation (methionine, threonine), activation of macrophage functions and elimination of pathogenic micro-organisms (lysine), activation of immunoglobulin production (serine, threonine), modulation of pro or anti-inflammatory cytokine production [64], inhibition or stimulation (tryptophan), antioxidant defense (cysteine, leucine, tyrosine and methionine), etc. [62].

Furthermore, several studies have shown that the addition of omega-3 fatty acids in the animal ration increases the production of antibodies and reduces the incidence of certain infections. Although a too high or too low ratio of omega-3 and omega-6 may have adverse effects on the immune response [60]. According to Malosse [62], essential fatty acids are associated with the production of antimicrobial substances or biological mediators, some of which, such as eicosanoids (thromboxanes, leukotrienes, lipoxins, hydroperoxy-eicosatetraenoic acid and hydroxyeicosatetraenoic acid), are chemical messengers acting on the immune system. Moreover, these nutrients interact with transcription factors, such as the factor NF-κB, which modulates the expression of genes encoding cytokines, cell adhesion molecules, growth factors and acute phase proteins. He also reported that omega-3 and omega-6 would have immunosuppressive effects (a decrease in immune cell chemotaxis or phagocytosis activity followed by a decrease in superoxide production, or in the ability of lymphocytes to respond to mitogen stimulation). Moreover, unlike omega-3, which has shown anti-inflammatory effects, omega-6, however, promotes pro-inflammatory effects.

3.2.2 Antiviral activity

Nowadays, emerging viral infections constitute a major threat to the mankind. Medicinal plants exhibiting broad antiviral effects could be brought into the antiviral discovery programs for such infection [64]. Plants from tropical rainforests represent a rich source of potential immunomodulating substances and leads from ethnobotanical practices have been the primary source of plant selection in recent years [65]. Both the attribute of reciprocal natural co-evolution and the concept of shared chemistry among species are characteristics that allow humans to use plants as antiviral and immunomodulating medicines. In an age of emerging new viruses with stunning virulence, natural antiviral and immunomodulating substances could play a significant role in human disease prevention and treatment [65]. A number of plants previously shown to possess broad-spectrum antiviral effects could be screened for newly emerging/resistant viral strains [64]. This author reported the case of Glycyrrhizin, a bioactive component of liquorice (*Glycyrrhiza uralensis* Fisch), and lycorine isolated from *Lycoris radiata* L. initially used for certain other indication, showed strong anti-SARS-CoV activity [64].

The molecular mechanisms associated with the antiviral effects of plant extracts may vary among different viruses. However, the potentials of plant extract to boost inherent antiviral defense of human body, which involves an intricate immune system might utilize common pathways. In recent past, a number of studies have explored immunostimulatory properties of plant extracts having antiviral properties [64]. Moreover, recent studies showing antiviral potential of plant extracts against viral strains resistant to conventional antiviral agent have challenged the modern drug discovery practices, and deem a very careful look toward exploring natural antiviral components of medicinal plants [64].

In the same framework that literature data from several studies on indicated that *C. longa, Z. officinale* and *A. melegueta* extracts are active against various viral species. Although the spectrum of the activity of *C. longa*extracts is broader. The findings of molecular docking as per Siti et al. [14], showed that some ingredients of *C. longa* and *Z. officinale* (Curcumin, demethoxy-curcumin, gingerol, zingerol, etc.), can inhibit the action of Covid-19 virus protease. This predicts that these plants can be used for the management of Covid-19; although further extensive testing is required.

Based on all the above information, it can be fairly concluded that medicinal plants offer a variety of anti-infectious compounds, particularly antiviral agents. Screening programs aimed at identifying potential anti-infectious agents from medicinal plants offer a great potential in the field of pharmaceutical developments. Hopefully, in the future these medicinal plants especially *Z. officinale, A. meleugeuta* and *C. longa* can serve as an important source for developing new anti-viral drugs.

Compounds from natural sources are of interest as possible sources to control viral infection. For *Z. officinale*, [66,67] it was reported that the fresh one was found to inhibit plaque formation induced by human respiratory syncytial virus (HRSV) in respiratory tract cell lines. As well, it was effective in blocking viral attachment and internalization. In a clinical trial, ginger extract decreased hepatitis C virus (HCV) loads, the level of alpha-fetoprotein (AFP), and markers relevant to liver function, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), in Egyptian HCV patients [67,68].

3.2.3 Toxicological studies

The various plants mentioned above have been used in food and/or traditional medicine for hundreds of years and inspire great confidence [3]. By analyzing the data of toxicological studies published in the literature, we noticed that few toxic elements are reported on the different plants investigated. However, we believe that misuse should be avoided.

4. CONCLUSION

At the end of this work, which consisted in making an inventory of data on the phytochemistry or antiviral actions of a few plant species of the family Zingiberaceae (*C. longa*, *Z. officinale* and *A. melegueta*), We believe that different plants investigated are good candidates for the management of Covid-19, as they can boost the immune defense, or inhibit the proliferation of the Covid-19 virus due to the presence of certain constituents of essential oils (gingerols, zingerol, etc.), or polyphenolic compounds, especially curcumin and its derivatives. Furthermore, the extracts of these plants have less toxic effects. We believe that in-depth studies are necessary to find other active ingredients in these plants and to identify their virucidal mechanisms of action. The present mini-review can therefore help inform future scientific research towards the development of antiCovid-19 herbal drugs of relevance as well as nutraceuticals from these three plants speciesfor the improvement of human health and wellbeing using reverse pharmacology approach. Studies on other species of the family Zingiberaceae are also desirable. Molecular docking of some naturally occurring isolate compounds against SARS-CoV-2 proteases is in progress.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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