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A Systematic Review of Garlic and Ginger as Medicinal Spices against Viral Infections

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ABSTRACT

Garlic (Allium sativum) and Ginger (Zingiber officinale) are globally utilized herbal medicinal spices. This systematic review discussed available evidence on the direct and indirect antiviral activities of garlic and ginger. Studies investigating the antiviral activities of garlic and ginger were searched and retrieved from four databases, including Google Scholar, PubMed, Science direct, and MEDLINE. Data search and retrieval were done up to 15 October 2021. A total of 28 studies were included in this systematic review (garlic = 18 studies; ginger = 10 studies). Fresh garlic aqueous extract and fresh ginger hot water extract were the most investigated forms of garlic and ginger, respectively. There was minimal evidence on the prophylactic antiviral effect of garlic and ginger, moderate evidence on the therapeutic and prophylactic/therapeutic antiviral effects, and minimal evidence on the enhancement of the immune system against viral infections. The low-moderate quality evidence on the direct and indirect antiviral effects of garlic and ginger has provided the necessary background to instigate further high-quality investigations to validate the current information, address the grey areas, and provide valuable insights into the possible utility of garlic and ginger as raw materials in drug development against viral infections.

Keywords: Garlic and Ginger, Antiviral activity, Viral Infections

1 Introduction

Over the years, the outbreak of new viral infections has expanded the list of viruses belonging to the Arenaviridae, Bunyaviridae, Filoviridae, Hepeviridae, Coronaviridae, Paramyxoviridae, and Togaviridae families [1]. Among the emerging/re-emerging viruses are hepatitis B virus (HBV), hepatitis E virus (HEV), human immunodeficiency virus (HIV), chikungunya virus (CHIKV), dengue virus (DENV), Torque Teno virus (TTV), West Nile virus (WNV), Zika virus (ZIKV), Lassa virus (LASV), hantavirus (HTNV), respiratory syncytial virus (RSV), Ebola virus (EV), avian influenza A strain (H7N9) (bird flu virus), and Middle-East respiratory syndrome (MERS)-CoV.[1] Moreover, the recent outbreak of a novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) in Wuhan city, China [2] was declared a global pandemic on March 11 2020 by WHO [3], which includes it in the seemingly unending list of emerging viral infections. Generally, the outbreak of a novel viral infection creates a huge challenge for scientists to proffer solutions in terms of vaccination, prophylaxis, and therapy. In this regard, several interventions, including alternative medicines, are co-opted to find sustainable solutions to emerging/re-emerging viral infections.

Garlic (*Allium sativum*), a member of the Alliaceae family of plants, is a widely-known spice that is utilized as herbal medicine in Asia, America, Europe, and Africa [4–7]. Garlic, as a functional food [8], offers various health benefits on consumption. Furthermore, garlic and/or its constituent compounds, such as Allicin and Allitridin, has been shown to exhibit anti-bacterial [9], antifungal [10], anticancer [11], anti-inflammatory [12], and antioxidative activities [13], among others.

Ginger (*Zingiber officinale*), a member of the Zingiberaceae family of plants, is another recognized spice that is largely utilized as herbal medicine in Australia, Asia, Europe, America, and Africa [14–18]. Ginger and/or its constituent compounds (mainly essential oils, such as 6-gingerol and 6-shogaol) have been shown to exhibit antioxidative [19], anti-inflammatory [20], antibacterial [21], antifungal [22], and anticarcinogenic activities [23], among others.

As a major challenge to research, there is an ongoing debate on the efficacy of garlic and ginger against viral infections. Furthermore, the 2019 coronavirus disease (COVID-19) pandemic has fuelled the debate on the possible utility of garlic and ginger as prophylactic and/or therapeutic remedies for viral infections. Although there is a number of studies on the antiviral activities of garlic [24, 25] and ginger [25, 26], there are no elaborate discussions on the direct and indirect effects of garlic and ginger against viral infections. This systematic review aimed to highlight the available evidence on the direct and indirect antiviral activity of garlic and ginger. In addition, based on studies retrieved from databases, this systematic review analyses and discusses the efficacy of garlic and ginger as potential prophylactic and/or therapeutic remedies for viral infections.

2 Review Criteria

2.1 Search strategy

Studies investigating the antiviral activity of garlic and ginger were searched and retrieved from four (4) databases: Google Scholar, PubMed, Science direct, and MEDLINE. The search strings included: garlic AND antiviral activity; ginger AND antiviral activity; garlic AND antiviral activity AND immune system; ginger AND antiviral activity AND immune system. Data were searched and retrieved up to 15 October 2021.

2.2 Study selection criteria

Articles retrieved from the various databases were screened and checked for eligibility using the following criteria: studies investigating the antiviral activity (viral reduction assays) of garlic and ginger; studies investigating the effect of garlic and ginger on the immune system in virus-infected models, with and/or without viral reduction assays. The exclusion criteria were *in silico* studies of antiviral activity of garlic and ginger; studies investigating the antiviral activities of garlic and ginger using plant viral models; studies investigating the combined antiviral effect of garlic and ginger with other herbs, drugs/compounds, and dietary supplements; review articles on the antiviral activity of garlic and ginger.

2.3 Data extraction

The included articles were critically evaluated and data regarding the utilized form(s) of garlic and ginger, virus(es), host(s), the antiviral activity of garlic and ginger via pre-infection, post-infection, and co-infection treatment(s), the virucidal activity of garlic and ginger, as well as immune system enhancement by garlic and ginger, were extracted. Meta-analysis was not performed on the extracted data because of the heterogeneous nature of the outcomes of the included articles.

3 Analysis

3.1 Selection of study

A total of 102 articles were identified from 4 databases (Figure 1). Duplicates were eliminated and titles and abstracts were screened. The full-text of 39 articles were assessed for eligibility and a final total of 28 studies were included in this systematic review. Of the 28 studies included, 18 studies were on garlic, while 10 studies were on ginger.

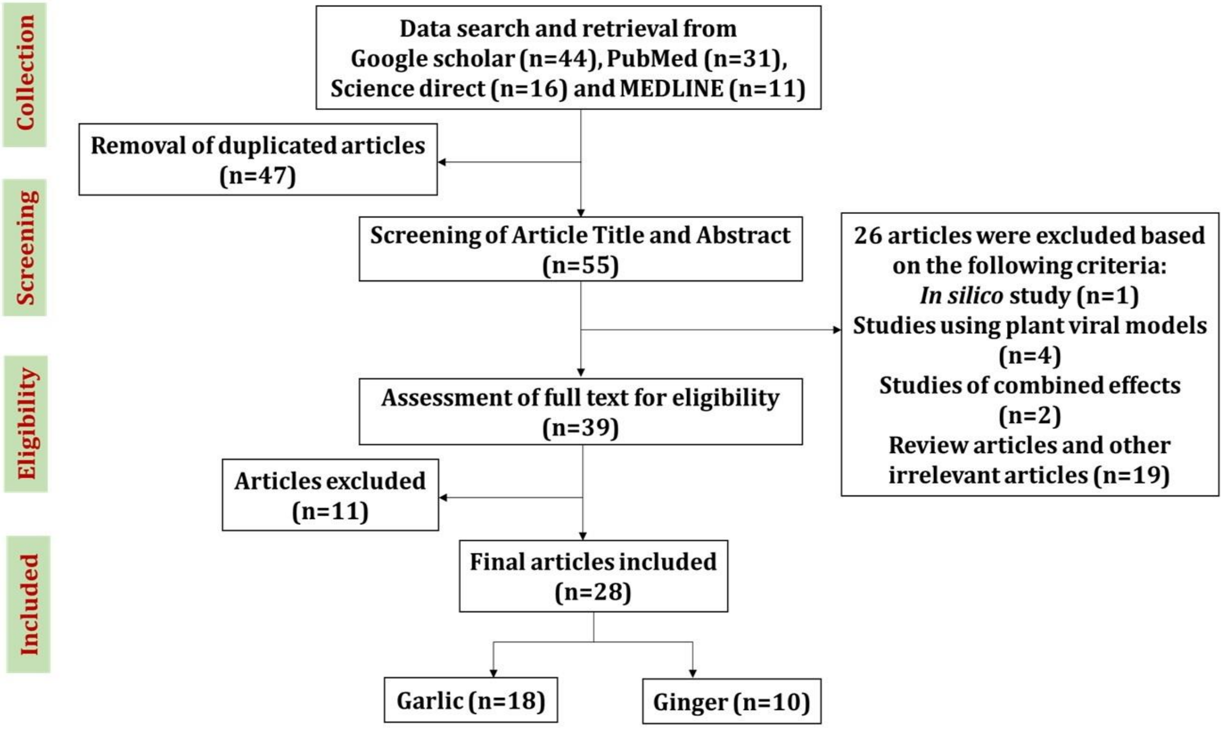

Figure 1: The review strategy workflow

3.2 Characteristics of included studies

3.2.1 Garlic

Of the 18 studies on garlic, 9 studies were conducted *in vitro*, 4 studies were conducted *in vivo*, and 5 studies were conducted *in ovo*. Among these studies, the direct antiviral activity of garlic was investigated in terms of pre-infection treatment (4 out of 18), post-infection treatment (13 out of 18), co-infection treatment (11 out of 18), and virucidal activity (1 out of 18), while indirect antiviral activity was investigated in terms of immune system enhancement (2 out of 18). Fresh garlic aqueous extract (FGAE) (n = 9) was the most investigated form of garlic, followed by compounds isolated from garlic (Allitridin = 5, Allicin = 2, and Ajoene = 1). Garlic was investigated against Influenza B/Lee/40 virus, Herpes simplex virus 1 and 2 (HSV-1 and -2), Coxsackie Bl virus, Parainfluenza virus type 3 (Para-3), Human rhinovirus type 2 (HRV-2), Vesicular stomatitis virus (VSV), Vaccinia virus (VV), Human immunodeficiency virus 1 (HIV-1), Cytomegalovirus (CMV), SARS coronavirus strain Frankfurt 1 (SARS-CoV FFM1), Influenza A (H1N1) virus, Avian infectious bronchitis virus (IBV), Feline Calicivirus (FCV), Avian influenza virus H9N2, Newcastle disease virus (NDV), and Kaposi sarcoma-associated herpesvirus (KSHV) (Table1).

3.2.2 Ginger

Of the 10 studies on ginger, seven studies were conducted *in vitro* and three studies were conducted *in ovo*. Among these studies, the direct antiviral activity of ginger was investigated in terms of pre-infection treatment (6 out of 10), post-infection treatment (8 out of 10), co-infection treatment (7 out of 10), and virucidal activities (2 out of 10), while indirect antiviral activity was investigated in terms of immune system enhancement (2 out of 10). Fresh ginger hot water extract (FGHE) (n = 4) was the most investigated form of ginger, followed by essential oils from ginger (n = 3). Ginger was investigated against Rhinovirus IB (RVIB), Influenza A virus (H3N2) HSV-1 and -2, Human respiratory syncytial virus (HRSV), FCV, Avian influenza virus H9N2, NDV, Caprine alphaherpesvirus 1 (CpHV-1), and Chikungunya virus (CHIKV) (Table 2).

Table 1: *Garlic as a medicinal spice against viral infections*

Reference	Form	Virus; Host	Anti-viral activity				
			Pre	Post	CoI	Vd	IME
[27]*	Ajoene from garlic	Human immunodeficiency virus (HIV)-1; Human CD4+ Molt-4 (clone 8) cells	PE	PE	PE	NC	NC
[28]#	Allitridin from garlic	Cytomegalovirus (CMV; CMV-infected mice	NE	PE	NC	NC	NC
[29]#	Allitridin from garlic	Cytomegalovirus (CMV); Human embryo lung (HEL) cells and CMV-infected mice	NC	PE	NC	NC	NC
[30]#	Allitridin from garlic	Mice cytomegalovirus (MCMV); female BALB/c mice	NC	PE	NC	NC	PE
[31]*	Allitridin from garlic	Human cytomegalovirus (HCMV); Human embryo lung fibroblast (HEL) cells	NC	PE	NC	NC	NC
[32]*	Fresh garlic aqueous extract.	SARS coronavirus strain Frankfurt 1 (SARS-CoV FFM1); Vero E6 cells	NC	PE	NC	NC	NC
[33]*	Fresh garlic aqueous extract	Influenza A/New Caledonia/20/99 (H1N1) standard Virus; Madin-Darbey Canin Kidney (MDCK) cells.	NC	PE	PE	NC	NC
[34]*	Fresh garlic aqueous extract	Herpes simplex virus (HSV-1 and HSV-2), parainfluenza virus type 3 (Para-3), human rhinovirus type 2 (HRV-2), vesicular stomatitis virus (VSV and vaccinia virus (VV); Vero cells and HeLa cells.	NC	NE	PE	NC	NC
	Allicin from garlic		NC	NE	PE	NC	NC
[35]*	Fresh garlic aqueous extract	Influenza B/Lee/40 virus; embryonated chicken eggs	NC	NC	PE	NC	NC
		Herpes simplex virus (HSV) type 1; rabbit skin cells	NC	NC	PE	NC	NC
		Coxsackie Bl virus; HeLa cells	NC	NC	NE	NC	NC
[36]#	Allitridin from garlic	murine cytomegalovirus (MCMV); Inbred female BALB/c mice	NC	NC	NC	NC	PE
[37]$	Fresh garlic aqueous extract	Newcastle disease virus (NDV); Embryonated Chicken eggs	PE	NE	PE	NC	NC
[38]*	Fresh garlic aqueous extract	Feline Calicivirus (FCV) (Surrogate for Human Norovirus); Crandell-Reese feline kidney (CRFK) cells	NE	NE	NE	NE	NC
[33]*	Fresh garlic ethanol extract	Influenza A (H1N1) pdm09 virus; Madin-Darby Canine Kidney (MDCK) cells	NC	PE	PE	NC	NC
	Fresh garlic methanol extract		NC	PE	PE	NC	NC
[39]$	Fresh garlic aqueous extract	Avian infectious bronchitis virus (IBV), a coronavirus; Embryonated Chicken eggs	NC	PE	PE	NC	NC
[40]*	Allicin from garlic	Kaposi sarcoma-associated herpesvirus (KSHV); primary effusion lymphoma (PEL) cell line BC-3	NC	PE	NC	NC	NC

*, *in vitro* study; #, *in vivo* study; $, *in ovo* study; Pre, Pre-infection treatment; Post, Post-infection treatment; CoI, co-infection treatment; Vd, virucidal activity; IME, immune system enhancement; NC, not conducted; NE, negative; PE, positive

Table 1 *(continued)*

Reference	Form	Virus; Host	Anti-viral activity				
			Pre	Post	CoI	Vd	IME
[41]$	Dried garlic aqueous extract	Avian influenza virus H9N2; 9-day old embryonic hen eggs	NC	NC	PE	NC	NC
[42]$	Fresh garlic aqueous extract	Field isolates of Newcastle disease viruses (NDV); 10 days-old Embryonated Chicken Eggs	NC	NC	PE	NC	NC
[43]$	Fresh garlic aqueous extract	The velogenic strain of Newcastle disease virus (VNDV); 9 days-old Embryonated Chicken Eggs	NC	NC	NE	NC	NC

*, *in vitro* study; #, *in vivo* study; $, *in ovo* study; Pre, Pre-infection treatment; Post, Post-infection treatment; CoI, co-infection treatment; Vd, virucidal activity; IME, immune system enhancement; NC, not conducted; NE, negative; PE, positive.

Table 2: *Ginger as a medicinal spice against viral infections*

Reference	Form	Virus; Host	Anti-viral activity				
			Pre	Post	CoI	Vd	IME
[38]*	Fresh ginger hot water extract	Feline Calicivirus (FCV) (Surrogate for Human Norovirus); Crandell-Reese feline kidney (CRFK) cells	NE	PE	PE	PE	NC
[44]*	Fresh ginger hot water extract	Human respiratory syncytial virus (HRSV); Human upper (HEp-2) and low (A549) respiratory tract cell lines	PE	PE	PE	NC	PE
	Dried ginger hot water extract		NE	NE	NE	NC	NC
[45]$	6-gingerol from ginger	Newcastle disease virus (NDV); Embryonated chicken eggs	PE	PE	PE	NC	NC
[46]*	Fresh ginger hot water extract	Chikungunya virus (CHIKV); Vero cell-line	PE	NC	PE	NC	NC
[47]*	Essential oils from ginger	Herpes simplex virus type 2 (HSV-2); RC-37 cells	NE	NE	PE	NC	NC
[48]*	Essential oils from ginger	Caprine alphaherpesvirus 1 (CpHV-1); Madin Darby bovine kidney (MDBK) cells	NE	NE	NC	PE	NC
[49]*	Sesquiphellandrene from ginger	Rhinovirus IB (RVIB); M-HeLa cells	NC	PE	NC	NC	NC
[50]*	Essential oils from ginger	Acyclovir-resistant clinical isolates of herpes simplex virus type 1 (HSV-1); RC-37 cells	NC	PE	PE	NC	NC
[51]$	Fresh ginger hot water extract	Influenza A/Aichi /2/68 (Aichi) virus (H3N2 subtype); 10-day old embryonic hen eggs	NC	NE	NC	NC	PE
[41]$	Dried ginger water extract	Avian influenza virus H9N2;9-day old embryonic hen eggs	NC	NC	PE	NC	NC

*, *in vitro* study; #, *in vivo* study; $, *in ovo* study; Pre, Pre-infection treatment; Post, Post-infection treatment; CoI, co-infection treatment; Vd, virucidal activity; IME, immune system enhancement; NC, not conducted; NE, negative; PE, positive

3.3 Direct effects of garlic and ginger against viral infections

3.3.1 Prophylactic effect

To infect a host, a virus must gain entry into a host's cell by attachment to receptors on the host's cell, followed by a spontaneous induction of conformational changes in the viral proteins, which results in either penetration (for virus without envelopes) or fusion (for virus with envelopes) of the virus with the host's cell membrane [52]. This entry process, which ultimately results in the transfer of viral genomes into hosts' cells, can be halted by certain inhibitors, such as nucleic acids, small organic molecules, antibodies, and peptides, among others [52], which can serve as prophylactic antiviral agents. Based on the findings from this systematic review, in terms of their potential prophylactic antiviral activities (via pre-infection treatments), there is low and unelaborate evidence on the use of garlic (2/18) or ginger (3/10) against viral infections.

Although potential prophylactic antiviral effects were exhibited by garlic [27, 37] and ginger [44–46], the mechanisms underlying these findings still remain unclear. However, Walder et al., [27] reported that 2 hours ajoene (compound isolated from garlic) treatment of Molt-4 cells prior to infection with HIV-1 showed a potential prophylactic antiviral effect, suggesting the prevention of viral attachment and adsorption or penetration. Moreover, Doostmohammadian et al., [37] suggested that the pre-treatment antiviral activity of FGAE against the velogenic strain of NDV (*in ovo*) was due to the reduction of viral infectivity via inhibition of protein kinase C (PKC), a protein that mediates viral adsorption. On the other hand, FGHE was reported to exhibit prophylactic antiviral effects against HRSV [44] and CHIKV *in vitro* [46], while 6-gingerol (compound isolated from ginger) exhibited a prophylactic antiviral effect against NDV *in ovo* [45]. Similarly, the authors reported that the antiviral effects were via prevention of viral attachment and adsorption. Based on these findings, it is obvious that garlic and ginger contain certain bioactive agents that can serve as raw materials for the development of prophylactic drugs against viral infections. It is possible that these bioactive agents in garlic and ginger are capable of destabilizing viral proteins' sequence, reducing the affinity of viral proteins for cellular receptors, and inducing the production of antibodies that prevent viral entry.

Therefore, to verify and validate the foregoing claims of the potential prophylactic antiviral activities of garlic and ginger, further studies are needed to investigate the effects of garlic and ginger on viral proteins, receptors/mediators on hosts' cell surface, and affinity of viral proteins for hosts' cell receptors. In addition, there is a need to investigate whether garlic and ginger are capable of mobilizing certain antibodies (immunoglobulins) against viral infections in host cells as a part of their prophylactic effects. The lack of prophylactic antiviral activity of garlic against CMV [28] and FCV [38] infections and that of ginger against HSV-2 [47], HRSV [44], FCV [38], and CpHV-1 [48] infections indicates that the prophylactic antiviral activities of garlic and ginger may depend on the viral type and strain, as well as the pathogenesis of the viral infection. Moreover, it is known that viral proteins, which mediate the entry of viruses into hosts' cells are diverse in nature [52] and thus may exhibit different entry mechanisms in hosts' cells, some of which may overwhelm the prophylactic potential of garlic and ginger.

3.3.2 Therapeutic effect

After gaining entry into host cells, viruses release their genome, which is either transcribed or translated. This process, also known as viral replication, culminates in the synthesis of viral proteins and genomic nucleic acids. Following the viral genome and protein syntheses, which can be subjected to posttranslational modification, the viral proteins are assembled with the newly synthesized genome into new virions that are then released from hosts' cells either by cell lysis (for cytolytic viruses) or budding. Several molecular mechanisms have been proposed for viral replication [53, 54] and virion release [55, 56]. At present, various strategies, including compounds that target viral genome and protein syntheses [57, 58] and compounds that target host cellular processes that promote viral replication [59, 60], are being employed to develop effective antiviral therapies. Furthermore, the inhibitory effects of bioactive compounds isolated from plants and several plant extracts on numerous viral replication targets have been extensively reviewed [61].

Based on available information in literature, there is moderate-quality evidence on the potential therapeutic use of garlic and ginger against viral infections. There seems to be more elaborate evidence to support the potential therapeutic antiviral use of garlic than ginger. For instance, Walder et al., [27] demonstrated that ajoene from garlic reduced the replication of HIV-1 via the inhibition of reverse transcriptase (RT) activity *in vitro*. Similarly, Mehrbod et al., [34] demonstrated the reduction of influenza A (H1N1) viral replication by FGAE *in vitro* through reverse transcription-polymerase chain reaction (RT-PCR). Zhang et al., [31] reported that allitridin from garlic inhibited HCMV replication via suppression of the expression of the HCMV gene family, including IE (encoding immediate-early antigens such as ul122 and ul123 proteins), E (encoding early antigens viral DNA polymerase), and L (encoding late antigens, such as viral structural proteins) *in vitro*. Furthermore, Liu et al., [28] reported that allitridin significantly inhibited CMV replication via reduction of the viral DNA load in mice. Although Vijgen et al., [32] reported that FGAE inhibited SARS-CoV FFM1 replication *in vitro*, there was no elaborate mechanism illustrated. Taken together, it is apparent that garlic may exert its potential therapeutic antiviral activity via interruption of viral DNA synthesis, thus impeding viral growth or replication. However, further studies with human and animal subjects are required to validate these findings.

On the other hand, although sesquiphellandrene, 6-gingerol, essential oils from ginger, and FGHE showed potential therapeutic activities against RVIB [49], NDV [45], HSV-1 [50], and HRSV [44] and FCV [38], respectively, there was no elaborate mechanistic evidence to substantiate the reductions in the viral titers, considering the fact that these studies only conducted viral reduction assays. Given this limitation, it is apparent that there is a huge information dearth on the effect of ginger on molecular indicators of viral replication. To properly ascertain the potential therapeutic effect of garlic and ginger against viral infections, there is a need to investigate the effect on viral genome replication and/or expression machinery, including enzymes (such as viral DNA polymerase, viral protease, and RT), co-factors, and viral DNA and RNA levels, among others. The studies reporting negative potential therapeutic activity of garlic against HSV-1 and -2, Para-3, HRV-2, VSV, VV, FCV, and NDV [34, 37, 38], as well as ginger against Influenza A virus (H3N2), HSV-2, HRSV, and CpHV-1 [44, 47, 48, 51], are indications that the success or failure of garlic and ginger as antiviral therapies may be much dependent on the taxonomic features and pathogenesis of the viruses they are used against [1].

3.3.3 Prophylactic/therapeutic effects

Certain medicinal plants can serve as both prophylaxis (preventives) and therapy (treatment) against viral infections. For instance, it was recently reported that some medicinal plants prevented SARS-CoV-2 infection of healthy individuals and showed an improvement of symptoms in SARS-CoV-2-infected individuals [62–65]. Based on the findings in literature, there is moderate evidence of the potential prophylactic/therapeutic use of garlic and ginger against viral infections. Studies investigating only the effect of co-infection treatment with a mixture of garlic and virus, such as avian influenza virus H9N2 [41], NDV [42], influenza B/Lee/40 virus, and HSV-1 [35], reported positive antiviral activities but did not provide any clue on the prophylactic and therapeutic effects, considering that they did not conduct experiments involving pre-infection and post-infection treatments. Similarly, Rasool et al., [41] demonstrated a positive antiviral effect by co-infection treatment with the mixture of ginger water extract and NDV without conducting experiments on pre-infection and post-infection treatments. These limitations re-echo the need for elaborate research in this aspect.

Nevertheless, there are very few studies investigating the effect of co-infection treatment together with pre-infection and post-infection treatments with garlic and ginger. Walder et al., [27] reported positive antiviral effects of ajoene against HIV-1 via co-infection, pre-infection, and post-infection treatments, which suggest the potential prophylactic/therapeutic effects of garlic. In contrast, Aboubakr et al., [38] found no antiviral activity following co-infection, pre-infection, and post-infection treatment with FGAE against FCV. However, Doostmohammadian et al., [37] reported positive anti-NDV activity of FGAE via co-infection and pre-infection treatments but found no activity via post-infection treatment, thus suggesting only a prophylactic potential. On the other hand, Chang et al., [44] reported an anti-HRSV activity via co-infection, pre-infection, and post-infection treatment with FGHE but not with dried ginger hot water extract. In addition, Subbaiah et al., [45] reported an anti-NDV activity via co-infection, pre-infection, and post-infection treatment with 6-gingerol. Aboubakr et al., [38] reported positive anti-FCV activity of FGHE via co-infection and post-infection treatments but found no activity via pre-infection treatment, thus suggesting only a therapeutic potential. Surprisingly, Koch et al., [47] reported positive anti-HSV-2 activity of essential oils from ginger via co-infection treatment but found no activity via pre-infection and post-infection treatments, thus suggesting a virucidal effect (that is, inactivation of the virus before entry into the host). Based on these findings, it is apparent that garlic and ginger are potential broad-spectrum antiviral medicinal spices as a result of their dual activity (prophylaxis and therapy). Although the mechanism underlying this dual activity is yet to be determined, it is possible that the bioactive components in garlic and ginger may act synergistically through the mechanisms illustrated above (sections 3.3.1 and 3.3.2) to exhibit this dual effect. Nevertheless, more mechanistic studies are required to shed light on these grey areas.

3.3.4 Virucidal effect

A virucidal assay is used to ascertain the possible physical disruptive effects (leading to inactivation or neutralization) on viral particles (such as envelope and capsid proteins) after a virus is directly incubated with a substance [66]. In this systematic review, there is insufficient data on the virucidal effects of garlic (1/18) or ginger (2/10). Apart from the study by Aboubakr et al., [38], in which a negative virucidal effect of FGAE against FCV was reported, there is no other study investigating the virucidal effect of garlic. On the other hand, only two studies investigated the virucidal effect of ginger. Aboubakr et al., [38] and Camero et al., [48] reported a positive virucidal effect for FGHE (against FCV) and essential oils from ginger (against CpHV-1), respectively. Although ginger showed positive virucidal effects against FCV and CpHV-1, there is a need for further investigation of this outcome using other viral models. It is obvious that the differences in the outcomes for garlic and ginger may be influenced by the viral type, strain, and pathogenesis. However, further elaborative experiments are required to validate the current findings and address the grey areas highlighted.

3.4 Indirect effects of garlic and ginger against viral infections

In this systematic review, the potential indirect antiviral activities of garlic and ginger were analyzed in terms of immune system enhancement. The relationship between the immune system and viral infections has been extensively reviewed [67–69]. The first defense set against viral infection is the innate immune response, which prevents the spread of the virus. Invading viruses are recognized by several innate immune receptors, including Toll-like receptors (TLRs), the retinoic acid-inducible gene I (RIG-I), and NOD-like receptors (NLRs), which are expressed on the host cell surface. These receptors recognize the viral nucleic acids, double-stranded RNA intermediates, genomic RNA, and genomic DNA [59]. Activation of these receptors leads to the production of chemical messengers, such as interferons (IFNs), which activate the antiviral immune response involving the maturation and recruitment of dendritic cells (DCs), natural killer (NK) cells, and macrophages to produce anti-inflammatory molecules, such as interleukin-10 (IL-10), a well-established multifunctional cytokine in viral infections [69], and transforming growth factor-beta (TGFβ). Unfortunately, certain classes of viruses, such as the human respiratory RNA viruses, have evolved several mechanisms for evading the innate immune response [70]. Following a persistent viral infection, the adaptive immune response is activated and this involves the recruitment of cytotoxic CD8+ T lymphocytes (CTL) and T helper 1 (Th1) cells, which can directly kill the virus-infected cells or produce cytokines, such as tumor necrotic factor (TNF), that can destroy the infected cells. In addition, Th1 cells stimulate the virus-specific CD8+ T cells to differentiate into CTLs, which kills the viral-infected cells through recognition of the viral particles [58].

There is sufficient evidence to support the immunomodulatory effects of garlic [71–75] or ginger [73, 77–80] in non-viral models. However, based on the findings from this systematic review, there is low evidence on the immunomodulatory effects of garlic or ginger against viral infections. Yi et al., [36] investigated the effects of allitridin on the expression of the transcription factors T-bet and GATA-3 in mice infected with murine cytomegalovirus (MCMV). They found that while MCMV-infection down-regulated the expression IFN-gamma and T-bet and up-regulated the expression of IL-10 and GATA-3, allitridin up-regulated the expression of T-bet and IFN-gamma and inhibited the expression of GATA-3 and IL-10 in the MCMV-infected mice. Since T-bet and GATA-3 are known transcriptional regulators or orchestrators of Th1/Th2 cell differentiation [76], the investigators suggested that allitridin could stimulate a Th1 dominant state, which should enhance the specific cellular immune reactions against CMV. Similarly, in another study, allitridin up-regulated the expression of Th1, down-regulated the expression of IL-10 and TGFβ, and suppressed the viral loads in MCMV-infected mice [30]. On the other hand, Imanishi et al., [51] demonstrated that FGHE had no direct antiviral effect against influenza A (H3N2) virus *in vitro* but significantly exerted its antiviral effect via macrophage activation, which led to the production of TNF-α, a cytotoxic ligand that destroys virus-infected cells. In contrast, Chang et al., [44] reported that although FGHE showed direct antiviral effects against HRSV *in vitro*, it did not stimulate cells to secrete TNF-α, thus suggesting that it did not necessarily exert its antiviral effects via a cellular immune response. In comparison, there seems to be better-quality evidence for garlic than ginger. Nevertheless, these findings indicate that the immunomodulatory potential of garlic and ginger against viral infections still needs to be further investigated through assays of several distinctive immunomodulatory markers in different viral models, including the novel SARS-COV-2. Notably, considering the fact that FGAE and FGHE were the most investigated form of garlic and ginger, respectively, it clearly imperative that these forms may likely be reservoirs of potential antiviral agents that are yet to be unraveled. Future studies are also encouraged to substantiate the common usage of these forms of garlic and ginger against viral infections.

4 Conclusions and Perspective

This systematic review identified low-moderate quality evidence on the direct and indirect antiviral effects of garlic and ginger. At present, there is low-quality evidence on the prophylactic potential of garlic and ginger against viral infections. While there is moderate quality evidence on the therapeutic potential of garlic and ginger against viral infections, better-quality evidence was identified for garlic than ginger. Furthermore, although low-quality evidence was identified for garlic and ginger in terms of enhancement of the immune system against viral infections, there seems to be more elaborate evidence for garlic than ginger. Overall, this systematic review suggests that the potential direct and indirect antiviral activities of garlic and ginger cannot be generalized, considering the likely influence of the differences in viral types, strain, and pathogenesis. As a limitation to this systematic review, the concentration/dosage of the various forms of garlic and ginger reported by the included studies were not discussed, since it is not the main focus. Moreover, due to the fewer number of included studies and the heterogeneous study types (that is, *in vitro*, *in vivo,* and *in ovo*), it is somewhat elusive to make inferences on the concentrations/dosages at the current stage. To make an inference regarding optimal dosage, large-sample randomized clinical trials are therefore required, provided that the potential outcomes and grey areas discussed in this review have been validated and addressed.

5 Declarations

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5.2 Competing interest

The author has no competing interest to declare.

5.3 Publisher's Note

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