

A Review on the Potential Species of the *Zingiberaceae* Family with Anti-viral Efficacy Towards Enveloped Viruses

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Abbreviations: ZBE: *Zingiberaceae*, BPC: Bioactive phytocompounds, FDA: Food and Drug Administration, WHO: World Health Organisation, GRAS: Generally recognized as safe, iNOS: cytokine-inducible and calcium/calmodulin-independent.

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Abstract

Natural products are a great wellspring of biodiversity for finding novel antivirals, exposing new interactions between structure and operation and creating successful defensive or remedial methodologies against viral diseases. The members of *Zingiberaceae* traditional plant and herbal products have robust anti-viral action, and their findings will further lead to the production of derivatives and therapeutic. Additionally, it highlights the insight of utilizing these phytoextracts or their constituent compounds as an emergency prophylactic medicine during the pandemic or endemic situations for novel viruses. In this connection, this review investigates the potential candidates of the *Zingiberaceae* family, consisting of bioactive phytochemicals with proven antiviral efficacy against enveloped viruses. The present study was based on published antiviral efficacy of *Curcuma longa*, *Zingiber officinale*, *Kaempferia parviflora*, *Aframomum melegueta* *Elettaria cardamomum*, *Alpinia Sps* (belongs to the *Zingiberaceae* family) towards the enveloped viruses. The relevant data was searched in Scopus, Scifinder, Springer, Pubmed, Google scholar, Wiley, Web of Science, Cochrane Library, Embase, Dissertations, theses, books, and technical reports. Meticulously articles were screened with the subject relevancy and categorized for their ethnopharmacological significance with in-depth analysis. We have comprehensively elucidated the antiviral potency of phytoextracts, major composition, key compounds, mode of action, molecular evidence, immunological relevance, and potential bioactive phytochemicals of these five species belonging to the *Zingiberaceae* family. Conveniently, these phytoextracts exhibited multimode activity in combating the dreadful enveloped viruses.

Keywords: *Zingiberaceae*, Anti-viral compound, Immune boosters, Enveloped viruses, Immunomodulators, Phytochemicals

INTRODUCTION

The outbreak and pandemic of novel contagious viruses such as Severe Acute Respiratory Syndrome (SARS), respiratory syncytial, dengue, Human Immunodeficiency Virus (HIV), rotaviruses, para-influenza, and influenza viruses SARS-CoV-2 is a serious threat to human health across the globe. The unavailability of the drugs to combat the viral propagation during the endemic or pandemic situation worsens the situation. The unavailability of the molecular mechanism of novel viruses drags the efforts to control the virus spread and the development of antiviral drugs or vaccines. Even the proposed antiviral drugs expend a lot of time-period to pass clinical phase trial and Food and Drug Administration (FDA) approval. Also, vaccines developed against viruses are meant for prophylactic treatment. Moreover as vaccines defined to target the molecular pathway, several times they tend to cause side effects. The drugs such as Amantadine and Rimantidine (ion-channel blockers) used against Influenza type pose a disadvantage of causing side effects in the central nervous system and the gastrointestinal tract,^{1,2} also the emergence of resistance against these drugs.³⁻⁵ The enzyme neuraminidase which is an

exoglycosidase plays a key role in the release of virions from infected host cells.¹ Moscona has reported the application of neuraminidase inhibitors has prohibited the connection between the host cell and newly built virions.⁶ Developments of neuraminidase inhibitors such as Oseltamivir and zanamivir which are approved to use against Influenza A viruses were also found to develop resistance occasionally.⁷ Moreover, viruses pose every emerging capability to mutate it and develop a novel progeny making it more adaptive to infect. Also, the production capacities for these neuraminidase inhibitors are limited and too expensive for several countries. An effective drug during the disease outbreaks should contain the disease manifestation, should be affordable, easier production, safer and low cost.

Since ancient times several herbs and spices were utilized in the human diet as a flavoring agent, preservative, for aroma and color. More significantly, herbs and spices played a life-saving role in traditional medicines to treat several dreadful diseases as an antioxidant, antimicrobial, and immunity boosters.⁸ About 65-80% of the population in the developing countries were using medicinal and traditional

plants as remedies to treat diseases.⁹ The research on biological compounds brings more number of active molecules against different diseases and their number (approved drugs) becomes more than 70 as on 2019 compared to < 30 on 1980s.¹⁰ One major plant family, consisting of several medicinal value plants is *Zingiberaceae* (ZBE), commonly called a ginger family. ZBE is a class of perennial herbaceous plants spanning around 1400 species in 47 genera, which includes several numbers of medicinal plants with potent bioactive phytochemicals (BPC).^{11,12} Pancharoen et al.,¹³ have summarised the isolation of biologically active compounds and further categorized them as terpenoids. Mono and sesquiterpenoids, diarylheptanoids, arylalkanoid, phenylpropanoid, cyclohexane oxides and flavonoids, and flavonoid related derivatives present among *Aframomum*,

Alpinia, *Amomum*, *Boesenbergia*, *Costus*, *Curcuma*, *Hedychium*, *Kaempferia* and *Zingiber* of ZBE family. Moreover, several members of the ZBE family were generally recognized as safe (GRAS) by FDA, and largely used as an important constituent in traditional medicine, as a spice and food supplement in several parts of Asia. This also emphasizes the non-toxicity, which makes it in essential to fulfill the clinical trials and stringent regulatory requirements for therapeutic applications.¹⁴ In accordance several researchers have explored the efficacy of several members of the ZBE family for novel structures and biologically activity towards viruses. On the other hand, several BPC of the ZBE family acts as immunomodulators, which have further raised its clinical importance. By taking accord of this, the present review article summarises the potential

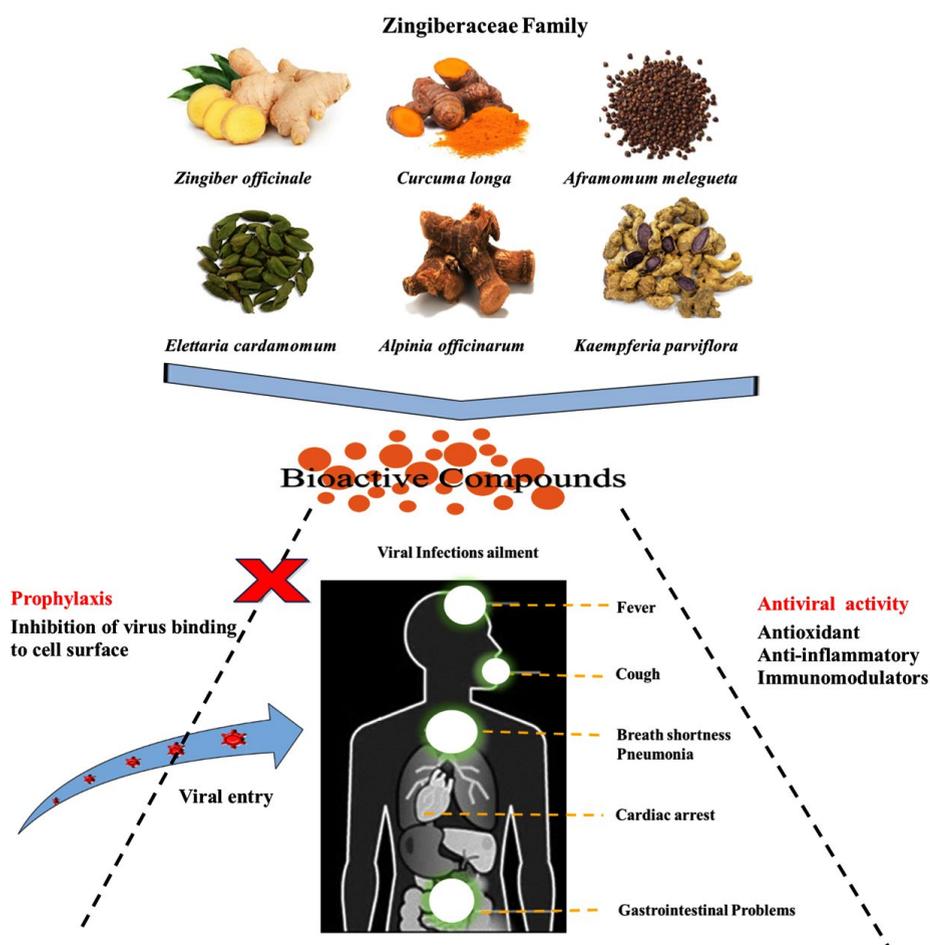


Fig. 1. Representation of bioactive compounds and multimode action towards enveloped viruses

candidates with bioactive components belong to ZBE with antiviral efficacy towards enveloped viruses (Fig. 1). The review also signifies the molecular mechanisms of antiviral compounds or components (of ZBE family) against the enveloped virus which provide insights on prophylaxis and novel drug development.

METHODOLOGY

The review was based on published antiviral efficacy of *Curcuma longa* L., *Zingiber officinale* Roscoe, *Kaempferia parviflora* Wall. ex Baker, *Aframomum melegueta* K. Schum., *Elettaria cardamomum* (L.) Maton, *Alpina* sp., (belongs to the *Zingiberaceae* family) towards the enveloped viruses. The relevant data was searched in Scopus, "Scifinder", "Springer", "Pubmed", "Google scholar", "Wiley", "Web of Science", "Cochrane Library", "Embase", Dissertations, theses, books, and technical reports. Meticulously articles were screened with the subject relevancy and ethnopharmacological significance and the systematic review was constructed with in-depth analysis.

Anti-viral efficacy towards enveloped viruses *Curcuma longa* L.

Curcuma longa commonly called as turmeric, which is a bright yellow spice. It is perennial herb with pulpy, orange tuberous roots, or rhizome. The turmeric is widely used in a curry powder for unique spicy flavor and color and known for its medicinal purposes in traditional Indian ayurvedic, Siddha, and Chinese systems of medicine.¹⁵ The main phytochemical classes of compounds present in the rhizome consist of volatile oils containing turmerone, atlantone, zingiberene, and curcuminoids a polyphenolic pigment attributing to the bright yellow color. The major curcuminoids present in turmeric are curcumin, demethoxycurcumin, and bisdemethoxycurcumin which comprise about 3–6% of turmeric powder.¹⁶ Curcumin is an orange-yellow crystalline water-insoluble powder, which attributes around 70-75% of the curcuminoids, while demethoxycurcumin and bisdemethoxycurcumin attribute about 15-20% and 3% respectively (See Fig. 2).¹⁶ Curcumin is also known as 'Golden spice' owing to its potency as

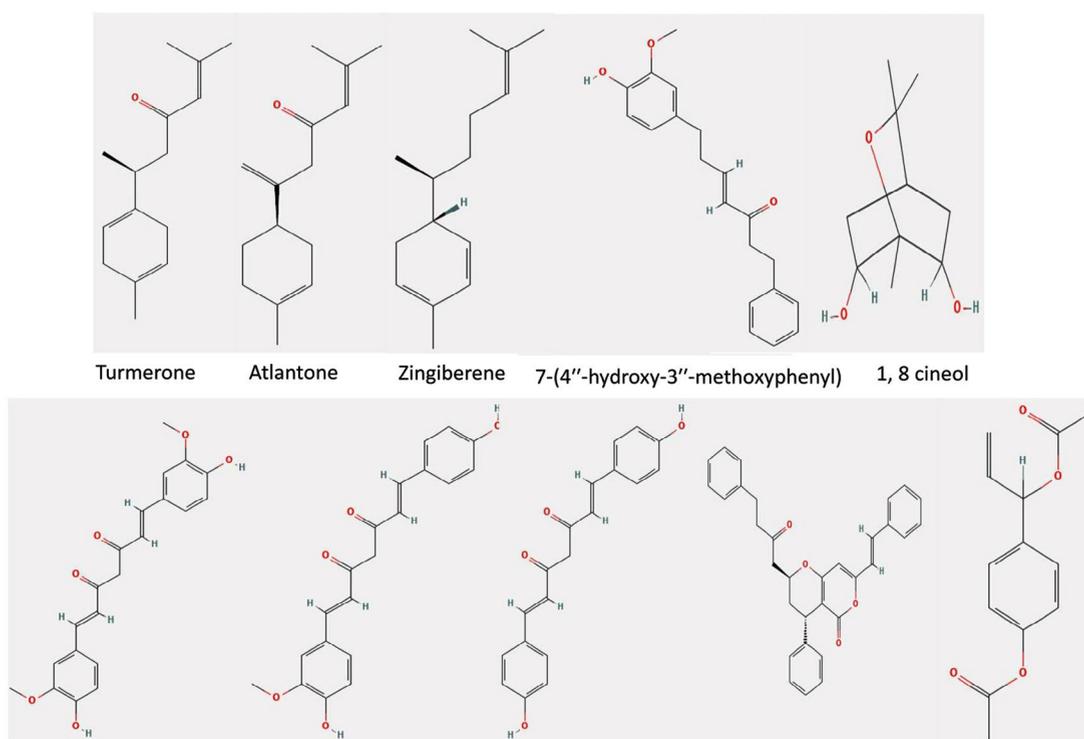


Fig 2. The two dimensional chemical structure of the most important compounds present in zingiber species.

an antibacterial, antiviral, antifungal agent over a wide spectrum of microbes.^{17,18} Several preclinical and clinical studies of curcumin are carried out through the world due to its wider therapeutic application¹⁹ and antimicrobial activity.¹⁸

Mounce et al.,²⁰ have comparatively investigated the efficacy of curcumin against the enveloped virus (Zika and Chikungunya virus) and non-enveloped virus (Coxsackievirus B3). 1mM dose concentration of curcumin treatment led to cause above 99% consequences in enveloped viruses than the non-enveloped viruses. A decrease in viral infectivity of vesicular stomatitis virus, an enveloped virus was also reported upon curcumin treatment. Due to its, lipophilic nature the curcumin binds with the viral envelop or host receptor (at viral entry point) and hence, alters the membrane fluidity. This kind of alteration brings an obstacle for binding and fusion of viral proteins in to the host tissues. In particular, it alters the glycoproteins of enveloped viruses that aid in viral entry.²¹⁻²³ Further, authors have explored the potency of curcumin analogs i.e demethoxycurcumin and bisdemethoxycurcumin against the enveloped and non-enveloped viruses. For the experiment, EF-24 ((3E,5E)-3,5-bis[(2-fluorophenyl)methylene]-4-piperidinone; IC50 1.49 μ m), and FLLL31 ((E,E)-1,7-Bis(3,4-dimethoxyphenyl)-4,4-dimethyl-1,6-heptadiene-3,5-dione; IC50 6.85 μ m) were used as controls along with curcumin. Meanwhile, Mounce et al²⁰ showed that curcumin had lower cytotoxicity and viral inhibitory efficiency than the above drugs.²⁰ The curcumin analogs, such as results bisdemethoxycurcumin, demethoxycurcumin also possess similar potency against such viral envelop proteins. In addition, toxicity towards the HeLa cells of curcumin and curcumin analogs remains similar. These results emphasized the higher potency and specificity of curcumin and curcumin analogs (modification in methoxy group) towards the enveloped virus. Further, Mounce et al., have postulated that curcumin inhibits the cellular association i.e. inhibition of the viral binding to the cell surface thereby halting the viral replication. Similar results were reported by Chen et al.,²⁴ as curcumin and curcumin analogs pose a direct effect on the human influenza virus (H1N1) and avian influenza virus (H6N1). Also, curcumin with two enones possessing higher inhibitory actions

towards the virus than the analogs.²⁵

As evident to above finding chicken RBCs pre-treated with the 31.2 μ M or higher concentration of curcumin have resulted in non-hemagglutination, upon infecting with paramyxovirus for 60 min.²⁴ To further explore the plaque formation assay was conducted on the enveloped viruses Japanese encephalitis virus and Dengue (type 2; DV-II) concerning the time of curcumin addition. The curcumin addition (upon viral attachment) and full-time addition throughout the time of infection resulted in similar results. While overall effect was observed upon viral entry into the cells. In addition to these findings, authors have extrapolated that curcumin exerts a direct or indirect inhibitory effect on viral envelope protein. Further disruption efficacy study on liposome-based systems (as it mimics the viral envelope) revealed that the 30 μ M concentration of curcumin-induced leakage. Also, the potency of curcumin was found higher towards smaller nanometric liposome-based systems of 120 nm as compared to 300 and 220 nm.²⁴ The above findings were conclusive with the virus size-dependent curcumin effect on the Influenza virus, Vaccinia virus, and Pseudorabies virus. In which, EC50 concentration of curcumin required to reduce the plaque formation was found to be 1.15 μ M, 4.61 μ M for Influenza, and Pseudorabies virus respectively. While more than 60 μ M concentration of curcumin was required to reduce 30% plaque formation in the Vaccinia virus to that of control. Higher toxicity of curcumin exerted in the Influenza virus followed by the Pseudorabies virus and Vaccinia virus (owing to the larger size). Further Chen et al., have proposed the higher potency of curcumin towards the enveloped virus was due to the hydrophobic property of membranes and the presence of phenolic ring in the curcumin favoring the intercalation with hydrogen bonding sites. The efficiency of curcumin against several dreadful enveloped viruses such as Hepatitis C Virus replication²¹ and human immunodeficiency virus type-1,²⁶ cytomegalovirus^{27,28} were recognized. A strong shred of evidence on preventing the replication and budding of respiratory Syncytial virus on Human Nasal Epithelial Cells without cytotoxicity and controlling the respiratory tract disease was demonstrated by Obata et al.²⁹

Several molecular mechanisms on the

antiviral efficacy of curcumin were proposed by several research groups. The efficiency of curcumin to reduce the human cytomegalovirus replication and inhibition of human embryonic lung fibroblast cell apoptosis. In addition, *in-vivo* studies were carried out to demonstrate the potency in human cytomegalovirus-infected mice. In which, curcumin has convincingly decreased the human cytomegalovirus IgM and DNA load. Also, it decreased the serum level of aspartate aminotransferase, alanine aminotransferase, creatine kinase, lactate dehydrogenase, tumor necrosis factor (TNF- α), and interleukin-6 in infected mice. Moreover, authors have proposed that curcumin efficiency suppressed oxidative damage in mice by downregulating the malondialdehyde and upregulating the superoxide dismutase and glutathione levels. Ingolfson et al.,³⁰ have reported the influence of curcumin in modulating the host lipid bilayer as well as influencing the membrane protein function. Chen et al., have inferred that the influenza A virus treated with curcumin has delayed the synthesis of viral protein such as haemagglutinin, neuraminidase, and matrix protein (M1), also strongly inhibited the NF- κ B signaling and thereby impacting the viral propagation. These findings were coinciding with the report by Mazur et al.,³¹ that inactivation of NF- κ B signaling by aspirin suppressed the viral RNA export leading to inhibition of viral replication. Further, Narayanan et al.,³² have explored the molecular cascade mechanism and host signaling events in the human small airway lung epithelial cells infected by the MP-12 strain of Rift valley fever virus and the inhibitory effect of curcumin. The aforementioned infers that curcumin binds to the IKK-B2 complex and inhibits the kinase activity. Also, further, impede with IKK-B2-mediated phosphorylation of the viral protein and inhibits replication. This elucidates the efficacy of curcumin to downregulate viruses in both *in vitro* and *in vivo* models. In addition, Padillas et al.,³³ have implicated the inhibition of ubiquitin-proteasome system by curcumin on Dengue serotype 2, while Dutta et al.,³⁴ have reported the inhibition of deregulated ubiquitin-proteasome system and ubiquitinated proteins accumulation. The decreased herpes simplex virus infectivity and immediate-early (IE) gene expression by inhibiting the recruitment of RNA polymerase II to IE gene promoters by

curcumin was also reported by Kutluay et al.,³⁵ These findings imply the recruitment of RNA polymerase II by curcumin was independent of p300 or CBP histone acetyltransferase activity. The inhibition of arachidonic acid metabolism *in-vitro* by curcumin proceeded through the inhibition of lipoxygenase, cyclooxygenase activities, and inhibition of 12-O-tetradecanoylphorbol-13-acetate.³⁶ Remarkably, the inhibition of arachidonic acid generation mediated via inhibition of phosphorylation of phospholipase A2, a key molecule catalyzes the hydrolysis of membrane phospholipids into arachidonic acid³⁷ and inhibition of sterol synthesis regulation in hepatitis C virus³⁸ displays a curcumin specificity on the enveloped virus. Moreover, the lipophilic property of curcumin may also attribute to the key interaction with the virus envelope. Conclusively, several mechanisms proposed above imply that curcumin possesses multi-molecular interaction with the virus envelope and non-toxicity towards the host.

In complementary to the antiviral activity posed by curcumin, it also possesses the immunomodulatory activity, i.e., the capability to modify the host's response towards the antigen, thereby protecting the host from infection. Antony et al.,³⁹ have reported the ability of curcumin to enhance the humoral immunity as evidence of increased antibody, phagocytic activity, production of antibody-forming cells and increase in lymphoid organ weights such as spleen and thymus. In the same way, enhanced phagocytic activity of peritoneal macrophages with curcumin, and non-toxicity up to 200 μ mol/L on murine spleen lymphocytes and peritoneal macrophages were reported.⁴⁰ 5 weeks of dietary exposure to curcumin at 40 mg/kg, led to an increased level of IgG levels significantly.⁴¹ An elaborate study conducted by Jagetia et al.⁴² on the involvement of curcumin in multiple pathways in the biological system has provided several pieces of evidence on initiating a cascade of downstream inflammatory and immunogenic events including proliferation and activation of T cells.

Since curcumin is non-toxic to the human body and cells,⁴³ it can be administered in various ways, including orally.⁴⁴ As a safeguard measure, consuming curcumin in the regular human diet could further provide a simple means

to prevent infection against enveloped viruses. In conclusion, improved antiviral efficacy and immunomodulatory efficacy posed by curcumin signify it as a potential antiviral drug. However, several non-curcuminoids present in curcumin such as turmerone, atlantone, and *zingiberene* were yet to be explored.

Zingiber officinale Roscoe

Zingiber officinale, commonly called Ginger, is known for its fragrance and medicinal property. Its rhizome is used widely in traditional ayurvedic medicine and as a food spice. FDA has regarded ginger into the category of “generally recognized as safe” (GRAS). Kubra and Rao⁴⁵ have reported around 128 compounds and structures in ginger with several pharmacological and physiological activities and medicinal properties. Ginger rhizome is an essential drug in Indian, Chinese, and Japanese traditional therapeutic systems and is known for its antimicrobial activity.⁴⁶ The rhizome part of numerous *Zingiber sp* tends to possess several Bioactive phytochemicals including gingerols, shogaols, diarylheptanoids, phenylbutenoids, flavonoids, diterpenoids, sesquiterpenoids, and gingerols are identified as the primary active components in the fresh rhizome of the plant.⁴⁷ The two dimensional chemical structure of the most important compounds present in *zingiber* species is presented in Fig. 2.

Denyer et al.⁴⁸ have extracted sesquiterpenes from ginger, namely α -curcumene, β -sesquiphellandrene, α -*zingiberene*, β -bisabolene, and flavans such as dichloroflavan. Their efficacy was tested against the rhinovirus IB., among which β -sesquiphellandrene is efficacious in plaque reduction test. Joyce et al⁴⁹ showed that the β -sesquiphellandrene and α -*zingiberene* also bind with the enzyme, ADP ribose phosphatase (ADRP) that helps for viral replication. Hence β -sesquiphellandrene could be more efficacious due to multi targeted and further more analysis on its anti-viral mechanism is required.

Similarly, Chang et al.⁵⁰ have studied the efficacy of the hot water extracts of fresh ginger and dried ginger against the human respiratory syncytial virus. In the antiviral assay dried ginger has shown a lesser efficacy than the fresh ginger towards the Human larynx epidermoid carcinoma cell (human upper respiratory tract cell lines) and Human lung carcinoma cell (low respiratory

tract cell lines). Further inferred the inhibition of viral attachment, internalization, and plausible stimulation of IFN- β secretion executed by fresh ginger. Jolad et al.^{51,52} have summarised the constituents of ginger, which include paradols, dihydroparadols, gingerols, acetyl derivatives of gingerols, shogaols, 3-dihydroshogaols, gingerdiols, mono-acetyl derivatives of gingerdiols, diacetyl derivatives of gingerdiols, 1-dehydrogingerdiones, diarylheptanoids, and methyl ether derivatives, in which [6]-gingerol(5-hydroxy-1-(40-hydroxy-30-methoxyphenyl)decan-3-one) is present enormously.⁵³ The shogaol family is present naturally in ginger, or during long-term storage or synthesized from corresponding gingerols at pH 2.5-7.2 media and by thermal processing.⁵¹⁻⁵³ The thermal degradation products of ginger were found to be 4-(4-Hydroxyphenyl)-2-butanone, 4-Hydroxy-3-methoxybenzenepropanal, 3,4-Dimethoxybenzenepropanal, Zingerone, Zingerone methyl ether, Gingerol, Zingerol, 2-methyl ether detected by Gas chromatography–mass spectrometry (GC-MS).⁵¹ The preparation of hot water extracts of fresh ginger⁵⁰ may lead to the formation of thermal degradation products reported above causing improved antiviral property. The tendency of gingerol to suppress the cyclooxygenase and lipoxygenase metabolites of arachidonic acid was reported by Srivastava.⁵⁴ Similarly, Park and Lee⁵⁵ have screened a boiled water extract of 101 medicinal plants for the inhibitory activity against influenza type A virus. Among these, ginger has exerted higher antiviral activity at 0.0487 μ g/ml to 100 mg/ml against the Influenza virus (H1N1) with no cytotoxicity on RBC cells. In corroboration to this, the plaque reduction activity against Human influenza viruses 45 and antiviral efficacy on Avian influenza virus H9N2 was reported.⁵⁶

Apart from extracts, the essential oils derived from ginger were known to exhibit antiviral efficacy against drug-resistant clinical herpes simplex virus type 1 Strains⁵⁷ and herpes simplex virus type 2.⁵⁸ In which, ginger oil constituting majorly *zingiberene* (18.9%), limonene/cineol (15.5%), β -sesquiphellandrene (6.8%), camphene (6.2%) and pinocamphene (6.8%) has yield total concentration TC50 value of 0.004. Also, the infectivity was reduced by more than 90% when pre-treated. This clearly, indicates the

effectiveness of the virus before the adsorption period implying its efficacy to interfere with viral envelope structure or by impairing the bridge molecules between a virus and host cell.

Macrophages are the first barrier of the defense mechanism, which in turn produces several cytokines. Imanisai et al.⁵⁹ have reported that the lyophilized powder of *Z. officinale* extracts, induces macrophage activation leading to the production of TNF- α in the dose and stimulation period depend manner against Influenza A/Aichi /2/68 virus (H3N2 subtype). As evidence to aforementioned, virus cell-membrane proteins such as haemagglutinin and neuraminidase proteins of the influenza virus involved in infection and proliferation are hydrolyzed by the cysteine residue present in the *Z. officinale* extracts.⁶⁰ To elucidate, inventors have conducted the antiviral drug assay against Ross River Virus and Murray Valley Encephalitis with *Z. officinale* extract. The obtained results signify up to 80% inhibition of Ross River Virus with 7.5 Units activity/ml of extract and roughly 5-fold inhibition of Murray Valley Encephalitis viral replication with 330 Units/mL of extract.

Likewise, Wang et al.⁶¹ have investigated the efficacy of hot water extract potency of Sheng-Ma-Ge-Gen-Tang (Shoma-kakkon-to), a Chinese traditional medicine consisting of 111 mg of Rhizome of *Zingiber officinale* (other constituents; 333 mg radix root of *Pueraria lobata*, 222 mg radix root of *Paeonia lactiflora*, 222 mg Rhizoma of *Cimicifuga foetida*, 111 mg radix root and stolon of *Glycyrrhiza uralensis*). The crude extracts have inhibited the human respiratory syncytial virus (RSV Long strain: ATCC VR-26) induced plaque formation in upper respiratory tract cell lines (Human larynx epidermoid carcinoma cells- HEp-2) and low respiratory tract cells (Human lung carcinoma cells - A549). The efficiency of the extract was higher when administrated before infection which attributes the inhibition of internalization, and induced the secretion of cytokines, IFN- β , TNF- α for viral defense mechanism.

***Kaempferia parviflora* Wall. Ex Baker**

Kaempferia parviflora or Krachaidam, which has a place with the family ZBE, is initially found in the North and Northeast of Thailand. The rhizomes of *K. parviflora*, otherwise called dark ginger, are mainstream as well being advancing

herbs and customarily utilized as a society medication for dealing with an assortment of ailments, including aggravation, ulcers, gout, colic issue, abscesses, hypersensitivity, and osteoarthritis.⁶² Important advantages of *K. parviflora* have asserted by various pharmacological researches for a variety of diseases.

K. parviflora used to examine the anti-viral activity against H5N1 virus infection.⁶³ The flavones extracted from *K. parviflora* have also shown inhibitory effects against viral proteases. 5-hydroxy-7-methoxyflavone and 5,7-dimethoxyflavone, inhibited HIV-1 protease (IC₅₀ 19 μ M). Also, 5-hydroxy-3,7-dimethoxyflavone has inhibited HCV protease and HCMV protease with IC₅₀ values of 190 and 250 mM, respectively.⁶³ Moreover, plants that demonstrated antiviral activity were explored for their capacity to induce the expression of cytokine mRNA in the tested cell line. The findings obtained from this research suggest that crude extracts from the plants tested will in the future be used as an effective therapeutic agent in the treatment of patients or animals infected with H5N1 influenza and the anti-viral activity of TNF- α has been demonstrated to be controlled by the expression of the NF- κ B-initiating inhibitor of the κ B kinase complex IKK- α/β , and the over-expression of the latter inhibits hepatitis B virus replication.⁶⁴ The report shows a crude extract of *K. parviflora* act against the H5N1 influenza virus mechanism by an upregulation of the TNF- α and IFN- β . It also determined that medicinal plants are the alternative antiviral compounds against avian, swine, and human flu viral infection in the natural host. NF- κ B is a redox-cellular transcription factor that is another potential mediator of *K. parviflora* antiviral effects.⁶⁵ NF- κ B is triggered by oxidative stress and inhibited by antioxidants, and plays a crucial role in HIV1 replication by activating HIV1 transcription. Consequently, the effects of Nitric oxide on NF- κ B activity in virally infected cells are likely to depend on the redox state of infected cells and may vary between viruses. The ethanol extract of KP exhibits cardioprotective effect⁶⁶ and calcium attenuation and defense against ROS mechanism by activating Nitric oxide through cGMP signaling. Pentamethoxyflavone (PMF) plays an important role in enhancing the expression of Nitric oxide and Hydrogen sulphide

(H2S), which increased the vasodilatation capacity and decreased phenylephrine contraction. PMF further lowers plasma glucose concentration but elevates plasma high-density lipoprotein cholesterol (HDL) levels. The Nitric oxide provided by cytokine-inducible and calcium/calmodulin-independent (iNOS) specifically enhances COX-2 activity through peroxynitrite-mediated activation of COX-2 peroxidase activity. The mechanism of *K. parviflora* decreased the amount of cellular iNOS mRNA while the inhibitory effect on the expression of COX-2 mRNA was partially impacted. An excessive Nitric oxide was found to interact with oxygen radicals and form highly reactive peroxynitrite, which induces inflammatory cell cytokines and COX-2.⁶⁷ Therefore the product of inhibition of PGE2 may also be directly mediated by down-regulation of the expression of iNOS. In addition, it has been stated that inhibition of iNOS mRNA expression can require the inflammatory blocking activity of the iNOS gene transcription.⁶⁸ Certain viruses that encode cysteine proteases, such as Picornavirus family members and the Coronavirus family, cannot be replicated by the Nitric oxide mechanism. To sum up, endogenously synthesized *K. parviflora* Nitric oxide prevents the replication of many human viruses. This remains to be elucidated the exact mechanism by which Nitric oxide exerts its anti-viral effects,^{69,70} but is likely to include reactions with both viral and cellular targets. Because the antiviral effects of Nitric oxide do not require immune recognition of infected cells, and because Nitric oxide can easily pass into cells, it provides a good early defense against viral pathogens before a specific immune response develops.

***Aframomum melegueta* K. Schum**

Aframomum melegueta is commonly known as Alligator pepper (of ZBE) is one of the plants with medicinal and nutritional qualities. It is popularly used as a herbal remedy for a wide variety of diseases in Nigeria and many other countries worldwide.⁷¹ The significant properties of seed extracts are well known as a treatment for stomach aches, looseness of the bowels, inflammatory conditions, and baby blues hemorrhage. Its documented anti-ulcer, cytoprotective, antimicrobial, and so on.⁷² Previous reports identified as the whole extract of *A.*

Melegueta responsible for the hepatoprotection from severe infections. These seeds of plants are used as flavoring foods and as components of traditional African medicine. They were a highly valued spice in medieval Europe that was gradually replaced by black pepper and other spices after opening the Asian trade routes.⁷³ It has been shown that the aqueous seed extract reduces the frequency of abdominal constrictions induced by the acetic acid in mice and has significant anti-inflammatory action. Beyond inhibiting the COX-2 enzyme, paradise grain extract has also been tested to inhibit pro-inflammatory genes. The genes tested were alpha (tnf α), interleukin-1beta (IL-1 β), interleukin-6 (IL-6), COX-2, and inducible synthase of nitric oxides (iNOS). The plant materials phytochemical analysis unraveled several antiviral-activated chemical substances. Flavanones exhibit inhibitory effects on viruses such as HIV and respiratory syncytial viruses. Acute kidney injury is a severe symptom of the 2019 novel coronavirus disease (COVID-19), particularly for patients in critical condition. Liver dysfunction has been documented in up to 60% of SARS374 patients and seen in MERS-CoV patients. The viral infection of the liver cells may directly cause liver damage in patients with coronavirus infection. Immune dysfunction including lymphopenia, reductions in CD4 + T-cell rates, and strange cytokine rates (including cytokine storm) is a feature in COVID-19 cases and may be a critical factor in disease severity and mortality.⁷⁵⁻⁷⁷ The impact of *A. Melegueta* on the liver injury was linked to curcumin, a significant dynamic phenolic compound with potent antioxidant, anti-inflammatory, and hepatoprotective activity. To evaluate the mechanisms of hepatoprotection in *A. Melegueta*, oxidative liver damage, the potential for antioxidant protection, inflammatory mediators such as tumor necrosis factor- α (TNF- α), and interleukin 1 β (IL-1 β), just as caspase-3 and caspase-9 enactment were resolved.⁷⁸ The inflammatory processes in the liver lead to a variety of pathological events following exposure to specific hepatotoxins. TNF- α is a pleiotropic pro-inflammatory cytokine generated primarily by activated macrophages and monocytes. It is engaged with a wide range of biological and pathological processes, including inflammation,

autoimmune diseases, and cancer.

TNF- α activates the expression of different cytokines, such as IL-1 β , inflammatory cell invasion and activation, and hemostatic system impairment.⁷⁹ Most likely, the anti-viral behaviors found with these plants are due to the plant phytochemicals. The lipophilic compounds are thought to be active against viruses by envelope disruption. Alkaloids have commonly been identified as having antimicrobial properties. It is also helpful against HIV infection and AIDS-related bowel infections. According to Ojo et al.,⁸⁰ these phytochemicals include tannin, phenolic compounds, saponins, flavonoids, and protocatechuic acid. Such phytochemicals are known to activate infected individuals' lymphocytes and prevent resistance formation in viruses and virus replication through several cytokine (viz. IL10, IL6, IL12 etc) regulation.⁸¹ Therefore it should be recommended that extracts from these plants can be used to treat severe infectious viral diseases with acute hepatic side effects.⁸² Despite the financial status of the population at large, the significant attention of *A. Melequeta* on managing some of these viral infections was that of prophylaxis, whereby every attempt was made to avoid infections through prudent utilization of immunizations.

***Elettaria cardamomum* (L). Maton**

In traditional spices, cardamom (*Elettaria cardamomum*) plays a vital role in the Unani system of medicine of ZBE. Cardamom seeds are broadly utilized to treat various diseases, including intense respiratory issues, terrible breath, sore throat, colds, fever, hacks, asthma, and heartburn. As we know, cardamom is an essential component of the Indian spice mix of garam masala⁸³; there are several studies underway to investigate the beneficial effects of garam masala on health, if any. The properties of cardamom oil incorporate antiseptic, antispasmodic, against cancer-causing, stomach related, diuretic, expectorant, and energizer properties, just as its stomachic property, which may be credited to attributed, hostile to oxidant and antimutagenic activities.⁸⁴ Notwithstanding its wide use for a culinary reason, cardamom has been utilized in daily medication for asthma, clogging, colic, looseness of the bowels, dyspepsia, hypertension, epilepsy and is viewed as helpful as antibacterial, antifungal,

antiviral, carminative, diuretic and stomachic. Acetylcholine (ACh) is the most important neurotransmitter which present in the cardamom oil has been ending in the parasympathetic nerve to trigger smooth muscular contractions. Acetylcholine is released from the primary exciting motor neurons in the gastrointestinal tract, and mediates an immediate smooth muscle contraction. The dominant autonomic innervation of airways is provided by parasympathetic nerves. Acetylcholine release from parasympathetic nerves activates post-junctional muscarinic receptors that are present on airway smooth muscle, submucosal glands, and blood vessels, causing bronchoconstriction, mucus secretion, and vasodilation, respectively. Phytochemical examines uncovered that cardamom contains α -terpineol, myrcene, heptane, subinene, limonene, cineol, men-thone, α -pinene, β -pinene, linalol, nerolidol, β -sitos-tenone, phytol, eugenyl acetic acid derivation, bisabolene, borneol, citronellol, geraniol, geranyl acetic acid derivation, stigmasterol and terpinene.⁸⁵ One examination has announced 1,8-cineole to be a solid inhibitor of cytokines that may be reasonable for long haul treatment of aviation route aggravation in bronchial asthma and other steroid-delicate disorders.⁸⁶ The increasing evidence of the role of 1,8-cineole in controlling hypersecretion of airway mucus may be due to blockage of muscarinic receptors.⁸⁷ The anti-inflammatory activity of the cardamom extracts used in this study may be associated with the presence of high amounts of 1,8-cineole (eucalyptol), since this compound has previously been reported to mitigate inflammatory signaling pathways in the lung alveolar macrophages. The infectious virus triggers the pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) which could be responsible for the acute inflammation for a differing scope of flagging occasions inside cells, prompting necrosis or apoptosis. IL-1 a d tumor necrosis factor (TNF) stimulate neutrophil and macrophage functions by expanding expression of leukocyte adhesion particles on the respiratory epithelium and both the cytokines stimulate IL-6 production.⁸⁸ 1,8-cineole is a solid inhibitor of TNF- α and IL-1 β ⁸⁹ may represent a wide scope of pharmacological impacts displayed by cardamom and additionally 1,8-cineole, controlling airway fluid hypersecretion, giving assurance against liver

injury, etc. The NF- κ B signaling pathway involves the transcription of pro-inflammatory genes and helps to maintain a chronic inflammatory state in many inflammatory diseases.⁹⁰⁻⁹³ Therefore, Gupta et al.,⁹⁴ reported the hindrance of NF- κ B translation factor could be promising treatment and anticipation of chronic inflammatory disorders, including periodontal illnesses. The effects of the phytochemical investigation indicated that cardamom contains alkaloids, flavonoids, saponins, sterols, and tannins. The flavonoids are notable for their bronchodilatory action⁹⁵ and the mixture of compounds in cardamom is probably going to contribute in its airway relaxing activity. However, the commitment of different constituents can't be overlooked.

Alpinia sps.,

The genus *Alpinia* is considered as the gold mine for the future therapeutics, due to the large presence of BPC and therapeutic application. *Alpinia* is an angiosperm, monocotyledonous plants span more than 200 species distributed in Asia pacific region possess plenty of flavonoids, tannin and other polyphenolics.⁹⁶ *Alpinia officinarum*, commonly known as lesser galangal widely used in ancient traditional medicine. Konno et al.,⁹⁷ have extracted diarylheptanoids namely 1,7-Diphenyl-4E-hepten-3-one, 7-(4''-Hydroxyphenyl)-1-phenyl-4E-hepten-3-one, 7-(4''-Hydroxyphenyl)-1-phenyl-4E-hepten-3-one, 7-(4''-Hydroxy-3''-methoxyphenyl)-1-phenyl-4E-hepten-3-one, (5R)-5-Hydroxy-1,7-diphenyl-3-heptanone, (5R)-5-Hydroxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3-heptanone, (5R)-5-Methoxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3-heptanone, (5S)-5-Methoxy-1,7-diphenyl-3-heptanone, (5S)-5-Methoxy-7-(4''-hydroxyphenyl)-1-phenyl-3-heptanone, (3R,5R)-1,7-Diphenylheptan-3,5-diol from *A. officinarum* (See Fig. 2). These diarylheptanoids tend to pose antiviral activity (EC₅₀) against respiratory syncytial virus (5-42 μ g/ml), poliovirus (8-44 μ g/ml) and measles virus (17- 47 μ g/ml) at different concentration levels⁹⁷ in which (5R)-5-Methoxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3-heptanone was found to exert higher efficacy against, poliovirus, measles virus, and herpes simplex virus type 1. Similarly⁹⁸ have reported the anti-influenza viral activity of diarylheptanoids isolated from *Alpinia officinarum*. Among them

7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-4E-hepten-3-one (see Fig. 2) has significantly reduced the virus titers in bronchoalveolar lavage fluids levels (5- 30 μ g/g) and reduced body weight loss in mice models. In addition to this, even oseltamivir-resistant strain, have shown susceptibility against the 7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-4E-hepten-3-one by suppressing the expression of viral mRNA and antigens, however, no effect on virus adsorption was reported. In contrast Kim et al.⁹⁹ have reported the strong inhibition of haemagglutinin against bovine G8P[7] and porcine G5P[7] rotaviruses. Other species of *Alpinia* such as *A. daniellii* contains diterpenoid dialdehyde. The extracts of the plant were found to contain three novel diterpenoids like aulacocarpinolide, aulacocarpin A, and aulacocarpin, which may also contribute to the efficacy against enveloped viruses.¹³

Alpinia katsumada were commonly used in traditional Chinese medicine and recommended against "phlegm-dampness breathing issues."¹⁰⁰ *Alpinia katsumadai* seeds are rich in diarylheptanoids, monoterpenes, sesquiterpenoids, flavonoids, and chalcones.¹⁰¹ Jang et al.¹⁰² have isolated four acyclic triterpenoids from *Alpinia katsumadai* seeds in which [2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18-tetraene] and [2,3,5,22,23-pentahydroxy-2,6,10,15,19,23-hexamethyl-tetracos-6,10,14,18-tetraene] were found to exert potent inhibitory activity towards IL-6 induced STAT3 activation. Kwon et al.¹⁰³ have investigated the *in-vitro* anti-influenza viral mechanism of *Alpinia katsumadai* extracts and fractions using time-of-addition and haemagglutinin inhibition assays. Their results indicated that the extracts and fractions inhibit H1N1 and H9N2 influenza viruses by inhibiting viral haemagglutinin binding to the sialic acid receptor in the host cell and inhibiting the viral attachment. Their IC₅₀ was lower than (0.8 \pm 1.4 to 16.4 \pm 4.5 μ g/mL) against H1N1 and (<0.39 \pm 0.4 to 2.3 \pm 3.6 μ g/mL) against H9N2 respectively.

In Okinawa, Japan, *Alpinia* leaves were used to prepare the traditional food, *muchi* used to protect from the common cold.¹⁰⁴ The BP of alpha-pyrone such as dihydro-5,6-dehydrokawain, and 5,6-dehydrokawain present in leaves and rhizomes of *Alpinia zerumbet* poses

strong inhibitory action against HIV-1 integrase and neuraminidase.^{105,106} The activity against HIV-1 integrase was found similar to that of a suramin which is widely used as a positive control (IC₅₀ 36.6 μ M). Dihydro-5,6-dehydrokawain was posing slow and time-dependent inhibition and the efficacy was proposed due to the presence of methoxy group present in the C-5.¹⁰⁶ Also, the aqueous extract of leaves was found effective than the rhizome extract. Likewise, Katsumadain-A (see Fig. 2) a potent neuraminidase inhibitor isolated from *Alpinia katsumadai* seeds found to exert superior efficacy against the human influenza virus and H1N1 swine influenza.¹⁰⁷

Watanabe et al.¹⁰⁸ have demonstrated that a new class of nuclear export inhibitors, 1'-acetoxychavicol acetate (see Fig. 2) from *Alpinia galanga* regulates the nuclear export of influenza viral ribonucleoprotein complex and effectively suppresses virus production. Among the major medicinal plants of ZBE, *Alpinia galanga* have majorly inhibited the HIV-1 protease.⁶³ 1'S-1'-acetoxychavicol acetate, a small molecular compound isolated from *Alpinia galanga* tends to inhibit the transport in HIV replication,¹⁰⁹ while the ability of *Alpinia katsumadai* seed extract to inhibit cyclooxygenase-2 was reported by Choi et al.¹¹⁰ The combination these two may exert synergetic combination, which can be a remedy towards viruses like SARS-CoV-2. The rhizome of *Alpinia* was found to possess more BPC, which can be extracted efficiently by ethanol-based extraction and fractionalization.⁹⁶ In conclusive *Alpinia* species poses several BPC which were known to exert multimode action towards enveloped viruses.

Significance of Phytocompounds

Phytocompounds are found to be an easier, safe choice to combat the enveloped viruses as they are known for their defensive impacts against a wide scope of microbes, protozoa, parasites, and viruses.^{111,112} A variety of studies have demonstrated their protective impacts against H1N1, H6N1, and H3N8 influenza viruses using medicinal plant extract.¹¹³ In any case, just uncommon reports have identified the impacts of medicinal plants on H5N1 viral infection.²⁴ H5N1 infected patients typically have symptoms in the respiratory system with infrequent infections of the intestinal and nervous system. Presently, influenza virus patient medications are based

primarily on supportive treatment, depending on the conditions of the patient, along with antiviral therapy.¹¹⁴ The endorsed enemy of flu drugs, up until this point, are ordered in gatherings of neuraminidase inhibitors, for example, oseltamivir and zanamivir, and an M2 particle channel inhibitor, for example, amantadine and rimantadine.¹¹⁵ While anti-influenza drugs have been used successfully against human influenza A virus infection, expanded reports of medication against influenza viruses have brought the consideration back on the disease that has become a public concern.¹¹⁶

Song et al.¹¹⁷ have reported the key players to control the SARS-CoV-2 is to target envelope protein, membrane protein, spike proteins, and viral replication process. The receptor-binding domain in spike protein located on the viruses mediates the receptor binding angiotensin-converting enzyme 2, the host cell receptor for its cell entry, and plays a major role in virus entry.^{118,119} Numerous mechanisms of BPC pertaining to the inhibition of contact between the virus envelope and induction of the immunity were discussed in the present article which could efficiently interact with angiotensin-converting enzyme 2 and inhibit the cell binding. A recent molecular docking study by Khaerunnisa et al.¹²⁰ on the medicinal plant compounds against the SARS-CoV-2 strain main protease inhibitor have inferred the effective BPC of ZBE such as Zingerol, Gingerol, Curcumin, Demethoxycurcumin. These are present abundantly in ginger and turmeric extracts and several antiviral studies were carried out extensively.¹²¹ Several BPC compounds isolated from nine genera *Aframomum*, *Alpinia*, *Amomum*, *Boesenbergia*, *Costus*, *Curcuma*, *Hedychium*, *Kaempferia*, and *Zingiber* of *Zingiberaceae* family in which terpenoids, mono- and sesquiterpenoids are commonly present.¹³ Wen et al.¹²² have screened 221 compounds and found 20 BPC attributing antiviral efficacy against SARS-CoV. This consisting of ten diterpenoids (ferruginol; dehydroabieta-7-one; sugiol; cryptojaponol; [8 α -hydroxyabieta-9(11),13-dien-12-one]); 7 β -hydroxydeoxycryptojaponol; 6,7-dehydroroyleanone; 3 β ,12-diacetoxyabieta-6,8,11,13-tetraene; pinusolidic acid; forskolin); two sesquiterpenoids (cedrane-3 β ,12-diol; α -cadinol); two triterpenoids (betulinic acid; betulonic acid); five lignoids (hinokinin; savinin;

4,4'-O-benzoylisolariciresinol; honokiol; magnolol) and curcumin. Among these betulinic acid, savinin, curcumin, and niclosamide possess higher efficacy towards SARS-CoV 3CL Protease Activity. Sawamuwa et al.¹²³ have also demonstrated the potential of diarylheptanoid against influenza virus. Most of the BPC are found to present predominantly in ZBE.

DISCUSSION

Viral proteases play an efficient role in the life cycle of the replication, developing the protease inhibitors possess a potent role in developing new drugs. In accordance Sookkongwaree et al.⁶³ have evaluated *Kaempferia galanga*, *Curcuma zedoaria*, *Curcuma longa*, *Kaempferia parviflora*, *Boesenbergia pandurata*, *Zingiber zerumbet*, *Zingiber officinale*, and *Alpinia galanga* extracts of ZBE family. These have exerted superior inhibition efficiency against HIV protease, Hepatitis C Virus protease, and human cytomegalovirus proteases. The methanol extracts of *Alpinia galanga* was found to be effective against HIV-1 protease and human cytomegalovirus proteases at 20µg/ml, while *Curcuma zedoaria* was found effective at this concentration against Hepatitis C Virus protease. At 200 µg/ ml *Curcuma zedoaria* and *Alpinia galanga* exerted similar efficacy against HIV-1 protease, while *Zingiber officinale* and *Curcuma longa* were found to be effective against Hepatitis C Virus protease and human cytomegalovirus protease respectively. However, the efficacy was found to be lower in the aqueous extracts as compared to methanol extracts, except 200 µg/ml aqueous extract of *Curcuma longa* and *Zingiber officinale* against HIV-1 protease and HCV protease respectively. These imply the less polar BPC present in *Curcuma longa* and *Zingiber officinale* plays a significant role against HCV proteases.⁶³ Wang et al.¹²⁴ have proposed the anti-influenza mechanism of herbal drugs is mediated either directly or indirectly by inducing the immune system such as promoting phagocytosis, inducing interferons, enhancing macrophage activation and stimulating IL-1 production and so on. As immune response stimulated by a compound directly implies the molecular pathways involved in pathogenic interaction,¹²⁵ several BPC of ZBE family executes antiviral as well as immunomodulatory activity providing molecular clues for drug development.

CONCLUSION AND PERSPECTIVES

In the face of the persistent threat of contagious viral diseases have caused pandemic and epidemic diseases such as Chikungunya, Ebola virus disease, Influenza, MERS-CoV, Nipah virus infection, Lassa fever, Rift valley fever, SARS, Zika virus, Yellow fever, and at present SARS-CoV-2. These enveloped viruses have expended several human lives across the globe. A variant to unleash the infection, cure against these dreadful human pathogens during the epidemic and pandemic situation is of serious concern to save human lives. As effective antiviral or vaccine developments towards the viruses are time-consuming as the pathogenesis, molecular mechanisms were unknown. The urge and global impact have thrown the spotlight to look for alternative medicines, which were already known to be safe and antiviral activity.

Natural products fill in as a great wellspring of biodiversity for finding novel antivirals, exposing new interactions between structure and operation and creating successful defensive or remedial methodologies against viral diseases. The members of *Zingiberaceae* family discussed in the present review have seen to exert robust antiviral action and their findings will further lead to the production of derivatives and therapeutic. Additionally, an expanding need is felt towards using huge pharmaceutical organizations to reinvent their natural drug development wing and to inspire the academic world to create dedicated frameworks for conducting herbal research. There is no solution for the vast majority of viral infections and among the therapy patients, there are several viral diseases that require lifelong therapy, with high treatment costs. Considering the reactions and financial non-reasonability associated with anti-viral chemotherapy, antiviral particles or extract compounds from natural sources may be considered as a feasible other option, thereby providing enormous potential for study and discovery.

The antiviral activity of individual BPC and in combination differs. The individual compounds exhibiting antiviral activity *in-vitro* shall be toxic than the combination. Also, the individual BPC showing non-viral efficacy *in vivo* shall pose a significant role in boosting the immune response,

when whole plant extract is used.¹²⁴ As in ancient medicine such as Siddha, Ayurveda, traditional Chinese and Japanese medical systems extract of a complete plant part or a combinational extract of different plant parts are used, to pose a synergetic effect. These extracts have several BPC pooled together to execute multi molecular interaction inside the biological system and consolidate the antiviral activity so-called multi-drug combination therapy. As BPC possess different size, shape, structure among themselves and exerting the potency against the viral complexes, the development of resistance is unfeasible. In addition, combining the several BPC as one using emulsion technology into a nanometric form alters the polarity with improved drug delivery and higher bioavailability.^{126,127} Moreover the BPC possessing the complex molecular entity could also deceive the molecular tropism of viruses from the prepon targets.¹²⁸ Given the abundance of literature evidence on the potential bioactive plant compounds or components of *Zingiberaceae* family with antiviral and immune booster's efficiency revealed the simple and immediate remedy in controlling the enveloped viruses. In addition these phytochemicals could serve as an immediate choice towards the novel viruses during the endemic or pandemic situations and provide insight for drug development and prophylaxis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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