Ashraf Z, et al., J Food Sci Nutr 2021, 7: 085
DOI: 10.24966/FSN-1076/100085

HSOA Journal of Food Science and Nutrition

Review Article

Bioactive Compounds from Plant Sources as Natural Antivirals in Combating RNA Based Viruses Including COVID-19

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Abstract

The novel Coronavirus Disease (COVID-19) is causing chaos worldwide due to its high morbidity, mortality and contagiousness nature. It is declared a pandemic by WHO as it spreads more rapidly. In spite of advancements made in vaccination and drug development, there is still no medicine and vaccine available against COVID-19. Worldwide scientists are racing to develop possible antiviral drugs and preventive vaccines to fight the COVID-19. So, there is an urgent need for a natural alternative method to combat viral disease including COVID-19. Therefore, bioactive compounds from plant sources including allicin, kaempferol, myricetin, peptides, resveratrol, ajoene and quercetin, etc. are an excellent source for such innovation and finding novel antiviral agents against viral infections including COVID-19. Also, these bioactive compounds have an incredible antiviral effect and have already been used to successfully treat different viral diseases. Hence, in this review we have highlighted the antiviral activities of bioactive compounds from plant sources which we assume can play a possible role in combating COVID-19 as they have proven antiviral activity against certain virues.

Keywords: Alicin; Ajoene; Flavonoids; Mechanism; Myricetin; Resveratrol

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Citation: Ashraf Z, Gani A, Shah A, Gani A, Noor N, et al. (2021) Bioactive Compounds from Plant Sources as Natural Antivirals in Combating RNA Based Viruses Including COVID-19. J Food Sci Nutr 7: 085.

Received: January 05, 2021; **Accepted:** January 07, 2021; **Published:** January 15, 2021

Introduction

RNA viruses are microscopic pathogenic agents responsible for human pathogenicity. They have RNA as genetic material which is either single-stranded RNA or a double stranded RNA, surrounded by a protein covering and sometimes with a lipid envelope or enzymes [1,2]. There are two types of single stranded RNA viruses i.e. positive-sense single-stranded RNA (PssRNA) virus and negative sense single-stranded RNA virus (NssRNA). PssRNA is a virus that uses positive sense single stranded RNA as its genetic material for replication. PssRNA is similar to mRNA and thus can easily be translated by the host cell. PssRNA viruses accounts for different viruses, comprising pathogens viruses such as the SARS(severe acute respiratory syndrome coronavirus) and MERS (Middle East respiratory syndrome coronavirus) coronaviruses, hepacivirus C, dengue virus, West Nile virus and SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2 [3]. In the past two decades, SARS and MERS coronaviruses have led to global pandemic with high morbidity and mortality. In the SARS-CoV pandemic near about 8098 persons were infected and 774 died whereas MERS-CoV had infected 2494 individuals and 858 deaths were reported.

On December 2019 coronavirus-19 outbreak arose in a wholesale seafood market in Wuhan city, China [3]. Coronavirus named (COVID 19) by WHO, on February 11, 2020, is the pathogenic disease caused by (SARS-CoV-2) Severe acute respiratory syndrome coronavirus-2 [4,5]. It belongs to family Coronaviridaeis containing an RNA virus of positive-sense single-stranded RNA [3]. They are spherical in shape with crown like spikes on the surfaces [6,7]. These spikes are proteinious in nature that act as a key to get into the cell of human body and built component of viruses [8]. The spike protein has the Receptor-Binding Domain (RBD) which acts as a hook to grips onto host cells and the cleavage site, which allows the virus to enter host cells [8]. A protein shell provides hard protective enclosure for genetic material [9]. The sequence analysis indicated that SARS-CoV-2 have a similar genome structure of coronavirus as SARS-CoV and MERS-CoV [10]. It causes contagious viral infection that attacks primarily throat and lungs causing an inflammatory storm in the lungs that leads to acute respiratory distress, and death. Globally, as of 5 January 2021 (WHO, 2021) the number of confirmed positive cases with the COVID-19 are 83, 322, 449 confirmed cases of COVID-19, including total confirmed deaths of 1,831,412 [11]. It has rapidly spread to near about 222 Countries [11]. Currently, there is no medicine available which can suppress its replication, as COVID -19 have high mutation rate. Furthermore, development of preventive vaccines against covid-19 has not been explored yet. So there is an immediate requirement of an alternate method to curb the disease. Bioactive compounds from plant sources are reported to have antiviral activity which is helpful in reducing the severity of viral infection as they have proven health benefitting agents including antioxidant and anti-inflammatory [12]. Also, the anti-inflammatory strategy, either by nutrients, foods, phytochemicals, or medicines is a viable option for the management of COVID-19. So, these bioactive ingredients

are studied to have robust antiviral activity and their discoveries can further help to develop therapeutic approaches against viral infections [1,13]. Moreover, several bioactive compounds are reported to boost type 1 interferon response to the different viruses, which is the body's primary way to help create antiviral antibodies to combat viral infections [14]. Hence, antivirals from the plant sources is the possible way to combat COVID-19 as no specific drug has been discovered so for. Therefore, we review the natural therapeutic options available from the natural food sources which could prove pivotal in the treatment and management of novel COVID-19.

Main source of Antiviral Derived from Plants

Garlic and onion

Garlic and onion belongs to the Allium family and have excellent antiviral activity [15,16]. They are good source of organosulfur compound such as allicin and quercetin that plays an important role in inhibiting viral infections by obstructing virus attachment to host cell [17]. They also contain important bioactive compounds such as myricetin, kaempferol, ajoene and isorhamnetin that have remarkable antiviral effect against various RNA viruses. Several studies have reported the antiviral activity of these bioactive compounds against different viruses such as Dengue virus hepatitis B virus, influenza virus A&B, and coronavirus [17-19].

Quercetin and kamferol is the main bioactive compound present in onion and broccoli [20]. They act as an anti-infective and anti-replicative [21]. A literature studies revealed that quercetin has been successfully used as an anti-viral agent against RNA viruses [20]. Quercetin prevented the entry of Ebola virus, inhibited translation of polio virus and Hepatitis C and it was also found to inhibit SARS-Cov-protease which is important enzyme used for multiplication of SARS Virus [22-25]. Furthermore, quercetin is effective in enhancing immune response in host cell.

Allicin is the important bioactive compound present in garlic which have strong antiviral property. It inhibits the virus multiplication and modulates immune system in response to viral infection. The antiviral role of garlic against influenza virus was reported [26]. Besides, alicin it also contains selenium which possesses antiviral property [27]. The selenium compound was reported to inhibit the replication of Coxsackie virus [28]. Hence, Allicin, Kamferol, myricetin and quercetin can be used as a novel antiviral agent against COVID-19.

Mushroom

Mushrooms are good source of bioactive compounds such as nucleosides, terpenoids, peptides, glycoproteins, alcohols, mineral elements and antioxidants like phenolic compounds, tocopherols, ascorbic acid etc. [29]. They possess antiviral activity in addition to anticancer, antimicrobial, antiviral, antioxidant, and anti-inflammatory activities. Both edible and nonedible mushrooms were found to have antiviral activity [29]. Certain studies reported the antiviral effect of bioactive compounds isolated from different variety of mushrooms against different RNA virus such as herpes simplex virus, human immunodeficiency virus, hepatitis B, influenza and C viruses [30]. A Reverse transcriptase activity of Human Immunodeficiency Virus (HIV) was inhibited by novel PPC (Polysaccharide-Peptide Complex) from mushroom sources (Pleurotus abalonus and Russula paludos) [31,32]. Similarly an extract obtained from the mycelium of Lentinus edodes inhibited the HIV antigen expression thereby inhibiting HIV [33]. Also, the antiviral protein isolated from fruiting body of Grifola frondosa was found to have an effective antiviral activity against Herpes Simplex Virus [34]. Furthermore, the antiviral activity of Pleurotus ostreatus extract against swine flu (H1N1) was also testified [35]. Also, the Phenolic extracts of Inonotus hispidus showed the antiviral effect against Influenza A and B [36]. Likewise, Hwang et al testified the antiviral effect of polyphenolic extract isolated from Phellinus baumii against influenza A, H1N1, H5N1, and H3N2 [37]. Saboulard et al reported basidiomycete Macrocystidia cucumis showed antiviral response against herpes simplex in virus baby hamster kidney cells [38]. Apart from this, bioactive compounds in mushroom boosts the immune system by activating the cellular immune function and helps to defend against viral infections by inhibiting the entry of virus.

Blueberries, grapes and cranberries

Resveratrol is the important polyphenol present in blueberries, grapes and Cranberries responsible for antiviral activity [39]. It also possesses antioxidant property. The mechanism responsible for antiviral activity of resveratrol includes inhibition of viral replication, protein synthesis, gene expression, and nucleic acid synthesis [39]. The antiviral effects of resveratrol has been proven against various viral infections, including EPSTEIN-BARR VIRUS (EBV), Herpes Simplex Virus (HSV), also respiratory viral infections caused by influenza, rhinovirus and MERS-CoV infections [40-44]. Resveratrol can also be used therapeutic option for treatment of this novel covid-19. Furthermore, cranberry extracts possess antiviral activities against reovirus, enterovirus, and influenza virus by preventing viral attachment to target cells [45-49]. Also, blueberries are rich in anthocyanin that inhibited the replication of influenza virus A/H3N2, coxsackievirus and Human Respiratory Syncytial Virus A2 (HRSV-A2) [50]. Grapes seed extract contain bioactive compounds such as catechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate which possess antiviral, antioxidant, anti-inflammatory, anticancerous property. The extract of grape seed showed the antiviral effects against HIV, herpes virus and hepatitis by effecting viral binding [51].

Citrus fruits

Citrus fruits are rich source of vitamin C. It is a powerful an antioxidant which scavenge the free radicle. Recent studies have found that antioxidants can significantly improve immune responses against various bacteria and viruses. It may help to boost immune system, thus making it easier to fight off the virus**.** Vitamin C is reported to act as antihistamine agent responsible for aid in flu symptoms like sneezing, a running nose, and swollen sinuses [52]. Vitamin C-supplemented was found to reduce the rate of pneumonia in human trails suffering from SARS coronavirus suggesting that it may inhibit the exposure to lower respiratory tract infections caused by COVID-19 [53]. Hence, vitamin C could be explored as an effective option for the treatment of COVID-19 [54].

Antiviral activity of β-glucan

β-glucan is a non- starch polysaccharide present in various sources like cereals, yeast, fungi and bacteria. They possess antioxidant, anticancerous, antimicrobial property and act as immunomodulant [55]. β-glucan boasts the immune system (innate and adaptive

immune response) making it more efficient. It stimulates the action of macrophages that swallow and demolish invading pathogens and stimulate other immune cells to attack. Furthermore, macrophages release a chemical compound called cytokines that enable the communication of immune cells. β-glucan also stimulate lymphocytes (white blood cells) that bind to viruses, and release chemicals to destroy it. In stressed woman the supplement of betaglucan was reported to reduce upper respiratory symptoms and improved the mood swing [56]. Jesenak et al., reported the immunomodulatory effect of β-glucan in children with respiratory infections [57]. Similarly a study reported by Graubaum et al., showed that beta-glucan reduced cold symptoms like sore throat, hoarseness, cough, and runny nose [58]. In addition, in the study of Auinger et al., consumption of yeast β-glucan caused a milder progression of the severe common cold [59]. Also, the immunomodulatory effects of brewer's yeast beta glucans have been shown in regard to the stimulation of monocytes to release elevated levels of anti-inflammatory interleukin (IL)10 [59].

Phytochemicals as antivirals

Phytochemicals mainly flavonoid, alkaloids and terpenes possess antiviral activity [60]. World Health Organization (WHO) reported that the 80 % of world's population depends on plants to meet their basic health requirements as plants possess the bioactive compounds among which phytochemicals are the largest group synthesized [27,28]. Further, these phytochemicals are reported to possess the antioxidant and antiviral activity.

The mechanism involved in antiviral activity of phytochemicals is that it inhibits the synthesis of RNA or hinders the reproduction of virus by blocking cellular receptors and enzymatic function [61]. Subsequently, numerous studies have been reported about the antiviral activity of various phytochemicals present in natural food products and herbal plants. Natural food product derived antivirals have been used for two previous coronavirus outbreaks of SARS-CoV and MERS-CoV which suggests it's potential to provide treatment for the on-going epidemic of COVID-19. The anti-coronavirus activity of some flavonoids (Herbacetin, rhoifolin and pectolinarin) was reported due to the inhibition of 3C-like protease (3CLpro). Other flavonoids such as Herbacetin, quercetin, and helichrysetin) were reported to inhibit the enzymatic activity of MERS-CoV/3CLpro. Flavonoids are among the principal group of phytochemicals that are widely distributed in plant kingdom. Their vast structural makes them available for antiviral research. Flavonoids such as chalcone, flavonone, iso-flavonone are commonly known for its antiviral research. The mechanisum behind the antiviral activity of flavonoids might be attributed to its antioxidant activity, scavenging ability and DNA inhibition, inhibition of entry of virus or its reproduction [62]. Furthermore, flavonoids also play a role as an immunomodulator as they have the capacity to direct macrophages from pro inflammatory to anti-inflammatory phenotypes. This anti-inflammatory activity of flavonoids have been attributed to various mechanisms which involves activation of nuclear factor κ- light chain amplifier of activated B cells (NF-κB) , modulation of mitogen –activated protein kinase, cytokine synthesis and inhibition of reactive oxygen species. Various types of flavonoids are also reported to have Immunomodulatory activities like that of apigenin, oligomeric proanthocyanidin, isoflavonoids, flavones and anthocyanidin Also, biflavonoids from Torreya nucifera were testified to inhibit SARS-CoV/3CL (pro) [62]. Moreover, the antiviral activity of terpeonids against (SARS-CoV) was also reported. Deng et al reported the antiviral activity of chalcones [63]. A bioflavonoid myricetin has been reported to possesss excellent antiviral activity against hepatitis B virus, influenza virus, and SARSCoV [64]. The mechanisum of antiviral activity of myricetin against SARSCoV is it inhibits SARSCoV protease [62]. The polyphenols epicatechin, epigallocatechin, and epigallocatechin gallate, delphinidin, cyanidin, were found to be effective aganist West Nile Virus (WNV), hepatitis C &B virus, herpes simplex virus, influenza A virus, dengue virus, adenovirus, reovirus, and, ZIKV [65]. The catechin compound was found to inhibit viral entry and attachment [62]. Other polyphenols such as honokiol, baicalein and naringin have also been described to have antiviral activity [66]. Also, polyphenolic compounds from plant extracts have been known to possess wide spectrum antiviral activities [65].

Mechanism of action of natural antiviral on human health

Natural products with good antiviral and nutraceutical properties can provide relief from viral infections. They can decline the viral infections like Covid-19 as they have been proven effective against two earlier coronavirus outbreaks of SARS-CoV and MERS-CoV which suggests its potential use in treatment for on-going epidemic of COVID-19. Natural antivirals work by stimulating the immune system which plays a key role to suppress viruses. The immune responses are mediated by various immune cells having the capability to recognize foreign particles and provide protection against invading viruses bacteria, fungi [67]. The cells of the innate immunity system include monocytes, macrophages, natural killer (NK) cells, B cells, T cells and granulocytes. Upon entering the host body, Dendritic cells/ Macrophages recognise the invasion of virus. These cells possess specific Toll like receptors TLRs for recognising the foreign particle in body. Some toll like receptors like TLR3 TLR7, TL9 are able to recognise the viral dsRNA and dsDNA. Upon recognition these receptors go to nearby lymph nodes to alarm the T helper cell. T helper cell inturn binds to a B cell and activates the B cell. Some B cells turn into plasma cells while some of the B cells become B memory cells which help in combating second exposure. Plasma cells are released in the blood. These cells secrete antibodies against the viral infection which binds to antigens to fight the invading virus and prevent the entry of virus [68]. Also, many of the macrophages and dendritic cells express Fc receptor that engulfs the virus and presents the pathogen's antigens by a process called Phagocytosis. Besides, T cells, mainly CD4+ and CD8+cells also play an active role as antivirals against the virus by inducing their effector function to stop further invasion and decrease the risk of inflammation [69]. However, Chen et al reported an essential role of both T cells, CD8+ and CD4+ T cells in SARS-CoV clearance [70]. Janice et al reported that development of SARS-CoV specific neutralizing antibodies requires CD4+ T helper cells [71] (Table 1).

S.no	Natural Antiviral Food Sources	Antiviral Bioactive Agent	Reported Mechanism of Action	Effective Against Virus
1.	Garlic	Allicin Selenium	Inhibits virus multiplication	Influenza [26] Coxsackie [28]
2.	Onion	Quercetin Kaempferol Myricetin	Inhibits viral entry and translation	Ebola virus [22] Hepatitis C [24] Polio virus [23] Coronavirus [26]
3.	Mushroom	Polyphenol extract Peptides Glycosides Lignin Terpinoids	Inhibits entry, reverse transcriptase and spread ability of virus	H1N1 [35] H5N1 [37] HIV [35] HSV [34]
4.	Blueberries	Resveratrol	Inhibits replication, protein synthesis, gene expression, and nucleic acid synthesis of virus	HSV [41] Influenza [50] Rhinovirus [43] MERS-CoV [44] CA [40]
5.	Cranberries	Resveratrol	Inhibits viral attachment	Reovirus [45] Enterovirus [46] Influenza [47]
6.	Grapes	Resveratrol Catechin Epicatechin Epicatechin gallate	Inhibits viral binding	HIV [51] Herpes [51] Hepatitis [51]
7.	Cereals and yeast	Beta-glucan	Boosts immune system	Influenza [58]

Table 1: Natural source of antiviral derived from plants.

Note: H1N1-Influenza A virus, H5N1-avian influenza, HIV-Human immunodeficiency virus, HSV-Herpes Simplex Virus, MERS-CoV-Middle East respiratory syndrome coronavirus, CA-coxsackievirus.

Conclusion and Future Perspective

This review, discussed the possible interventions for COVID-19 contagion according to earlier treatments used for different viruses including SARS, MERS. Several clinical trials and experimental studies suggested that bioactive compounds from plants possess antiviral activity against different RNA viruses. These bioactive compounds exhibit therapeutic potential for prevention of various viral infections by regulating the host immune response against RNA viral infection and possibly covid-19 as currently no potential vaccines and medicines are available to combat Covid-19. Natural antiviral product have been used for two previous coronavirus outbreaks of SARS-CoV and MERS-CoV which suggests its potential to provide treatment for the on-going epidemic of COVID-19.Therefore, nutraceutical property of bioactive compounds from plant sources can be used as effective method for cure and new antivirals drug designs against COVID-19. Moreover, in-vitro and in-vivo studies are compulsory to change these natural inhibitors into clinical drugs. Furthermore, these natural antivirals may contribute for discovering novel natural anti-COVID-19 in the near future.

Acknowledgement

Authors are thankful to the Department of Science & Technology, GOI (INSPIRE fellowship scheme) for financial support.

Conflicts of Interest

The authors declare that there are no conflicts of interest.
Written informed consent was obtained from all study participants.

Ethical Guidelines

Ethics approval was not required for this research.

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