Antiviral Activity of Natural Products and Herbal Extracts

Doğal Ürünlerin ve Bitkisel Özlerin Antiviral Etkinliği

Bilge Şener

Gazi University, Faculty of Pharmacy, Department of Pharmacognosy, Ankara, Turkey

ABSTRACT

Plants have been used as medicine by mankind to treat health-threatening diseases and still popular to develop new drug candidates. Plants have a combination of phytochemicals also known as secondary metabolites that are naturally occurred gives different therapeutic benefits. Natural products have been recognized as an important role in the drug discovery process moreover the other sources. Presently, over 100 natural product-derived pharmaceuticals are being used in modern medicine. Some of them play as important tools in the immune system exhibiting antiviral potentials. This review presents a survey of natural products and herbal extracts that have indicated broad antiviral activity.

Key Words: Antiviral activity, medicinal plants, extracts, phytochemicals.

Received: 07.03.2020 **Accepted:** 07.29.2020

ÖZET

İnsanoğlu tarafından sağlığı tehdit eden hastalıkların tedavisinde ilaç olarak kullanılmış olan bitkiler günümüzde de yeni ilaç adaylarının geliştirilmesinde önemlidir. Doğal olarak oluşan sekonder metabolitler ismiyle bilinen fitokimyasalları içeren bitkiler farklı tedavi edici özelliklere sahiptir. Diğer kaynaklar yanında doğal maddeler ilaç keşiflerinde önemli bir yere sahiptir. Bugün 100 den fazla doğal ürünlerden elde edilen farmasötikler modern tıpta kullanılmaktadır. Bazıları antiviral etkileri nedeniyle bağışıklık sisteminde önemlidir. Geniş spektrumlu antiviral aktiviteye sahip doğal maddeler ve bitki ekstreleri bu derlemede bir araya getirilmiştir.

Anahtar Sözcükler: Antiviral aktivite, tıbbi bitkiler, ekstreler, fitokimyaallar.

Geliş Tarihi: 03.07.2020 **Kabul Tarihi: 29**.07.2020

ORCID ID: B.S. 0000-0002-7672-3489

Address for Correspondence / Yazışma Adresi: Bilge Şener, PhD Gazi Üniversitesi Eczacılık Fakültesi Farmakognozi Anabilim Dalı, Etiler 06330 Ankara, Turkey E-mail: bigesener11@gmail.com

doi:http://dx.doi.org/10.12996/gmj.2020.116

INTRODUCTION

It is worth saying that the number of drugs derived from medicinal plants that are recently introduced into clinical use is increasing. Additionally, several standardized herbal extracts were approved by the authorities to be used in therapy. These traditional medicines can serve as the source of potential new drugs and initial research focuses on the isolation of bioactive lead compounds from natural sources for their ability to provide health benefits. Therefore, the discovery and development of new antiviral drugs from medicinal plant extracts and their bioactive compounds are realized to reduce toxicity in drug application and to minimize side effects when compared with current synthetic drugs. Bioassay-guided fractionation and isolation of secondary metabolites from medicinal plants according to their preliminary high throughput screenings provide mechanistic basis to the novel molecules.

Several plant species have shown remarkable antiviral activity, especially *Artemisia annua, Garcinia edulis, Justicia gendarussa, Phyllanthus pulcher, Rhus chinensis, Smilax corbularia, Terminalia paniculata* and *Tuberaria lignosa*. These plant species are worthy of further study for the development of new anti-Human Immunodeficiency Virus (anti-HIV) chemotherapeutic options. The effective antiviral chemotherapy has been mainly focused on the development of chemicals targeting viral proteins, which are essential for virus replication. In particular, *in vivo* testing and ultimately, human clinical trials need to be carried out on key lead plants and their phytochemicals. The anti-HIV activity of extracts from some medicinal plants has been given in our previous article (1). Among them *Calendula officinalis, Justicia gendarussa* and *Sceletium tortuosum* might be useful potential sources for new lead compounds in the development of new candidates with anti-HIV properties of therapeutic interest (2). These studies are considered to be one of the most important approaches toward effective therapy for AIDS. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new strain that was discovered in 2019 and has not been previously identified in humans. Antiviral activity of some medicinal plants such as *Artemisia annua, Lycoris radiate, Pyrrosia lingua* and *Lindera aggregata* were reported (3). Based on promoting CD_4^+ cells, some Chinese traditional medicinal plants such as *Panax ginseng, Astragalus membranaceus, Lycium barbarum, Trichosanthis kirilowii,* and *Viola mandshurica* were tested in about 1000 patients within different studies (4). Compared with placebo, treatment with traditional medical plants showed positive effect, increasing CD_4^+ cells, but studies need to be improved. Some Chinese herbal preparation which consists of *Coptis chinensis, Jasminum officinale, Wolfiporia extensa, Sparganium stoloniferum, Polygonatum odoratum, Scrophularia buergeriana* was investigated during 24 weeks and observed to have increased plasma CD_4^+ cells count and also showed.

Besides, 16 ethanolic extracts of Turkish medicinal plants were evaluated for their antiviral activities against herpes simplex virus (HSV1) and Sindbis virus (SINV). Among the extracts of *Galanthus elwesii* and *Rheum ribes* showed the most potent anti-HSV activities. On the other hand, *Galanthus elwesii* and *Leucojum aestivum* were the most potent anti-SINV (5). The present review paper tries to describe broad spectrum of antiviral activities against several viruses such as HIV, Influenza, Herpes simplex virus (HSV), Dengue, Chikungunya, Zika, Hepatitis A (HSV), Hepatitis B (HSB), Hepatitis C (HCV), etc. provided from medicinal plants used in traditional or folk medicine.

Plant extracts and natural compounds

It is known that the plants have to defend themselves against bacteria, fungi and viruses, it is not surprising that many secondary metabolites exert antimicrobial and antiviral effects. The level of existing defence chemicals is increased after infection in particular, new compunds with antimicrobial, antiviral or herbivore-deterring activities are synthesized named as phytoalexins. They are mainly furanocoumarins, chalcones, stilbenes, isoflavons and volatile compounds (6**).** In recent years, the research for selective antiviral agents is principally focused on different viruses (HIV, influenza A, poliovirus type 1 etc.). On the other hand, the treatment of viral infections is often insufficient and new viral pathogenes (such as COVID-19, $G4H_1N_1$) are to be discovered. Therefore, it is necessary to discover new compounds with not only intracellular but also extracellular virucidal specifications. The determination of antiviral natural compounds is based on the reduction in virus yield, inhibition of plaque formation and other mechanisms. Some plant extracts were evaluated for their antiviral potential against DNA nad RNA viruses by using *in vitro* tests. These tests are mainly based on the inhibition of cytopathogenic activities, the reduction of inhibition of plaque formation and reduction in the virus yield and some other viral mechanisms in selected host cell cultures. Secondary metabolites occured in living organisms in a high structural diversity such as alkaloids, flavonoids, coumarins, lignans, phenols, quinones, terpenes, and saponins have antiviral activities by inhibiting different stages in the replication of various viruses. Their different antiviral mechanisms like virus adsorption, virus-cell fusion, reverse transcription, protease and integrase inhibition have been reported in recent studies. Among the secondary metabolites, essential oils interfere with the virus envelope or masking viral compounds which are necessary for adsorption or entry into host cells. One of them, manuka oil significantly is reduced plaque formation of HSV-1 of about 40 % (7). From the phenolic volatiles, eugenol was shown to be a very effective against HSV-1 and HSV-2 *in vitro* (8). According to the data obtained from the antiviral effect of essential oils is against enveloped DNA and RNA viruses (9). In considering alkaloids, 33 isoquinoline alkaloids isolated from *Fumaria* and *Corydalis* species were tested against *Herpes simplex virus* (HSV) and *Parainfluenza*-3 *virus* (PI-3). Among them, protopine, fumarophycine, (+)-bulbocapnine, and (+)-ophiocarpine could be considered as new alternatives for the treatment of PI-3 (10). Berberine and hydrastine obtained from *Fumaria* species have been found as potential alkaloids against Hepatitis B virus (HBV) is the causative agent of B-type hepatitis in humans (11). Some *beta*-carboline alkaloids including harman, harmalol and quinazoline-type alkaloids like vasicine and vasicinone have showed antiviral effect against influenza virus (12). Moreover, the traditional medicines can serve as the source of potential new drug candidates and initial research focuses on the isolation of bioactive lead compounds.

Azadirachta indica A. Juss

The methanolic extract of leaves of neem (*Azadirachta indica* A. Juss) inhibited plaque formation in 6 antigenic types of Coxsackie virus B at a concentration of 1000 micrograms/mL at 96 h as a virucidal agent. The flavonoids and triterpenoids glycosides in the extract exhibited antiviral activity as *in vitro* for coxsackie B group of viruses (13).

Cistus incanus L.

The methanolic extract of *Cistus incanus* L. inhibited human immunodeficiency virus (HIV) infections *in vitro*. Antiviral activity was highly selective for virus particles, preventing primary attachment of the virus to the cell surface and viral envelope proteins from binding to heparin. Bioassay-guided fractionation indicated that the extract contained numerous antiviral compounds and therefore has favorably low propensity to induce virus resistance. The extract was also able inhibit infection by the virus particles pseudo typed with Ebola and Marburg virus envelope proteins, indicating that antiviral activity of the methanolic extract extends to emerging viral pathogens. Therefore, the extract was shown potent and broad *in vitro* antiviral activity against viruses that cause life-threatening diseases in humans and was promising sources of agents that target virus particles (14).

Coriandrum sativum L.

Coriandrum sativum L. is an ingredient in medicinal formulations due to specific properties which beneficial in the management of viral induced infective diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Human Immunodeficiency Virus (HIV), Hepatitis A virus (HAV) and Dengue fevers (DENG). Other than the management of clinical features in viral infections, coriander is beneficial as an immune enhancer to prevent from infective diseases. Owing to the strong evidence obtained through the present study, *Coriandrum sativum* might be a valuable source to lead for a novel antiviral compound which can be useful in the continuing fight against coronavirus (3).

Eugenia singampattiana Bedd.

The methanol and water extracts of the leaves of *Eugenia singampattiana* Bedd. exhibited the antiviral activity against Porcine Reproductive and Respiratory Syndrome Virus (PRRSV). The anti-PRRSV activity of the extracts was evaluated with different concentrations (25 μg to 1000 μg) for both the extracts. The Marc-145 cells served as control and the Marc-145 cells infected with PRRSV were used. The water extract was shown to be an effective inhibitor of PRRSV at above 100 μg and about 75 % of inhibition observed at 50 μg.

However, the methanol extract showed effective inhibition at above 10 μg. The Marc-145 cells show morphology changes, when it is treated above 500 μg.

Therefore, the above results revealed that 75 μg to 100 μg is an efficient activity of the water extract and 25 μg is an efficient activity of the methanol extract. The antiviral activity of both extracts against PRRSV was found as significant and reproducible (15).

Glycyrrhiza glabra L.

The ethanolic extract of *Glycyrrhiza glabra* L. and its active compound named as glycyrrhizin showed antiviral activity toward a number of viruses including hepatitis A,B, C, influenza A virus, varicella zoster, HIV, herpes simplex type-1, SARS related coronavirus and cytomegalo virus (16). Mechanisms for antiviral activity of *Glycyrrhiza* species include reduced transport to the membrane and sialylation of hepatitis B virus surface antigen, reduction of membrane fluidity leading to inhibition of fusion of the viral membrane of HIV-1 with the cell, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and reduction of viral latency. Therefore, licorice could be a potential source in the prevention and treatment of influenza A virus pneumonia and as an adjuvant treatment in patients infected with HIV resistant to antiretroviral drugs (16).

Gyrinops versteegii (Gilg.) Domke

The ethanolic extract of *Gyrinops versteegii* (Gilg.) Domke displayed better potential for antiviral activity against Dengue virus serotype 3 (DENV-3) on Reverse Transcription-Polymerase Chain Reaction (PCR) with up to 99.59 % virus inhibition compared with positive control of viral infection in distributions above 125 µg/mL. Groups of secondary metabolites found in are flavonoids, terpenoids, and phenolic compounds as responsible antiviral effect (17).

Humulus lupulus L.

It was reported that xanthohumol, a prenylchalcone flavonoid isolated from the ethanolic extract of the hop cones of *Humulus lupulus* L. was effective against HIV-1 and might serve as an interesting lead compound as a novel chemotherapeutic agent for HIV-1 infection (18,19).

Hypericum perforatum L.

The antiviral effect of *Hypericum perforatum* L. extract on influenza A virus (IAV) (H_1N_1) *in vitro* and *in vivo* was reported by Pu et al. (20). The extract of *H. perforatum* and ribavirin (reference drug) have shown similar efficacy against IAV infections, and the plant extract was considered to be less toxic. Besides, hypericin found in *H. perforatum* known as Saint John's Wort was provoked by the discovery that it possesses extremely high toxicity towards certain viruses notably the class of enveloped viruses that includes human immunodeficiency virus (HIV) (21).

Hyssopus officinalis L.

The methanolic extract from the leaves of *Hyssopus officinalis* L. was evaluated for *in vitro* and *in vivo* antiviral activity against herpes simplex virus (HSV) and shown that both the wild and resistant strains of HSV were sensitive to the extract (22).

Nigella sativa L.

The ethanolic extract of the seeds of *Nigella sativa* L. and its compound thymoquinone have been reported to possess antiviral activity against a number of human, animals, birds and plant cytopathogenic viruses including murine cytomegalovirus (MCMV), avian influenza (AIV) subtype H_9N_2 (23), Chistosoma Mansoni Infection (CMI) alongwith Broad bean mosaic virus (BBMV), Human immunodeficiency virus (HIV), virus, Hepatitis C virus (HCV), Zucchini Yellow Mosaic virus (ZYMV), Papaya Ring Spot virus (PRSV) and Newcastle Disease virus (NDV) (24).

Opuntia streptacantha Lem.

An extract of the cactus plant *Opuntia streptacantha* inhibited of both DNA and RNA virus replication, for example, herpes simplex, equine herpes, pseudorabies, influenza, respiratory syncytial and human immunodeficiency viruses, with normal protein synthesis in uninfected cells at extract concentrations which were 15-fold in excess of 50 % viral inhibitory concentrations. The extract was non-toxic on oral administration to mice, horses and human patients; the non-toxicity of intravenous administration of 70 mg to a mouse representing at least fifty tissue culture 50 % viral inhibitory dosages encourages clinical trial of this extract in virus disease of human (25).

The responsible compound from the activity of the extract was determined to be a protein derivative coded as GFAHP directly inactivates HSV-1 while simultaneously inhibiting HSV-1 penetration into vero cells. Gel electrophoresis showed that GFAHP had a molecular weight of 29.5 kDa. The N-terminal sequence of GFAHP consisted of an 11 amino acid peptide, NH_2-REQDNAPCGLN-COOH that did not match any known amino acid sequences, indicating that GFAHP is likely to be a novel antivirus protein (25). An antiviral protein, designated Opuntin B, was purified from the leaves of *Opuntia ficus-indica* (L.) Miller. Assessment of enzymatic activity of the purified protein showed that it degrades total plant genomic RNA, while causing electrophoretic mobility shifting of Cucumber mosaic virus (CMV) RNAs. However, heat-denatured viral RNA became sensitive to degradation upon treatment with antiviral protein. Opuntin B had no DNase activity on native (26).

Pelargonium sidoides L.

Pelargonium sidoides L. has been used by local communities for centuries as herbal treatments for respiratory infections. The ethanolic extract of the radix of *P. sidoides was* reduced rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells (27).

Sambucus nigra L.

The fruit extract of *Sambucus nigra* L. has been shown *in vitro* to significantly inhibit HSV-1 even in strains resistant to multiple traditional antiviral medications. It has also been determined to have a significant antiviral effect against HIV *in vitro*. *Sambucus nigra* is promising as an inexpensive and low-risk treatment for influenza and other viral and non-viral pathogens and potentially as a preventative for acute viral infections as well. However, further research on the potential preventative antiviral effects of *Sambucus nigra* is needed to verify the results of these promising initial studies in humans and to determine the efficacy of *S. nigra* as a broad-spectrum antiviral, as most studies focus on one or two specific viral pathogens (28).

Zingiber officinale L.

The lyophilized juice extract from *Zingiber officinale* L. at different concentrations (5, 25, 50, 75, 100, 150 and 200 µg/ml) was tested *in vitro* as antiviral effect on hepatitis C virus (HCV) of using the hepatocellular carcinoma HepG2 cell line infected with HCV and the inhibitory dose was found to be effective at 100 µg/mL (29). This extract has also antiviral activity against Human Respiratory Syncytial Virus (HRSV)-induced plaque formation on the epithelium of the airways through blocking viral attachment and internalization (30).

CONCLUSION

Recommended future directives incurring the design and conduct of comprehensive trials are pointed out to validate the usefulness of these active plant species and bioactive secondary metabolites either alone or in combination with existing conventional therapies. The antiviral agents from plants have interfered with many viral targets, ranging from adsorption of the virus to the host cell via the inhibition of virus-specific enzymes (*e.g.* reverse transcriptase, protease) to release virus from the cells. It is generally accepted that bioactive natural compounds are useful leads to synthesize new and more active antiviral constituents. Plant-derived natural products continue to serve as a reservoir for the discovery of new medicines, including antiviral agents. Therefore, herbal products with confirmed clinical safety features are attractive starting material for the identification of new antiviral activities. In this review, some secondary metabolites and plant extracts with antiviral properties and future key for the development of novel drugs from those identified compounds for the eradication of viral diseases were presented.

Abbreviations
Avian Influenza Virus (AIV) subtype H_9N_2
Broad Bean Mosaic Virus (BBMV)
Chikungunya Virus (CHICV)
Chistosoma Mansoni Infection (CMI)
Cucumber Mosaic Virus (CMV)
Dengue fevers (DENG)
Dengue Virus Serotype 3 (DENV-3)
Hepatitis A Virus (HAV)
Hepatitis B Virus (HBV)
Hepatitis C Virus (HCV)
HepatoHerpes Simplex Virus (HSV)
Human Immunodeficiency Virus (HIV)
Influenza A Virus (IAV) (H_1N_1)
Middle East Respiratory Syndrome (MERS)
Murine Cytomegalovirus (MCMV)
Newcastle Disease Virus (NDV)
Papaya Ring Spot Virus (PRSV)
Parainfluenza-3 *virus* (PI-3)
Polymerase Chain Reaction (PCR)
Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)
Severe Acute Respiratory Syndrome (SARS)
Sindbis Virus (SINV)
Zika (ZIKV)
Zucchini Yellow Mosaic Virus (ZYMV)

Conflict of interest
No conflict of interest was declared by the author.

REFERENCES

1. Salehi B, Kumar NVA, Sener B, Sharifi-Rad M, Kılıc M, Mahady GB, et al. Medicinal plants used in the treatment of Human Immunodeficiency Virus. Int J Mol Sci. 2018; 19: 1459-519.
2. Kaur R, Sharma P, Gupta GK, Ntie-Kang F, Kumar D, Structure-activity-relationship and mechanistic insights for anti-HIV natural products. Molecules, 2020.doi:10.3390/molecules25092070.
3. Ahmad A, Rehman MU, Alkharfy KM. An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections. Eur Rev Med Pharmacol Sci. 2020;24:4030-4.
4. Zhang L, Yue S-T, Xue Y-X, Attele, AS, Yuan C-S. Effects of Qian-Kun-Nin, a Chinese herbal medicine formulation, on HIV positive subjects: A pilot study. Am. J Chin Med. 2000;28:305-12.
5. Hudson JB, Lee MK, Sener B, Erdemoglu N. Antiviral activities in extracts of Turkish medicinal plants. Pharm Biol. 2000;38:171-5.
6. Kapoor R, Sharma B, Kanwar SS. Antiviral phytochemicals:An overview. Biochem Physiol. 2017;6.
7. Reichling J, Koch C, Stahl-Biskup E, Sojka C, Schnitzler P. Virucidal activity of a β-triketone-rich essential oil of *Leptospermum scoparium* (manuka oil) against HSV-1 and HSV-2 in cell culture. Planta Med. 2005;71:1123-7.
8. Benencia F, Courrges MC. *In vitro* and *in vivo* activity of eugenol on human herpes virus. Phytother Res. 2000;14:495-500.
9. Bakkali F, Averbeck S, Averbeck D, Idaomar M. Biological effects of essential oils. Food and Chem Tox. 2008;46:446-75.
10. Orhan I, Ozcelik B, Karaoglu T, Sener B. Antiviral and antimicrobial profiles of selected isoquinoline alkaloids from *Fumaria* and *Corydalis* species. Zeits Naturforsch C, 2007;62:19-26.
11. Aljofan M, Netter H, Aljarbou AN, HAdda TB, ERdogan Orhan I, Sener B. et al. Screening of anti-hepatitis B antiviral activity of the isoquinoline alkaloids of plant origin. Arch Virol. 2014;159:1119-28.
12. Mohammad-Taghi M, Moradi M-T, Karimi A, Kopaei M, Fotouhi F, In vitro antiviral effects of Peganum harmala seed extract and its total alkaloids against influenza virus. Micropath. 2017;110:42-9.
13. Anyaehie UB. Medicinal properties of fractionated acetaone/water nee (Azadirachta indica) leaf extract from Nigeria. Niger J Physiol Sci. 2009;24:157-9.
14. Rebensburg S, Helfer M, Schneider M, Koppensteiner H, Eberle J, Schindler M, et al. Potent in Vitro antiviral activity of Cistus incanus extract against HIV and filoviruses targets viral envelope proteins. Sci Rep. 2016; 2.
15. John KMM, Ayyanar M, Jeeva S, Suresh M, Enkhtaivan G, Kim DH. Metabolic variations, antioxidant potential, and antiviral activity of different extracts of Eugenia singampattiana (an Endangered medicinal plant used by Kani Tribals, Tamil Nadu, India) leaf. BioMed Res Int. 2014; Article ID 726145,
16. Asl NN, Hosseinzadeh H. Review of antiviral effects of Glycyrrhiza glabra L. and its active component, glycyrrhizin. J Med Plants 2007;6:1-12.
17. Masita R, Nuringtyas TR, Wijayanti N, Hidayati L. Antiviral activity of Gyrinops versteegii (Gilg.) Domke leaves ethanolic extract against Dengue Serotype 3 Virus in vitro. AIP Conf Proceed. 2020; 2231, 040077.
18. Wanga Q, Dingb Z-H, Liub J-K, Zhenga Y-T. Xanthohumol, a novel anti-HIV-1 agent purified from Hops Humulus lupulus. Antiviral Res. 2004;64:189-94.
19. Buckwold VE, Wilson RJH, Nalca A., Beer BB, Voss TG, Turpin JA, et.al. Antiviral activity of hop constituents against a series of DNA and RNA viruses. Antiviral Res Act. 2004;61:57-62.
20. Pu X-P, Liang J-P, Wang, X-H, Xu, T, Hua, L-Y, Shang R-F, et al. Anti-influenza A virus effect of Hypericum perforatum L. extract. Virologica Sinica 2009;24:19.
21. Miskovsky P, Hypericin - A new antiviral and antitumor photosensitizer: Mechanism of action and interaction with biological macromolecules. Current Drug Targ. 2002;3:55- 84
22. Behbahami M. Anti-viral activity of the methanolic leaf extract of an Iranian medicinal plant Hyssopus officinalis against herpes simplex virus. J Med Plants Res.2009;3: 1118-25.
23. Umar S, Munir MT, Sabir Subhan Azam T, Nisa Q, Irfan Khan MI, et al. Protective and antiviral activities of Nigella sativa against avian influenza (H_9N_2) in turkeys. J Saudi Soc Agr Sci. 2016; doi: http://dx.doi.org/10.1016/j.jssas.2016.09.004
24. Mohamed S, Hossain MS, Protective effect of black seed oil from Nigella sativa against murine cytomegalovirus infection. Int. J. Immunopharmacol. 2000;22:729-40.
25. Ahmad A, Davies J, Randall S, Skinner GR. Antiviral properties of extract of Opuntia streptacantha. Antiviral Res Act 1996;30:75-85
26. Rasoulpour R, Izadpanah K, Afsharifar A. Opuntin B, the antiviral protein isolated from prickly pear (*Opuntia ficus-indica* (L.) Miller) cladode exhibits ribonuclease activity. Microbial Pathogen. 2020;140.
27. Roth M, Fang, L, Stolz D, Tamm M. Pelargonium sidoides radix extract EPs 7630 reduces rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells. PLoS One 2019;14: e0210702.
28. Porter RS, Bode RF. A Review of the antiviral properties of black elder (Sambucus nigra L.) products. Phytother Res. 2017; doi: 10.1002/ptr.5782.
29. El-Wahab AA, El-Adawi H, El-Demellawy M, In vitro study of the antiviral activity of Zingiber officinale. Planta Med. 2009;75:PF7.
30. Chang JS, Wang KC, Yeh CF, Shieh DE, Chiang LC, Fresh ginger (Zingiber officinale) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. J Ethnopharmacol. 2013;145:146-51.