Antiviral Potential of Melissa officinalis L.: A Literature Review

Nutrition and Metabolic Insights
Volume 16: 1–13
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11786388221146683

Amirhossein Behzadi[1,2*], Sadegh imani[3*], Niloofar Deravi[4*], Zahra Mohammad Taheri[5], fatemeh mohammadian[6], zahra moraveji[6], Sepideh Shavysi[4], Motahareh Mostafaloo[7], Fateme Soleimani Hadidi[4], Sepehr Nanbakhsh[1,2], Sepehr Olangian-Tehrani[1,2], Mohammad Hesam Marabi[8], Parisa behshood[9], Mohadeseh Poudineh[10], Ali Kheirandish[11], Kimia Keylani[12] and Pooya Behfarnia[13]

[1]School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [2]Avicennet, Tehran, Iran. [3]Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran. [4]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [5]Hamedan University of Medical Sciences and Health Services, Hamedan, Iran. [6]Student Research Committee, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [7]School of Nursing and Midwifery, Iran University of Medical Science, Tehran, Iran. [8]Student Research Committee, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran. [9]Department of Microbiology, Young Researchers and Elite Club, Shahrekord Branch, Islamic Azad University, Isfahan, Iran. [10]School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. [11]Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran. [12]School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [13]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

ABSTRACT: The use of synthetic drugs has increased in recent years; however, herbal medicine is yet more trusted among a huge population worldwide; This could be due to minimal side effects, affordable prices, and traditional beliefs. Lemongrass (*Melissa officinalis*) has been widely used for reducing stress and anxiety, increasing appetite and sleep, reducing pain, healing wounds, and treating poisonous insect bites and bee stings for a long time. Today, research has shown that this plant can also fight viruses including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Herpes Simplex Virus (HSV), and Human Immunodeficiency Virus (HIV) through various mechanisms such as inhibiting HSV-1 from binding to host cell, inhibiting HSV-1 replication during the post-adsorption or inhibiting main protease and spike protein of SARS-CoV-2, furthermore, be effective in treating related diseases. This Review investigated the antiviral properties of *Melissa officinalis* and its effect on viral diseases. More in vitro and in vivo studies are needed to determine *Melissa officinaliss* underlying mechanism, and more randomized controlled trials should be done to identify its effect in humans. Also, due to the usefulness and lack of side effects, it can be used more as a complementary medicine.

KEYWORDS: *Melissa officinalis*, antiviral, herbal medicine, virus, natural medicine

RECEIVED: April 13, 2022. **ACCEPTED:** December 5, 2022.

TYPE: Mini Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHORS: Mohadeseh Poudineh, School of Medicine, Zanjan University of Medical Sciences, Iran-Zanjan-Shahrake Karmandan-12th Street, Zanjan, 4513956111, Iran. Email: mo.Poudineh@gmail.com

Pooya Behfarnia, School of Medicine, Isfahan University of Medical Sciences, Hezar Jerib Avenue, Isfahan, 19839-6311, Iran. E-mail: pooyabehfarnia@gmail.com

Introduction

A broad range of human sicknesses and health complications, from self-limiting to mortal diseases, are caused by viral infections.[1-3] Almost 20% of the globally reported deaths are caused by infectious diseases in which viral diseases play a key role.[1] It has been estimated that 37 million people are infected with HIV every year. Also, 257 million cases of hepatitis B virus (HBV), 70 million cases of hepatitis C virus (HCV), and about 3 to 5 million cases of flu are annually reported.[1] A group of viruses called "tumor viruses" (including viruses such as Epstein-Barr virus (EBV), Human Papilloma Virus (HPV), HBV, and HCV are regarded as risk factors in 12.1% of human cancer cases.[2,3] Mortalities caused by viral diseases have been greatly increased recently in the pandemic of Coronavirus Disease 2019 (COVID-19), which has lead to millions of deaths across the world.[4,5]

There are 13 functional groups of antiviral medicine consisting of 90 antiviral drugs (including ribavirin, lamivudine, oseltamivir, interferon, and several other antiviral drugs), which have been confirmed for treating 9 human viral infections, including HIV, HBV, HCV, HSV, Influenza virus, Cytomegalovirus, varicella-zoster, respiratory syncytial virus,

*The authors contributed equally to the article and shared first co-authorship.

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

and human papillomavirus.[6] Many articles have emphasized the side effects and harmful impacts of these antiviral drugs on human body systems and organs, including the endocrine system (thyroid disorders, osteoporosis, osteopenia, loss of libido, diabetes, metabolic syndrome, decrease in bone mineral density, and several other endocrine disorders),[7] as well as central nervous system (irritability, psychosis, mania, hallucinations, confusions, acute psychosis, perioral paresthesia, anxiety, depressed mood, insomnia, and many other psychiatric problems),[8] and kidneys.[9]

Several side effects of antiviral drugs and enhanced resistance of viruses to these drugs have led scientists to investigate alternative treatments such as herbal medicines with antiviral effects, which are safer, less expensive, and easily available.[7-11] *Melissa officinalis* is one of the herbal medicines used for treating several disorders such as gastrointestinal disorders. it is also utilized for its carminative, antispasmodic, sedative, analgesic, and tonic effects alongside its antioxidant and antiviral effects.[12-17] Moreover, many articles emphasized the antiviral effect of *Melissa officinalis* against several viruses (such as HSV-1,[18] CPV,[19] HBV,[11,20,21] HCV[11,20,21]) and confirmed its effectiveness as an alternative therapy against several viral infections.[11,18-21] In this review, we tried to summarize the findings of studies on the antiviral effects of *Melissa officinalis* against different types of viruses.

Lemon balm (Melissa officinalis) is one of the traditional herbal medicines belonging to the Lamiaceae family. This herbal medicinal plant grows in North America, Europe, and Asia. Its use as a medicinal plant originated from Mediterranean countries. The lemon balm has been used for several purposes, such as medicine. The extracts and Essential Oil (EO) of the lemon balm plant have some pharmacological effects, including antimicrobial, anticancer, antibacterial, antioxidant, anti-inflammatory, antispasmodic, and antiviral properties. Some studies have demonstrated the effectiveness of lemon balm against different diseases such as HIV-1, cancer, and Alzheimer's. Lemon balm is a rich source of phenolic compounds such as thymol and carvacrol, which are the potential reason for the antibacterial and antioxidant activity of the lemon balm plant. The antimicrobial characteristics of lemon balm have been used against Gram-negative bacteria, including Escherichia coli (E. coli), Salmonella typhi, Pseudomonas aeruginosa, Proteus, Klebsiella and Gram-positive bacteria, including Staphylococcus aureus (*S. aureus*), *Sarcina lutea*, beta-hemolytic Streptococcus, and *Bacillus cereus.* The antimicrobial activities of lemon balm are mainly explained through the C15 and C10 terpenes with phenolic hydroxyl groups and aromatic rings, as well as other active terpenes, such as esters, aldehydes, and alcohols.[25-27]

Moreover, these components have also demonstrated high antioxidant activity in lemon balm. Some studies evaluated the free radical scavenging ability of lemon balm together with positive results on lipid peroxidation. Other studies have revealed the antiviral activity of lemon balm's essential oil.[22] Today, advances in nanofiber technology make it possible to make nanofibers from a wide range of materials, including natural and synthetic polymer ceramics, metals, and organic / inorganic composite systems. For example, electro-spun nanoscale fibers were fabricated by using various polymers together with Titanium dioxide (TiO2) composites for wound dressing and tissue engineering. In-vivo studies of antibiotic-loaded nano-fibrous matrices presented augmented wound healing with negligible signs of inflammation, regeneration of the lost epidermal layers and hair follicles, and neovascularization. Electro-spun fibers are competent biomedical candidates, particularly for drug delivery purposes. Electro-spinning is usually effortlessly tuned and employed on a commercial scale to fabricate scaffolds and wound dressings of clinical purposes. This technology has been found promising in drug delivery and regenerative medicine. While antibiotic drugs and inorganic antimicrobial agents are commonly used for controlling infections, they show more acute side effects like cytotoxicity. Due to the toxicity and harmful effects of the previous antibiotic medicines, researchers have been trying to find new antimicrobial agents instead of the previous ones. On the other hand, herbal medicine features antimicrobial and antioxidant activities at low price. Herbal medicine can show positive effects on wound healing.[23]

Electro-spun nanofibers are one of the most effective wound dressing products because they have morphological similarities to Extracellular Matrix of the skin (skin ECM), such as a large specific surface area and a porous nature that promotes homeostasis, exudate absorption, gas permeability, cell adhesion, migration, and proliferation with the goal of improving healing process, among other things. Wound dressings made of nanofiber polymers with antibacterial effects and skin regeneration capabilities are good choices for preventing wound infection and speeding wound healing.[24] Figure 1 summarizes the medical applications of *Melissa officinalis*.

Since many chemical drugs have different side effects and are not 100 in 100 effective, new drugs and compounds that are less used need to be paid more attention to their properties in order to study their effectiveness in making better drugs and nature in this regard. It has always been helpful. It is good to look at more natural compounds in this area. One of the natural compounds used in various viral diseases is the melissa officinalis compound, we wanted to combine their properties for different diseases so that researchers could do more in the future.

So far, no review has been done in this field to examine all the properties of *Melissa officinalis* together, and the lack of review in this field was felt to conduct a general and comprehensive study, collect all studies, and discuss on the performance and efficiency of the combination.

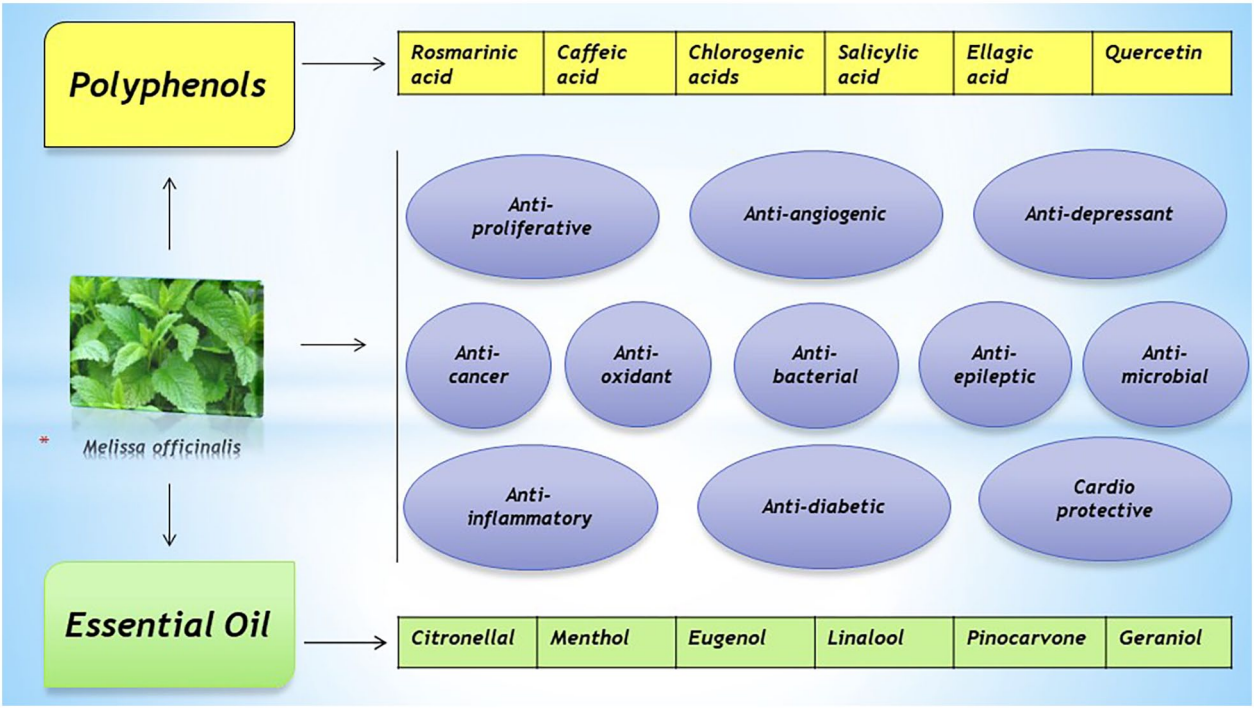


Figure 1. *Phytochemical components and Pharmacological effects of Melissa officinalis: Melissa officinalis* is a therapeutic plant rich in organic active components which contains predominantly essential oils (including Citronellal, Menthol, Eugenol, Linalool, Pinocarvone, and Geraniol) and Polyphenols (including Rosmarinic acid, Caffeic acid, Chlorogenic acid, Salicylic acid, Ellagic acid, and Quercetin) that determine several pharmacological effects with possible therapeutic uses (including anti-inflammatory effects, anti-diabetic effects, anti-proliferative effects, anti-angiogenic effects, anti-depressant effects, anti-cancer effects, anti-oxidant effects, anti-microbial effects, anti-epileptic effects, and cardio-protective effects).[25-27]

Ribonucleic Acid (RNA) Viruses

SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus whose nucleic acid is covered by a protein-capsid coating also it has enveloped and positive-sense. SARS-CoV-2 has a circle-like shape with a diameter and spikes that cause disease in their host by changing the spike protein, viruses reproduce using host cell facilities in order to contact the host cell, the viral surface glycoprotein binds to the Angiotensin-converting enzyme 2(ACE2) to the host cell; upon arrival, transcription, and translation occur from their genome.

SARS-CoV-2 is causing coronavirus disease (COVID-19),in the research the amount of 96/2% similarity is found with the bat corona virus(CoV RaTG13); SARS-CoV-2 is transmitted through sneezing and cough droplets and causes a pandemic (A pandemic means a global outbreak of a disease); viral droplets that are more than 5 micrometers are landing on different surfaces and depending on what surface of material is, the duration of stay on the virus is different for example, on the plastic 72 hours the virus survives.[28]

The COVID-19 disease attributed to SARS-CoV-2, a novel enveloped, single-stranded RNA beta coronavirus, has led to a global pandemic rising worldwide health concerns.[29-31] SARS-CoV-2 enters the host cells via identification by the spike glycoprotein on the exterior part of the virus envelope of angiotensin-converting enzyme 2 (ACE2) receptor, as formerly noticed for SARS-CoV. Other receptors may facilitate the entrance of SARS-CoV-2 into host cells, like CD147. After bonding, the human transmembrane protease serine 2 (TMPRSS2) splits and activates the spike protein as the outcome let SARS-CoV-2 go in to the cells by endocytosis or direct bonding of the viral envelope with the host membrane.[32] Research has shown that 3 phytoconstituents from *Melissa officinalis*, including, Luteolin-7-glucoside- 3′-glucuronide, Metric acid-A, and Quadranoside-III have revealed better fusion affinity and solidity with the targets of SARS-CoV-2 main protease and spike protein.[33,34]

Enterovirus-71

Human enterovirus (EV-A71 or EV71) from the Picornaviridae family, is a non-enveloped single-stranded RNA virus with a positive-sense genome that nearly has 7400 nucleotides and a capsid.[35,36] EV71 causes hand, foot, and mouth disease (HFMD) which occurs mostly in children and has been responsible for multiple outbreaks in recent decades. In most cases, HFMD is a mild disease but can lead to serious complications including brainstem encephalitis, meningitis, acute paralysis (AFP), and even death.[37-41] Even those who last from critical infection may have continuing motor and cognitive deficits.[42-44] No complete cure has been found yet. Therefore, it is so important to seek preventive and curative agents against EV71. In this regard, Choi et al[45] analyzed the antiviral effect

of *Melissa officinalis* on EV71 infection. This study showed that *Melissa officinalis* aqueous extract prevents loss of viability in EVA71-infected virus cells and *Melissa officinalis* has a high percentage of antiviral compounds. Subsequent studies by Chen et al[46] revealed that the antiviral effect of *Melissa officinalis* was due to the presence of rosmarinic acid in its methanolic extract.

Rosmarinic acid causes the following events:

1. Prevention of EV71 replication
2. Inhibition of EV71 infection in the attachment and post-attachment stages
3. EV71 suppression: suppresses helmet-dependent and IRES-dependent translation
4. Suppression of phosphorylation induced by EV71 p38 kinase
5. Suppression of EV71-induced phosphorylation of the epidermal growth factor 15 receptor substrate (EPS15).

Lin et al[47] and Hsieh et al[48] also proved the antiviral effect of rosmarinic acid against enterovirus 71 infection in vitro and in vivo, respectively. Accordingly, rosmarinic acid protected cells from the cytopathic of EV71 and protected infected cells from apoptosis and death.[47]

1. The second result shows that the time to add rosmarinic acid is very important Because cells infected with EV71 without rosmarinic acid had a very low shelf life at 24 to 48 hours, after 72 hours infection, all cells died.[47] Rosmarinic acid had the most inhibitory activity in the initial phases of viral infection.[47,48] The addition of rosmarinic acid before infection (−2 hour) had no significant inhibitory effect, whereas addition of RA during cellular infection (0 hour) and transfer (+2 hour) of it can effectively reduce viral VP1 mRNA[47]
2. Molecularly rosmarinic acid may target viral particles directly.[45]

HIV

HIV isolates are currently grouped into 2 types, HIV-type 1 (HIV-1), and HIV-type 2 (HIV-2). The main worldwide agent of Acquired Immune Deficiency Syndrome (AIDS) is HIV-1, while HIV-2 is restricted to some regions of Western and Central Africa. HIV is a genetically related member of the Lentivirus genus of the Retroviridae family. Infections with lentiviruses typically show a chronic course of the disease, with a long period of clinical latency, persistent viral replication and involvement of the central nervous system. The retrovirus genome is composed of 2 identical copies of single-stranded RNA molecules and is characterized by the presence of structural genes gag, pol, env. HIV-1 and HIV-2 viruses differ in the organization of their genome, although the basic structure (ie, the presence of the 3 structural Genes, gag, pol, and env) is the same one as for all retroviruses. In fact, in addition to having these 3 genes, the HIV-1 and HIV-2 genomes present a complex combination of other regulatory/accessory genes Transmission of HIV is highly dependent on the biological properties of the virus isolate, its concentration in the infected body fluid, and, finally, host susceptibility.

HIV is mainly integrated or replicated into the infected cells, which are the main vehicles of virus transmission. In fact, HIV-infected cells can transfer the virus to cells of the local immune system (eg, T-cells, macrophages, dendritic cells), as well as cells lining vaginal or anorectal mucose.[49]

The HIV, which leads to AIDS, is considered to attach to CD4+ (T4+) cells via the gp120 epithelial glycoprotein.[50,51] Plant lectin bind to glycoproteins through non-covalent interaction with particular hexose residues.[52] As a result, a lot of research has been done on the effects of plants on this disease In 1998, Yamasaki et al[53] showed notable inhibitory effects of *Melissa officinalis* against HIV-1 pathogenesis in MT-4 cells.

Geuenich et al[54] found 4 results:

1. The aqueous extract of lemon balm leaves (*Melissa officinalis*) With increasing virion density, shows strong anti-HIV-1 activity.
2. *Melissa officinalis* extract effectively inhibits HIV-1-sensitive strains.
3. Anti-HIV-1 activity in *Melissa officinalis* extract is rapid but has decreased against superficial virions.
4. Virion stability and levels associated with envelope and virion Processed chewing gum is not affected by lemon balm extract.

In 2008, Dubois et al[55] found antiviral activity without increased cytotoxicity. Rosmarinic acid found in *Melissa officinalis* under acidic situations, reacted with nitrate ions to form 6′-nitro- and *6′, 6″-dinitrorosmarinic acids*. Both compounds were active as HIV-1 integrase Inhibitors at the sub-micromolar level. Another function of these compounds is to inhibit viral replication in MT-4 cells.

Influenza

Influenza viruses contain a single-stranded negative-sense RNA genome that consists of 8 segments in influenza A and B viruses and 7 segments in influenza C viruses.[6] In all 3 species, the viral RNA (vRNA) genome segments are bound by a heterotrimeric RNA-dependent RNA polymerase, forming a viral ribonucleoprotein (vRNP) complex.[7,8] In the vRNP, the 5′ and 3′ termini of vRNA are bound to a polymerase heterotrimer, while the rest of the vRNA associates with oligomeric nucleoprotein (NP).

Influenza viruses belong to the family of Orthomyxoviridae and are the causative agents of influenza, a respiratory disease in humans. Influenza A and B viruses cause substantial morbidity and mortality in humans and a considerable financial burden worldwide, whereas influenza C viruses cause sporadic outbreaks of mild respiratory disease, mainly in children.[56]

Influenza, often known as "the flu," is an infectious sickness attributed to influenza viruses. Symptoms range from mild to severe and usually include fatigue, fever, headache, sore throat, pain in muscle, coughing, and runny nose. Mazurkova et al investigated the antiviral activities of Ethanol and Aqueous extracts derived from medicinal plants such as *Melissa officinalis* versus the A/Aichi/2/68 (H3N2) and A/chicken/Kurgan/05/2005 (H5N1) subtypes of influenza A virus (IAV) in Madin-Darby Canine Kidney (MDCK) cell cultures and found that Melissa had a significant effect on H5N1 and H3N2 subtypes. Jalali et al[57] investigated the antiviral activities of *Melissa officinalis* extracts against the influenza virus H1N1 in vitro. All concentrations used in *Melissa officinalis* extract were highly effective and decreased virus production in both experiments. Although hemagglutination tests showed a small titer, the amount of virus in both experiments decreased significantly. Pourghanbari et al[58] showed that *Melissa officinalis* L. essential oils (MOEO) might inhibit AVI (avian influenza A virus (H9N2)) replication through different phases of virus replication (P B 0.05). Also, the most antiviral activities of MOEO were observed when AIV had already been incubated with MOEO Cellular infection.

Deoxy Ribonucleic Acid (DNA) Viruses

HSV

Herpes simplex virus type 1 (HSV-1), and HSV-2 are highly prevalent human pathogens with worldwide prevalence levels of about 67% and 13%, respectively. HSV-1 and HSV-2 contain a large, linear double-stranded DNA genome protected by an icosahedral capsid surrounded by a proteinaceous layer termed the tegument and wrapped in an envelope containing viral glycoproteins Initial attachment to the plasma membrane occurs through the binding of glycoprotein B (gB) and gC to glycosaminoglycans (GAG).[12] HSV gG also binds to GAGs but its role in virus attachment has not been established.[13,14] Binding to GAGs is followed by interaction of gD with several entry receptors: herpesvirus entry mediator (HVEM), nectin-1 and -2 and 3-O-sulfated HS

Diseases caused by HSV include cold sores, genital herpes, Herpes stromal keratitis (HSK), eczema herpeticum, disseminated disease in the neonate, meningitis, and Herpes Simplex Encephalitis (HSE).[59]

HSV leads to long-lasting and continuous but self-limiting infections.[11] HSV causes hidden infections in the nervous system which may be reactivated over and over again and represented by initial symptoms including flu-like syndrome and malaise, fever, headache, diffuse myalgia, painful papules, and itching.[11,20] Several articles expressed the effectiveness of antiviral substances in lemon balm for treating the complications caused by HSVs.[11,18,20,21,60-62] Astani et al[11] discovered that lemon balm extract can inhibit the attachment and penetration of HSVs which are resistant to acyclovir.[11,20] A direct interaction between lemon balm extract and viral glycoproteins of HSV (such as glycoproteins gB and gD) was the main mechanism of inhibition of attachment and penetration of this virus into mucosal cells.[11,20] Rosmarinic acid in lemon balm extract seemed to be the only phenolic compound among the others that showed some anti-attachment activities versus HSV.[11,20] Vanti et al[18] loaded *Melissa officinalis* essential oil (MEO) inside glycosomes (MEO-GS) and tested its anti-viral activity against HSV-1. MEO-GS were very effective in inhibiting HSV-1 infection of mammalian cells and did not produce any cytotoxic effects. This study introduced MEO-GS as an effective instrument for treating HSV infections. Mazzanti et al[62] tested the anti-herpetic activities of a hydroalcoholic extract from lemon balm leaves versus HSV type 2 and compared its effectiveness with acyclovir. The hydroalcoholic extract of lemon balm seemed to show notable anti-herpetic activities in-vitro but was less effective than acyclovir. This study expressed that caffeic acid besides rosmarinic acid of lemon balm extracts showed some antioxidant activities against HSVs.[62] Schnitzler et al[60] examined the inhibitory activities of *Melissa officinalis* oil versus HSV type 1 and HSV type 2 on kidney cells of monkeys by a plaque reduction assay. 50% inhibitory concentration (IC50) of Melissa oil for HSV plaque formations has been found at high dilutions of 0.0004% and 0.00008% for HSVs type 1 and 2 and plaque formations were notably reduced by 98.8% for HSV type 1 and 97.2% for HSV type 2 at non-toxic concentration and last higher concentrations of the oil almost destroyed HSV infectivity completely. This study also suggested that lemon balm oil acted on HSV before penetration into the host cells. Allahverdiyev et al[21] examined the effectiveness of lemon balm volatile oil components versus HSV type 2 using 4 concentrations of 25, 50, 100, 150, and 200 $\mu g.mL^{-1}$. Anti-herpetic activities of non-toxic concentrations of lemon balm (up to a concentration of 100 $\mu g.mL^{-1}$ of lemon balm oil seemed to be non-toxic versus HEp-2 cells) were examined and results suggested that the replication of HSV type 2 was inhibited and viral infectivity of this virus was notably reduced showing that lemon balm extract contains anti-herpetic materials. Nolkemper et al[61] examined some plants of the Lamiaceae family including *Melissa officinalis*, pepper-mint, prunella, and some other plants for their inhibitory effect versus HSV type 1 and HSV type 2 and acyclovir-resistant strains of HSV type 1. This study suggested that all plants used in the trial including lemon balm revealed to have powerful anti-herpetic effects using the mechanism of neutralization. Koytchev et al[63] proved the performance of Lomaherpan cream for the therapy of Herpes simplex labialis and their assay demonstrated balm mint extract reversibly blocks virus entry into the cell. Wölbling and Leonhardt[64] provided the fact and supereminence that Melissa leaves against herpes simplex infections. Melissa cream treatment must be started in the very early stages of the infection to be effective.[64] Nicholson and O'Farrell[65] demonstrated that using Lomaherpan cream which is made with lemon balm mint (*Melissa officinalis*) and lysine in a basic situation of genital herpes by inhibiting the activity of arginine which promotes HSV replication, was useful. Ahadian et al[66] investigated *Melissa*

officinalis effects on Recurrent Herpes labialis (RHL) and they concluded, that although Melissa gel potently decreased pain intensity on the second and fourth days, it was not effective to treat RHL. Moradi et al[66] during their investigation and checked 25 plant extracts for their antiviral acting against HSV-1, found that Phenolic combination has been demonstrated to have antibacterial and antiviral effects. Vahabpour-Roudsari et al[67] treated cells with Lemon Balm extract before, during, and after infection. Their work has been shown that lemon Balm extract could block the growth and development of HSV-1 in cells in vitro. Astani et al[68] investigated the antiviral effect of monoterpenes on the HSV-1; which are the main component of essential oils.750 (μg/mL) of α-Terpineneand100 (μg/mL) of γ-Terpinene and α-Pinene, as a maximum non-cytotoxic concentration, reduced infection by more than 96%. Other monoterpenes, except 1,8 cineole, reduced HSV plaque 80% to 90%. Since viruses placed in monoterpenes caused much less infection, these substances affect the lining of viruses, preventing the virus from entering the cell. The mixture of monoterpene and essential oil caused toxicity, while the multinometerpene mixture had more effect than a monoterpene. Kucera et al[1] measured the effect of Melissa extract on HSV in embryonated eggs and tissue culture. *Melissa officinalis* protected the egg when was injected a few hours before and simultaneously with the virus. In other experiments where the extract and virus were added to chick embryo fibroblasts monolayer simultaneously, plaque was still formed, but plaque formation decreased as the dose of the extract increased. The addition of gelatin causes a reaction with tannins and neutralizes the antiviral effect.

Herpes zoster is another type of Herpes Virus that captures about 30% of the USA population. 99.5% of them have had varicella-zoster before. Its symptoms that last an average of 30 days, include burning and painful lesions on the skin. A severe symptom is a postherpetic neuralgia which leads to burning pain 3 days after healing. Using compound of Melissa officials,[11,20] Lavandula officials, Hypericum perforatum,[69,70] Glycyrrhiza glabra,[71,72] Eleutherococcus senticosus, and Sarracenia purpurerespo[73,74] mixed in Versabase gel, can be a good superseded. Because these herbs have anti-viral, anti-inflammatory, and analgesic prosupersede. In a case reported by Ferreira and Langland[75] a 26 years old woman with herpes zoster had severe painful burning lesions on her abdomen and back. A combination of herbal extracts was used to treat her (25% Sarracenia, 10% Lavandula officinalis, 6% *Melissa officinalis*, 4% Eleutherococcus senticosus, 2.5% Glycyrrhiza glabra, and 2.5% Hypericum perforatum solved in 50% Versabase gel). After 6 days, the lesions completely disappeared and in 14th day lesions were completely recovered. Thus, an herbal compound could cure 50% sooner, without any side effects.

Koi Herpes Virus is another type of HV that infects Koi carp and cause a high mortality rate.[76] This type of herpes became known in the US and Israel in 1998 at first.[77] Zitterl-Eglseer et al[78] designed 2 studies on 6 groups of fish to test 2 materials. They used Lemon balm extract and Rosmarinic acid as a complement to the same diets. Throughout the period, there was not much difference between rosmarinic acid and Lemon balm. In the last, survivals in the control group and Rosmarinic acid group were the same. however, the Lemon balm extract group had more survival.

Adenovirus

Human Adenovirus (HAdV)s are double-stranded, linear DNA viruses displaying genome sizes ranging from 34 to more than 37 kb and carrying some 40 genes.[36,37] All HAdVs share a similar organization of the genome, which is divided into early, intermediate, and late regions corresponding to the infectious cycle of the virus and reflecting the transcription patterns. The early region of the genome includes 4 transcript families, termed E1 to E4, which are required for viral replication. The E3 transcription unit, which is highly divergent between HAdV species, also encodes proteins modulating the host immune response. The intermediate genes are represented by 2 transcripts, termed IX and IVa2, and the late region contains 5 transcript families, referred to as L1 to L5, which are involved in the production of mature virions HAdVs can retain their infectious properties even after several weeks in moisture-free environments, and because they are nonenveloped viruses, they are resistant to many disinfectants. Treatment of surfaces with alcohol solutions (85%-95%) for at least 2 minutes or with sodium hypochlorite for 10 minutes is effective at inactivating the virus.[79]

Non enveloped viruses with icosahedral nucleocapsids including a double-stranded DNA genome. adenoviruses are common viruses that cause a range of illnesses. They can cause bronchitis, pneumonia, gastroenteritis, hepatitis, and myocarditis in humans. Ribavirin and Cidofovir are 2 anti-virus remedies that are used for therapy of adenovirus infections but are not very effective and until now no particular antiviral therapies accepted against this virus although a lot of studies manifested that ingredients isolated from medicinal herbs had effectual antiviral acting for instance the hydroalcoholic extract of *Melissa officinalis* that its activity was assessed on HEp2 cell lines using MTT experiment. Moradi et al[80] demonstrated that the extract of *Melissa officinalis* does not forbid the entrance of adenovirus into the Hep-2 cells but it acts following the influence of the virus into the cell. Hydroalcoholic extracts of *Melissa officinalis* are effective against intracellular HSV type2 though not similar to these results, Astani et al reported that aqueous extracts of *Melissa officinalis* and the corresponding compounds phenolic caffeic acid, *p*-coumaric acid, and rosmarinic acid remarkably inhibited the infectivity of Acyclovir- resistant HSV-1 only at initial steps of virus replication. The most important combination that has been shown to have antiviral and antibacterial is Phenolic which in the results of this study proved that *Melissa officinalis* have a high level of these compounds.[80] Table 1 summarizes the antiviral effects of *Melissa officinalis*

Table 1. Summary of studies on the effects of *Melissa officinalis* on the viral diseases.

FAMILY	VIRUS	THE MECHANISM AT THE VIRUS LEVEL	REFERENCES
Retroviridae	Human immunodeficiency virus	Inhibition of viral replication	Geuenich et al[54]
		Inhibition of reverse transcriptase	Yamasaki et al,[53] Dubois et al[55]
Orthomyxoviridae	Influenza A virus and Influenza B virus	Inhibition of different phases of viral replication	Pourghanbari et al[58]
		Antiviral activity of hydroalcoholic extracts and their synergistic activity on the replication of subtype H1N1	Jalali[57]
		Inhibition of reproduction of the H5N1 and H3N2 subtypes	Mazurkova et al[81]
Picornaviridae	Enterovirus71	Inhibition of plaque formation, cytopathic effect, and viral protein synthesis	Chen et al[46]
		Inhibition of the visible cytopathic effects' formation	Choi et al[45]
		Protecting cells from cytopathic effects and apoptosis	Lin et al[47]
		Inhibition of the interact between the Five-Fold Axis of Capsid VP1 and Cognate Sulfated receptors	Hsieh et al[48]
Herpesviridae	Herpes simplex virus type1 (HSV1)	Inhibition of viral adhesion and penetration into host cell	Astani et al[11]
		Non cytotoxic effects	Vanti et al[18]
		Antiviral properties at high lemon balm concentration with load on nanocarriers	Vanti et al[18]
	Herpes simplex virus 2 (HSV2)	Inhibition of virus replication	Allahverdiyev et al[21]
		High virucidal activity with polyphenolic compounds and low toxicity	Astani et al[20]
		Inhibition of HSV attachment to host cell	Astani et al[20]
		ICP0 did not inhibit viral protein expression	Astani et al[20]
		Decreased expression in the of gD HSV protein	Astani et al[20]
		Inhibition of HSV- 1 binding to host cells	Ahadian et al[66]
		Inhibition of HSV-1 replication during the post-adsorption	
		Inhibition of viral replication	Allahverdiyev et al,[21] Mazzanti et al[62]
		Inhibition of protein synthesis for replication and reduced viral infectivity in cells with melissa volatile oils (sitral and sitronellal)	Allahverdiyev et al[21]
		Did not prevent virus attachment	Mazzanti et al[62]
		Inhibition of virus penetration	Mazzanti et al[62]
		Inhibition of protein biosynthesis in liver cells with caffeic acid like components	Mazzanti et al[62]
	Herpes simplex virus 1 and 2	Reduced virus plaque formation at high concentrations	Schnitzler et al[60]
		Affecting the virus before absorption by reducing plaques	Schnitzler et al,[60] Nolkemper et al[61]
		Antiviral effect on free HSV by interacting with virus envelope (before adsorption)	Nolkemper et al[61]
		Interfering with the first step of infection of a cell by blocking the receptors responsible for viral adsorption	Koytchev et al[63]
		Hindering dissemination of the infection to the intact cells by blocking up the host cells and the virus receptors	Wölbling et al[64]
		Inactivation of free virus particles	Astani et al[68]

(Continued)

Table 1. (Continued)

FAMILY	VIRUS	THE MECHANISM AT THE VIRUS LEVEL	REFERENCES
Paramyxoviridae	Newcastle virus	Prevention of plaque formation, hemagglutination, and infected embryonated eggs death	
	Precipitation of virus from suspension through hydrogen bonding		Kucera and Herrmann[83]
	Building resistance by combining tannins with cell protein		Kucera and Herrmann[83]
	Decreased effect of tannic acid on the amount of nasal mucosa		Kucera and Herrmann[83]
Coronaviridae	Sars-Cov-2	Inhibition of main protease and spike protein of Sars-Cov-2	Prasanth et al,[33] Patel et al[34]
		Disruption of the replication domain of Sars-Cov-2 by hindering RNA-dependent RNA polymerase	Balkrishna et al[29]
Coronaviridae	Avian infectious bronchitis virus	Inhibition of viral replication compared to the virus control	Lelešius et al[84]

Oxidative Stress

Oxidative stress is an unbalanced condition between free radicals and antioxidants. It destroys various body tissues and causes a variety of diseases, including diabetes, hepatitis, and neurodegenerative diseases.[85] Many viruses induce oxidative stress; such as respiratory syncytial virus (RSV),[86] EBV,[87] Pseudorabies virus (PRV),[88] Canine distemper virus (CDV),[89] Hepatitis B virus (HBV),[90] Mayaro virus (MAYV),[91] SARS-CoV-2,[92] Hepatitis C virus (HCV),[93] Human immunodeficiency virus(HIV),[94] Human papillomavirus (HPV),[95] Rotavirus,[96] Rabies virus,[97] Rubella virus (RV),[98] HSV,[99] ZIKV,[100] Japanese encephalitis virus (JEV), West Nile virus (WNV), Tick-borne encephalitis virus (TBEV),[101] Dengue virus (DENV),[102] Chikungunya virus,[103] Nipah virus (NiV),[104] Bovine leukemia virus (BLV),[105] Influenza a virus,[106] Chandipura virus (CHPV),[107] Newcastle disease virus (NDV),[108] African swine fever virus (ASFV),[109] Grass carp reovirus (GCRV),[110] and E. huxleyi virus (EHV).[111] Melissa has been proven to have anti-oxidative properties[50] and applies one of its antiviral properties through the same property. Hence, future studies can target this issue.

Inflammation

Inflammation is an initial protective procedure of the body against both infectious and non-infectious diseases. This mechanism is non-particular and instant. There are 5 essential indications of inflammation including: heat (calor), redness (rubor), swelling (tumor), pain (dolor), and loss of function (functionless). Inflammation can be divided into 3 types according to the length of the procedure that replies to the injurious causes; acute which instantly after injuries and lasts for a few couple of days, chronic inflammation which may continue for months to years when acute inflammation mechanism cease to work properly, and subacute which is a transformational interval from acute to chronic which may remain from 2 to 6 weeks. The etiologies of inflammation can be divided into 2 main classifications: 1. Exogenous inducers: This grouping can be divided into 2 sub-classes; microbial and non-microbial exogenous inducers. 2. Endogenous inducers: Tissues which are deceased, injured, broke down, or stressed emit these signals. As an alternative, the inflammatory inducers can also be divided into 2 large groups, including the non-infectious factors and the infectious factors. Infectious factors include bacteria, viruses, and other microorganisms.[112] Examples of these viruses are Chronic Hepatitis B virus (HBV),[113] COVID-19,[114] HSVs,[115] Influenza A virus (IAV).[116] Lemon balm (*Melissa officinalis*) is a perennial herb in the mint family Lamiaceae, native to southern Europe and the Mediterranean region that is used medicinally as a herbal tea, or in extract form.[19] It is exhibited antibacterial, and antiviral properties.[12,84] This plant with antiviral properties in viruses that cause inflammation helps control inflammation caused by those viruses. Based on this, we want a direct study of this plant and its effect on inflammation in future research.

Discussion

Viral diseases are complex diseases with different aspects. Therefore, in its treatment, it is better to use drugs that fight it in different ways. Among the available drugs, herbal drugs can be recommended due to their multi-targeting properties. In addition to having this feature, herbal medicines are more available, cheaper and also have fewer side effects. Therefore, currently, research in the field of medicinal plants is of great importance.

During the conducted studies, rosmarinic acid is one of the most important compounds in lemongrass plant extract, which is known to have a wide antiviral activity. For this reason, Zitterl-Eglseer et al[78] designed 2 studies on 6 groups of fish to

test 2 substances. They used lemongrass extract and rosmarinic acid as supplements to similar diets. Across the course, there was no significant difference between rosmarinic acid and lemongrass. Finally, the survival rate was the same in the control group and the rosmarinic acid group. However, the lemongrass extract group had longer survival.

These results obtained by Hasselmeyer et al show that the use of the plant extract itself has a better effect than using only one of its antiviral compounds.

The current review supports the idea of using lemon balm extracts as effective alternative treatment for several types of viral infections.[18,19,68,75,117-119] Lemongrass extract has antiviral properties against the following 6 types of viruses:

1. SARS-CoV-2 :
   Two important proteins for the pathogenicity of this virus are the spike protein and its main protease.
   Three plant compounds in Melissa officinalis extract, including luteolin-7-glucoside-3′-glucuronide, Metric acid-A and Quadranoside-III are known to be able to bind to these 2 proteins and deactivate them, thus showing antiviral activity.[32,34,120]
2. Enterovirus-71:
   Rosemarinic acid in Melissa officinalis extract is known to be an antiviral compound for Enterovirus-71.
   Rosmarinic acid causes the following events on EV71:
   (a) Prevention of EV71 replication
   (b) Inhibition of EV71 infection in the attachment and post-attachment stages
   (c) EV71 suppression: suppresses helmet-dependent and IRES-dependent translation
   (d) Suppression of phosphorylation induced by EV71 p38 kinase
   (e) Suppression of EV71-induced phosphorylation of the epidermal growth factor 15 receptor substrate (EPS15).
   - The addition of rosmarinic acid before infection (−2 hour) had no significant inhibitory effect, whereas addition of RA during cellular infection (0 hour) and transfer (+2 hour) of it can effectively reduce viral VP1 mRNA[47]
3. HIV:
   Rosmarinic acid in Melissa officinalis extract effectively inhibits HIV1 strains through the following 2 methods.
   I. inhibit viral replication in MT-4 cells[53]
   II. Rosmarinic acid found in Melissa officinalis under acidic conditions reacted with nitrate ions to form 6′-nitro- and 6′, 6′. Both compounds inhibit HIV-1 integrase at a sub-micromolar level.[55]
4. Influenza:
   The Food and Drug Organization has emphasized that synthetic drugs that affect the M2 and NA proteins of the influenza virus create drug-resistant viruses. Therefore, the development of other compounds such as traditional and herbal medicines became more important.
   Melissa extract has antiviral effects against 4 types of influenza virus (H5N1, H3N2, H9N2 (AIV), and H1N1), which has the most effect on H5N1 and H3N2. Also, regarding the AIV virus, the most antiviral activities of MOEO were observed when AIV had already been incubated with MOEO Cellular infection.
   This extract was effective on the strains of this virus with different mechanisms:
   It had a destructive effect on the virus itself and also had an effect on intracellular processes. It also had an effect on the direct interaction of the virus with the cell. This extract also stimulated the immune system and the combination of rosmarinic acid in the extract, several inflammatory pathways of the Complement system specifically inhibited C5-convertase.[57,58]
5. Herpes simplex virus (HSV):
   Researchers noticed the high effectiveness of Melissa officinalis on HSV disease and conducted more extensive research on this matter. Although the antiherpetic effect of this extract was less than that of acyclovir drug. . .but this plant could show a significant therapeutic effect on patients who were resistant to acyclovir drug.[62]
   In herpes zoster disease, this herbal medicine can be effective 50% sooner than other medicines and also without causing any side effects in the treatment of this disease.[121]
   Researchers found that Melissa is effective in the treatment of this disease through the following mechanisms:
   a. The rosmarinic acid present in this extract interacts directly with the glycoproteins (gD and gB) of the HSV virus and prevents the adhesion and penetration of this virus to the mucous cells.[11,20]
   b. It inhibits the connection and penetration of HSV resistant to acyclovir.[11]
   c. Caffeic acid present in this plant, in addition to rosmarinic acid, has antioxidant activity against HSVs.[62]
6. Adenovirus:
   In adenoviral infections, 2 drugs ribavirin and cidofovir are used, which are not very effective. Therefore, it is important to find an effective medicine.
   Moradi et al[80] showed that the extract of Melissa officinalis works after the penetration of adenovirus into the cell and leaves its effect. Figure 2 summarizes the antiviral effects of *Melissa officinalis*

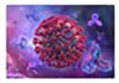
Conclusion

To conclude Articles included in our review proved antiviral effects of *Melissa officinalis* against a group of viruses including HSV1, HSV2, HIV, SARS-CoV-2, influenza, and some other viruses mentioned in our article. The greatest impact of antiviral activities of Melissa office nalis was on HSV type 1 and 2.

HERPES SIMPLEX VIRUS

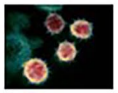
- It also has high antiviral activity by using phenolic compounds
- inhibit protein biosynthesis in liver cells with caffeic acid like components.
- inhibiting HSV attachment to host cell.
- did not inhibit ICP0 viral protein expression.
- decrease in expression of the gD HSV protein.
- Extract exert antiviral effect on free HSV by interact with virus envelope.

Newcastle virus



- From creating plaques formation, hemagglutination and an infected fetus Prevents egg death.
- precipitation of virus from suspension through hydrogen bonding
- By combining tannin to create resistance to cell growth
- decrease effect of tannic acid on amount of nasal mucosa

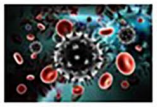
SARS-COV-2



- three phytoconstituents from Melissa officinalis, including, Luteolin-7-glucoside- 3′-glucuronide, Metric acid-A, and Quadranoside-III have revealed better fusion affinity and solidity with the targets of SARS-CoV-2 main protease and spike protein

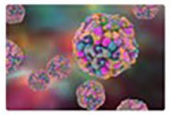
MELISSA OFFICINALIS

Human immunodeficiency virus



- The aqueous extract of Melissa officinalis With increasing virion density, shows strong anti-HIV-1 activity.
- Melissa officinalis extract effectively inhibits HIV-1-sensitive strains.
- Anti-HIV-1 activity in Melissa officinalis extract is rapid but has decreased against superficial virions
- Rosmarinic acid found in Melissa officinalis under acidic situations, reacted with nitrate ions to form 6'-nitroand 6', 6'. Both compounds were active as HIV-1 integrase Inhibitors at the sub-micromolar level. Another function of these compounds is to inhibit viral replication in MT-4 cells.

Enterovirus-71



- Melissa officinalis aqueous extract prevents loss of viability in EVA71-infected virus cells
- antiviral effect of Melissa officinalis was due to the presence of rosmarinic acid in its methanolic extract.
- suppresses helmet-dependent and IRES-dependent translation
- Suppression of phosphorylation induced by EV71 p38 kinase
- Suppression of EV71-induced phosphorylation of the epidermal growth factor 15 receptor substrate
- protected cells from the cytopathic of EV71 and protected infected cells from apoptosis and death
- The addition of rosmarinic acid before infection (-2 h) had no significant inhibitory effect, whereas addition of RA during cellular infection (0h) and transfer (+2h) of it can effectively reduce viral VP1 mRNA

INFLUENZA

- the most antiviral activities of MOEO were observed when AIV had already been incubated with MOEO Cellular infection.
- Melissa had a significant effect on H5N1 and H3N2 subtypes

Figure 2. A summary of the antiviral effects of *Melissa officinalis*.

Also, several articles proved the anti-oxidant and anti-inflammatory effects of *Melissa officinalis* which can introduce this herbal plant as an alternative treatment for a group of viral diseases which use these mechanisms of pathogenesis. There is a hope that using *Melissa officinalis* as an alternative treatment for viral diseases such as Covid-19 (which made a pandemic in the last 2 years) can have more attention. We suggest more randomized control trials to be done for examining the antiviral effects of Melissa office nalis in patients infected with viruses especially those who are infected with Covid-19 and also more in-vitro and in-vivo studies are suggested to be done for elucidating mechanisms used by *Melissa officinalis* for inducing its anti-viral effects in viral infected patients.

However, the very precise mechanisms of action of lemongrass have not been fully identified and further studies have examined the dose and further studies are needed in this regard.

Acknowledgements

The authors acknowledge with grateful appreciation the kind assistance provided by the colleagues from Avicennet who provided insight and expertise that greatly assisted the research.

Author Contributions

Manuscript drafting: AB, Si, ND, ZMT, fm, zm; Data collection: SS, MM, FSH; Study design: SN, SOT; Manuscript revision: MHM, Pb, AK, KK; Study supervision: PB, MP.

REFERENCES

1. Pronin AV, Narovlyansky AN, Sanin AV. New approaches to the prevention and treatment of viral diseases. *Arch Immunol Ther Exp*. 2021;69:10.
2. Herrington CS, Coates PJ, Duprex WP. Viruses and disease: emerging concepts for prevention, diagnosis and treatment. *J Pathol*. 2015;235:149-152.
3. Carrillo-Infante C, Abbadessa G, Bagella L, Giordano A. Viral infections as a cause of cancer (review). *Int J Oncol*. 2007;30:1521-1528.
4. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol*. 2020;92:1875-1883.
5. Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. *Int J Clin Pract*. 2021;75:e13868.
6. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. *Clin Microbiol Rev*. 2016;29:695-747.
7. Dyrka K, Miedziaszczyk M, Szałek E, Łącka K. Endocrine abnormalities induced by the antiviral drugs and frequency of their occurrence. *Pol Merkur Lekarski*. 2020;48:209-214.
8. Zareifopoulos N, Lagadinou M, Karela A, Kyriakopoulou O, Velissaris D. Neuropsychiatric effects of antiviral drugs. *Cureus*. 2020;12:e9536.
9. Leowattana W. Antiviral drugs and acute kidney injury (AKI). *Infect Disord Drug Targets*. 2019;19:375-382.
10. Lee JY, Abundo MEC, Lee CW. Herbal medicines with antiviral activity against the influenza virus, a systematic review. *Am J Chin Med*. 2018;46:1663-1700.
11. Astani A, Navid MH, Schnitzler P. Attachment and penetration of acyclovir-resistant herpes simplex virus are inhibited by Melissa officinalis extract. *Phytother Res*. 2014;28:1547-1552.
12. Miraj S, Rafieian-Kopaei M, Kiani S. Melissa officinalis L: a review study with an antioxidant prospective. *J Evid Base Compl Altern Med*. 2016;22:385-394.
13. ElhamKia M, Setayesh L, Yarizadeh H, et al. The interaction between dietary total antioxidant capacity and MC4R gene and HOMA-IR in metabolically healthy and unhealthy overweight and obese women. *Nutr Metab Insights*. 2022;15:11786388221105984.
14. Hosseinifard E-S, Bavafa-Valenlia K, Saghafi-Asl M, Morshedi M. Antioxidative and metabolic effects of Lactobacillus plantarum, inulin, and their synbiotic on the hypothalamus and serum of healthy rats. *Nutr Metab Insights*. 2020;13:1178638820925092.
15. Niemchick KL, Riemersma C, Lasker GA. Lipophilic antioxidants and cognitive function in the elderly. *Nutr Metab Insights*. 2020;13:1178638820903300.
16. Waldman HS, McAllister MJ. Exogenous ketones as therapeutic signaling molecules in high-stress occupations: implications for mitigating oxidative stress and mitochondrial dysfunction in future research. *Nutr Metab Insights*. 2020;13:1178638820979029.
17. Stavsky J, Maitra R. The synergistic role of diet and exercise in the prevention, pathogenesis, and management of ulcerative colitis: an underlying metabolic mechanism. *Nutr Metab Insights*. 2019;12:1178638819834526.
18. Vanti G, Ntallis SG, Panagiotidis CA, et al. Glycerosome of Melissa officinalis L. Essential oil for effective anti-HSV type 1. *Molecules*. 2020;25:3111.
19. Williams A, Scally G, Langland J. A topical botanical therapy for the treatment of canine papilloma virus associated oral warts: a case series. *Adv Integr Med*. 2021;8:151-154.
20. Astani A, Reichling J, Schnitzler P. Melissa officinalis extract inhibits attachment of herpes simplex virus in vitro. *Chemotherapy*. 2012;58:70-77.
21. Allahverdiyev A, Duran N, Ozguven M, Koltas S. Antiviral activity of the volatile oils of Melissa officinalis L. against herpes simplex virus type-2. *Phytomedicine*. 2004;11:657-661.
22. Parham S, Kharazi AZ, Bakhsheshi-Rad HR, et al. Antioxidant, antimicrobial and antiviral properties of herbal materials. *Antioxidants*. 2020;9:1309.
23. Parham S, Kharazi AZ, Bakhsheshi-Rad HR, et al. Electrospun nano-fibers for biomedical and tissue engineering applications: a comprehensive review. *Materials*. 2020;13:2153.
24. Parham S, Kharazi AZ, Bakhsheshi-Rad HR, et al. Antimicrobial synthetic and natural polymeric nanofibers as wound dressing: a review. *Adv Eng Mater*. 2022;24:2101460.
25. Sharifi-Rad J, Quispe C, Herrera-Bravo J, et al. Phytochemical constituents, biological activities, and health-promoting effects of the Melissa officinalis. *Oxid Med Cell Longev*. 2021;2021:1-20.
26. Sohrab S, Mishra P, Mishra SK. Phytochemical competence and pharmacological perspectives of an endangered boon—Costus speciosus (Koen.) Sm.: a comprehensive review. *Bull Natl Res Cent*. 2021;45:1-27.
27. Zam W, Quispe C, Sharifi-Rad J, et al. An updated review on the properties of Melissa officinalis L.: not exclusively anti-anxiety. *Front Biosci*. 2022;14:16.
28. Priyadarshi R, Purohit SD, Roy S, Ghosh T, Rhim J-W, Han SS. Antiviral biodegradable food packaging and edible coating materials in the COVID-19 era: a mini-review. *Coatings*. 2022;12:577.
29. Balkrishna A, Mittal R, Sharma G, Arya V. Computational insights of phytochemical-driven disruption of RNA-dependent RNA polymerase-mediated replication of coronavirus: a strategic treatment plan against coronavirus disease 2019. *New Microbes New Infect*. 2021;41:100878.
30. Haryalchi K, Heidarzadeh A, Abedinzade M, Olangian-Tehrani S, Tehran Ghazanfar S. The importance of happy hypoxemia in COVID-19. *Anesth Pain Med*. 2021;11:e111872.
31. Haryalchi K, Olangian-Tehrani S, Asgari Galebin SM, Mansour-Ghanaie M. The importance of myocarditis in Covid-19. *Health Sci Rep*. 2022;5:e488.
32. Romano M, Ruggiero A, Squeglia F, Maga G, Berisio R. A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. *Cells*. 2020;9:1267.
33. Prasanth DS, Manikanta M, Chandramohan V, et al. In-silico strategies of some selected phytoconstituents from Melissa officinalis as SARS CoV-2 main protease and spike protein (COVID-19) inhibitors. *Mol Simul*. 2021;47:457-470.
34. Patel A, Patel A, Hemani R, et al. Exploring the in-silico approach for assessing the potential of natural compounds as a SARS-CoV-2 main protease inhibitors. *Org Commun*. 2021;14:58-72.
35. Yamayoshi S, Fujii K, Koike S. Receptors for enterovirus 71. *Emerg Microbes Infect*. 2014;3:e53.
36. Dang M, Wang X, Wang Q, et al. Molecular mechanism of SCARB2-mediated attachment and uncoating of EV71. *Protein Cell*. 2014;5:692-703.
37. Ho M, Chen E-R, Hsu K-H, et al. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus epidemic working group. *New Engl J Med*. 1999;341:929-935.
38. Li P, Li T, Gu Q, et al. Children's caregivers and public playgrounds: potential reservoirs of infection of hand-foot-and-mouth disease. *Sci Rep*. 2016;6:36375.
39. Chan KP, Goh KT, Chong CY, Teo ES, Lau G, Ling AE. Epidemic hand, foot and mouth disease caused by human Enterovirus 71, Singapore. *Emerg Infect Dis*. 2003;9:78-85.
40. Wu J-M, Wang J-N, Tsai Y-C, et al. Cardiopulmonary manifestations of fulminant Enterovirus 71 infection. *Pediatrics*. 2002;109:e26.
41. Prager P, Nolan M, Andrews IP, Williams GD. Neurogenic pulmonary edema in Enterovirus 71 encephalitis is not uniformly fatal but causes severe morbidity in survivors. *Pediatr Crit Care Med*. 2003;4:377-381.
42. Teoh HL, Mohammad SS, Britton PN, et al. Clinical characteristics and functional motor outcomes of Enterovirus 71 neurological disease in children. *JAMA Neurol*. 2016;73:300-307.

43. Chang L-Y, Lin H-Y, Gau SS, et al. Enterovirus A71 neurologic complications and long-term sequelae. *J Biomed Sci*. 2019;26:57.
44. Chang L-Y, Huang L-M, Gau SS, et al. Neurodevelopment and cognition in children after Enterovirus 71 infection. *New Engl J Med*. 2007;356:1226-1234.
45. Choi HJ, Song JH, Ahn YJ, Kwon DH. Inhibitory effect on replication of Enterovirus 71 of herb methanol extract. *J Appl Biol Chem*. 2008;51:123-127.
46. Chen S-G, Leu Y-L, Cheng M-L, et al. Anti-enterovirus 71 activities of Melissa officinalis extract and its biologically active constituent rosmarinic acid. *Sci Rep*. 2017;7:12264.
47. Lin W-Y, Yu YJ, Jinn T-R. Evaluation of the virucidal effects of rosmarinic acid against enterovirus 71 infection via in vitro and in vivo study. *Virol J*. 2019;16:94.
48. Hsieh C-F, Jheng J-R, Lin G-H, et al. Rosmarinic acid exhibits broad anti-enterovirus A71 activity by inhibiting the interaction between the five-fold axis of capsid VP1 and cognate sulfated receptors. *Emerg Microbes Infect*. 2020;9:1194-1205.
49. Fanales-Belasio E, Raimondo M, Suligoi B, Buttò S. HIV virology and pathogenetic mechanisms of infection: a brief overview. *Ann Ist Super Sanita*. 2010;46:5-14.
50. Ashrafi E, Kasmaei P, Mehrabian F, et al. The effect of educational program based on the theory of planned behavior on HIV prevention skills. *HIV AIDS Rev*. 2020;19:180-186.
51. Ashrafi E, Kasmaei P, Mehrabian F, Omidi S, Zareban I, Haryalchi K. Predictive factors of behavioral intention in aids prevention in nursing and midwifery students at Guilan University of medical sciences. *Drug Invent Today*. 2019;12:239-242.
52. Robinson We Jr., Montefiori DC, Mitchell WM. Evidence that mannosyl residues are involved in human immunodeficiency virus type 1 (HIV-1) pathogenesis. *AIDS Res Hum Retroviruses*. 1987;3:265-282.
53. Yamasaki K, Nakano M, Kawahata T, et al. Anti-HIV-1 activity of herbs in Labiatae. *Biol Pharm Bull*. 1998;21:829-833.
54. Geuenich S, Goffinet C, Venzke S, et al. Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density. *Retrovirology*. 2008;5:27.
55. Dubois M, Bailly F, Mbemba G, et al. Reaction of rosmarinic acid with nitrite ions in acidic conditions: discovery of nitro- and dinitrorosmarinic acids as new Anti-HIV-1 agents. *J Med Chem*. 2008;51:2575-2579.
56. Te Velthuis AJ, Fodor E. Influenza virus RNA polymerase: insights into the mechanisms of viral RNA synthesis. *Nat Rev Microbiol*. 2016;14:479-493.
57. Jalali P, Moattari A, Mohammadi A, Ghazanfari N, Pourghanbari G. Melissa officinalis efficacy against human influenza virus (New H1N1) in comparison with oseltamivir. *Asian Pac J Trop Dis*. 2016;6:714-717.
58. Pourghanbari G, Nili H, Moattari A, Mohammadi A, Iraji A. Antiviral activity of the oseltamivir and Melissa officinalis L.essential oil against avian influenza A virus (H9N2). *VirusDisease*. 2016;27:170-178.
59. Zhu S, Viejo-Borbolla A. Pathogenesis and virulence of herpes simplex virus. *Virulence*. 2021;12:2670-2702.
60. Schnitzler P, Schuhmacher A, Astani A, Reichling J. Melissa officinalis oil affects infectivity of enveloped herpesviruses. *Phytomedicine*. 2008;15:734-740.
61. Nolkemper S, Reichling J, Stintzing FC, Carle R, Schnitzler P. Antiviral effect of aqueous extracts from species of the Lamiaceae family against Herpes simplex virus type 1 and type 2 in vitro. *Planta Med*. 2006;72:1378-1382.
62. Mazzanti G, Battinelli L, Pompeo C, et al. Inhibitory activity of Melissa officinalis L. extract on herpes simplex virus type 2 replication. *Nat Prod Res*. 2008;22:1433-1440.
63. Koytchev R, Alken RG, Dundarov S. Balm mint extract (Lo-701) for topical treatment of recurring herpes labialis. *Phytomedicine*. 1999;6:225-230.
64. Wölbling RH, Leonhardt K. Local therapy of herpes simplex with dried extract from Melissa officinalis. *Phytomedicine*. 1994;1:25-31.
65. Nicholson M, O'Farrell N. Genital herpes – diagnosis, treatments, attitudes and response to disclosure amongst members of the UK Herpes Viruses Association. *Int J STD AIDS*. 2021;32:23-29.
66. Ahadian H, Akhavan Karbassi MH, Ghaneh S, Hakimian R. Therapeutic effect of melissa gel and 5% acyclovir cream in recurrent herpes labialis: a double-blind randomized clinical trial. *Jundishapur J Nat Pharm Prod*. 2015;10:e26160.
67. Vahabpour-Roudsari R, Shamsi-Shahrabadi M, Monavari S, Sajjadi S, Sajjadi N. Evaluation of potential antiviral activity of the hydroalcoholic extract of lemon balm l. Against herpes simplex virus type 1. *Iran J Virol*. 2010;4:52-57.
68. Astani A, Reichling J, Schnitzler P. Comparative study on the antiviral activity of selected monoterpenes derived from essential oils. 2010;24:673-679.
69. Clewell A, Barnes M, Endres JR, Ahmed M, Ghambeer DK. Efficacy and tolerability assessment of a topical formulation containing copper sulfate and hypericum perforatum on patients with herpes skin lesions: a comparative, randomized controlled trial. *J Drugs Dermatol*. 2012;11:209-215.
70. Wölfle U, Seelinger G, Schempp CM. Topical application of St. John's wort (Hypericum perforatum). *Planta Med*. 2014;80:109-120.
71. Fiore C, Eisenhut M, Krausse R, et al. Antiviral effects of Glycyrrhiza species. *Phytother Res*. 2008;22:141-148.
72. Pompei R, Flore O, Marccialis MA, Pani A, Loddo B. Glycyrrhizic acid inhibits virus growth and inactivates virus particles. *Nature*. 1979;281:689-690.
73. Arndt W, Mitnik C, Denzler KL, et al. In vitro characterization of a nineteenth-century therapy for smallpox. *PLoS One*. 2012;7:e32610.
74. Ozçelik B, Kartal M, Orhan I. Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. *Pharm Biol*. 2011;49:396-402.
75. Ferreira V, Langland J. Treatment of herpes zoster with botanical interventions: Case report. *Med Case Rep Stud Protoc*. 2021;2:e0058.
76. Gotesman M, Kattlun J, Bergmann SM, El-Matbouli M. CyHV-3: the third cyprinid herpesvirus. *Dis Aquat Org*. 2013;105:163-174.
77. Hedrick RP, Gilad O, Yun S, et al. A herpesvirus associated with mass mortality of juvenile and adult koi, a strain of common carp. *J Aquat Anim Health*. 2000;12:44-57.
78. Zitterl-Eglseer K, Haselmeyer A, Nowotny N, El-Matbouli M, Heistinger H, Kolodziejek J, et al. Melissa officinalis L. Extract and its main phenolic compound rosmarinic acid as phytoprophylactic feed additives against koi herpesvirus infection in a pilot study. *Wien Tierärztl Monat*. 2018;105:175-183.
79. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. *Clin Microbiol Rev*. 2014;27:441-462.
80. Moradi M-T, Karimi A, Alidadi S, Hashemi L. In vitro anti-adenovirus activity, antioxidant potential and total phenolic compounds of Melissa officinalis L.(lemon balm) extract. *Int J Pharmacogn Phytochem Res*. 2016;8:1471-1477.
81. Mazurkova N, Protsenko M, Lobanova I, Filippova E, Vysochina G. Antiviral activity of Siberian wild and cultivated plants. In: *BIO Web of Conferences*, 2020: EDP Sciences.
82. Moradi M-T, Karimi A, Alidadi S, Hashemi L. In vitro anti-herpes simplex virus activity, antioxidant potential and total phenolic compounds of selected Iranian medicinal plant extracts. *Indian J Tradit Knowl*. 2018;17:255-262.
83. Kucera LS, Herrmann Jr EC. Antiviral substances in plants of the mint family (labiate). I. Tannin of Melissa officinalis. *Proc Soc Exp Biol Med*. 1967;124:865-869.
84. Lelešius R, Karpovaitė A, Mickienė R, et al. In vitro antiviral activity of fifteen plant extracts against avian infectious bronchitis virus. *BMC Vet Res*. 2019;15:178.
85. Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Mol Toxicol*. 2003;17:24-38.
86. Moreno-Solís G, Dela Torre-Aguilar MJ, Torres-Borrego J, et al. Oxidative stress and inflamatory plasma biomarkers in respiratory syncytial virus bronchiolitis. *Clin Respir J*. 2017;11:839-846.
87. Hu J, Li Y, Li H, et al. Targeting Epstein-barr virus oncoprotein LMP1-mediated high oxidative stress suppresses EBV lytic reactivation and sensitizes tumors to radiation therapy. *Theranostics*. 2020;10:11921-11937.
88. Lai IH, Chang CD, Shih WL. Apoptosis induction by pseudorabies virus via oxidative stress and subsequent DNA damage signaling. *Intervirology*. 2019;62:116-123.
89. Armando F, Gambini M, Corradi A, et al. Oxidative stress in canine histiocytic sarcoma cells induced by an infection with canine distemper virus led to a dysregulation of HIF-1α downstream pathway resulting in a reduced expression of VEGF-B in vitro. *Viruses*. 2020;12:200.
90. Cheng L, Sun P, Xie X, et al. Hepatitis B virus surface protein induces oxidative stress by increasing peroxides and inhibiting antioxidant defences in human spermatozoa. *Reprod Fertil Dev*. 2020;32:1180-1189.
91. da Silva Caetano CC, Camini FC, Almeida LT, et al. Mayaro virus induction of oxidative stress is associated with liver pathology in a non-lethal mouse model. *Sci Rep*. 2019;9:15289.
92. Schönrich G, Raftery MJ, Samstag Y. Devilishly radical network in COVID-19: oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. *Adv Biol Regul*. 2020;77:100741.
93. Saeed U, Piracha ZZ, Manzoor S. Hepatitis C virus induces oxidative stress and DNA damage by regulating DNAPKCs, ATM, ATR and PARP mediated signaling and guards cell from cancerous condition by upregulating RB, P53 and downregulating VEGF. *Acta Virol*. 2017;61:316-323.
94. Chettimada S, Lorenz DR, Misra V, Wolinsky SM, Gabuzda D. Small RNA sequencing of extracellular vesicles identifies circulating miRNAs related to inflammation and oxidative stress in HIV patients. *BMC Immunol*. 2020;21:57.
95. Kgatle MM, Spearman CW, Kalla AA, Hairwadzi HN. DNA oncogenic virus-induced oxidative stress, genomic damage, and aberrant epigenetic alterations. *Oxid Med Cell Longev*. 2017;2017:3179421.
96. Guerrero CA, Acosta O. Inflammatory and oxidative stress in rotavirus infection. *World J Virol*. 2016;5:38-62.
97. Jackson AC, Kammouni W, Fernyhough P. Role of oxidative stress in rabies virus infection. *Adv Virus Res*. 2011;79:127-138.
98. Zobel S, Lorenz M, Frascaroli G, et al. Rubella virus strain-associated differences in the induction of oxidative stress are independent of their interferon activation. *Viruses*. 2018;10:540.
99. Santana S, Sastre I, Recuero M, Bullido MJ, Aldudo J. Oxidative stress enhances neurodegeneration markers induced by herpes simplex virus type 1 infection in human neuroblastoma cells. *PLoS One*. 2013;8:e75842.

100. Lu W, Shi L, Gao J, et al. Piperlongumine inhibits Zika virus replication in vitro and promotes up-regulation of HO-1 expression, suggesting an implication of oxidative stress. *Virol Sin*. 2021;36:510-520.
101. Zhang Z, Rong L, Li YP. Flaviviridae viruses and oxidative stress: implications for viral pathogenesis. *Oxid Med Cell Longev*. 2019;2019:1409582.
102. Ferrari M, Zevini A, Palermo E, et al. Dengue virus targets Nrf2 for NS2B3-mediated degradation leading to enhanced oxidative stress and viral replication. *J Virol*. 2020;94: e01551-20.
103. Shrinet J, Bhavesh NS, Sunil S. Understanding oxidative stress in Aedes during Chikungunya and dengue virus infections using integromics analysis. *Viruses*. 2018;10:314.
104. Escaffre O, Saito TB, Juelich TL, et al. Contribution of human lung parenchyma and leukocyte influx to oxidative stress and immune system-mediated pathology following Nipah virus infection. *J Virol*. 2017;91: e00275-17.
105. Souza FN, Monteiro AM, dos Santos PR, et al. Antioxidant status and biomarkers of oxidative stress in bovine leukemia virus-infected dairy cows. *Vet Immunol Immunopathol*. 2011;143:162-166.
106. Liu M, Chen F, Liu T, Chen F, Liu S, Yang J. The role of oxidative stress in influenza virus infection. *Microbes Infect*. 2017;19:580-586.
107. Verma AK, Ghosh S, Basu A. Chandipura virus induced neuronal apoptosis via calcium signaling mediated oxidative stress. *Front Microbiol*. 2018;9:1489.
108. Rehman ZU, Qiu X, Sun Y, et al. Vitamin E supplementation ameliorates Newcastle disease virus-induced oxidative stress and alleviates tissue damage in the brains of chickens. *Viruses*. 2018;10:173.
109. Xia N, Wang H, Liu X, et al. African swine fever virus structural protein p17 inhibits cell proliferation through ER Stress-ROS mediated cell cycle arrest. *Viruses*. 2020;13:21.
110. Wan Q, Liao Z, Rao Y, et al. Transferrin receptor 1-associated iron accumulation and oxidative stress provides a way for grass carp to fight against Reovirus infection. *Int J Mol Sci*. 2019;20:5857.
111. Sheyn U, Rosenwasser S, Ben-Dor S, Porat Z, Vardi A. Modulation of host ROS metabolism is essential for viral infection of a bloom-forming coccolithophore in the ocean. *ISME J*. 2016;10:1742-1754.
112. Hannoodee S, Nasuruddin DN. *Acute Inflammatory Response*. StatPearls Publishing LLC; 2021.
113. Wu JF, Chang MH. Natural history of chronic hepatitis B virus infection from infancy to adult life -the mechanism of inflammation triggering and long-term impacts. *J Biomed Sci*. 2015;22:92.
114. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20:363-374.
115. Carr DJ, Tomanek L. Herpes simplex virus and the chemokines that mediate the inflammation. *Curr Top Microbiol Immunol*. 2006;303:47-65.
116. Laghlali G, Lawlor KE, Tate MD. Die another way: interplay between influenza A virus, inflammation and cell death. *Viruses*. 2020;12:401.
117. Rani JMJ, Kalaimathi K, Vijayakumar S, et al. Anti-viral effectuality of plant polyphenols against mutated dengue protein NS2B47-NS3: a computational exploration. *Gene Rep*. 2022;27:101546.
118. Nelson EO, Ruiz GG, Kozin AF, Turner TC, Langland EV, Langland JO. Focus: plant-based medicine and pharmacology: resolution of recurrent orofacial herpes simplex using a topical botanical gel: a case report. *Yale J Biol Med*. 2020;93:277.
119. Mehrbod P, Safari H, Mollai Z, et al. Potential antiviral effects of some native Iranian medicinal plants extracts and fractions against influenza A virus. *BMC Complement Med Ther*. 2021;21:246.
120. Prasanth D, Panda SP, Rao AL, et al. In-silico strategies of some selected phytoconstituents from Zingiber officinale as SARS CoV-2 main protease (COVID-19) inhibitors. *Indian J Pharm Educ Res*. 2020;54:s552-s559.
121. Opstelten W, Eekhof J, Neven AK, Verheij T. Treatment of herpes zoster. *Can Fam Physician*. 2008;54:373-377.