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Herbal Medication to Enhance or Modulate Viral Infections

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KEYWORDS

• Viral • Herbs • COVID-19 • Immune • Gastrointestinal • Respiratory

KEY POINTS

- With the increase in globalization and ease of travel, being able to prevent and treat viruses has become a big issue in public health. Despite advances in treatment, viruses persist.
- Antimicrobial resistance places a significant burden on the US health system because several regimens with various classes of antibiotics may be required for treatment. This is a global health issue leading to researchers turning to plant-based interventions as a way to combat this problem.
- Herbal medications may provide some antiviral activities and defenses against increased viral load. This exploration also may result in more cost-effective interventions that have the potential to reduce mortality and economic losses.

INTRODUCTION

Viral infections and their emergence continue to impose a threat on human lives. Up to the present time, there have been limited numbers of vaccines that effectively work and few antivirals are licensed for use in clinical practice.[1] Added to this is the increase in antiviral resistance, meaning that drugs that do work are at risk of reduced efficacy.[2] The recent global pandemic of coronavirus 2019 (COVID-19) has provided evidence for the need of a preventative vaccination and effective treatment of viruses, with the United States having passed 9.4 million confirmed cases and a total death rate over 233,000 in November 2020. The aim of this article is to review some traditional treatments of viral infections, specifically addressing gastrointestinal and respiratory system viral infections, and in turn explore alternative herbal medications that are

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Nurs Clin N Am 56 (2021) 79–89
https://doi.org/10.1016/j.cnur.2020.10.007
nursing.theclinics.com

used in their treatment and the role that an advanced practice nurse plays in the administration of these medications. It concludes by addressing potential novel treatments on the horizon for these viral infections.

HERBS AND VIRAL DISEASES

Viruses play an important part in human diseases. With the increase in globalization and ease of travel, being able to prevent and treat viruses has become a big issue in public health. Despite advances in treatment, viruses persist. Vaccinations can take many years to develop after a viral outbreak. This is evident in influenza pandemics as well as the most recent COVID-19 pandemic.[3] As a result of viral evolution and the development of different strains of viruses, the efficiency of vaccines can be short lived.

Exploration of herbal medicines and the role that they play in treatment of viruses is necessary to potentially identify novel antiviral medications. Viruses differ significantly from bacterial infections (**Table 1**). Regarding bacterial infections, herbal treatments were the primary treatment options available before the use of antibiotics, many of which are derived from herbal plants. Overuse of antimicrobials used to treat bacterial, viral, and fungal infections, however, has led to the development of antimicrobial resistance and subsequent difficulty in treating these infections. Antimicrobial resistance places a significant burden on the US health system, because several regimens with various classes of antibiotics may be required for treatment. This is a global health issue, leading to researchers turning to plant-based interventions as a way to combat this problem.

OVERVIEW OF THE IMMUNE SYSTEM

The human body is attacked by millions of different microorganisms, such as bacteria, viruses, and fungi, every second. The human immune system is a complex organization that protects the body from these potential harmful organisms. The immune system performs this essential job in different ways, such as producing antibodies, killing infected cells, marking or killing microorganisms, and causing inflammation.

There are 2 types of immunity responses: innate immunity and adaptive immunity.[4] Innate immunity is inherited from parents and already is present at birth. Innate

Table 1
Differences between bacterial and viral infections

Types of Microorganisms	Virus	Bacteria
Survival	Requires host cell for survival	Living organism
Disease examples	Rhinovirus (the common cold), influenza, acute bronchitis, SARS, MERS, COVID-19, hepatitis A–E	Strep throat, pneumonia, urinary tract infections
Treatment	Vaccinations can help prevent viruses and antivirals can help slow the course of the infection in some cases	Antibiotics
Symptoms	Systemic, fever, and inflammation	Localized but can become systemic

Abbreviations: MERS, middle east respiratory syndrome; SARS, severe acute respiratory syndrome.

immunity is not antigen-specific, meaning it does not have any specialized defense systems for different types of pathogens.[4] Adaptive immunity develops in response to infections over the lifetime. Adaptive immunity is antigen-specific immunity.[4] Adaptive immunity reacts on the pathogens that it recognizes, and it is more potent than innate immunity (**Fig. 1**).[4]

The human self-defense mechanism contains 2 lines: the first line of defense includes physical, mechanical, and biochemical barriers; and the second line of defense includes the inflammatory response.[5] The first line of defense acts like a gateway, which prevents harmful organisms from entering the body. The 2 important parts of this gateway are the mucus membrane and skin.[5] The second line of the defense—inflammatory response—occurs as a response to tissue injury or infection.[5] The inflammatory response consists of many cellular and biochemical defense mechanisms. White blood cells (WBCs), however, play the most important role in the inflammatory response. The normal range of WBCs usually is between 5000 per mm^3 blood and 10,000 per mm^3 of blood.[5] The number of WBCs changes in response to different types of infection. WBCs are made in bone marrow and found in blood and the lymphatic system.

When pathogens pass the first barrier of the immune system—skin or mucus membrane—they enter the body, start using the body's resources, and rapidly increase their numbers. The immune system comes into action after the pathogens reach a certain number. Macrophages, mast cells, and innate lymphoid cells reside in the tissues at the site of the insult; these are the first types of WBCs, which intervene in the defense process.[4] Macrophages can cause inflammation by causing the blood vessels to release water into the infected area. Neutrophils are the next type of WBCs that enter the process of defense. Neutrophils also can kill healthy body cells in the defense process. The other type of WBCs that are involved in the defense process are dendritic cells (DCs). DCs act like the brain of the immune system; they save the data of pathogens in their memory and prepare different antigens.[6] DCs initiate adaptive immune responses.[6] Natural killer cells are the other type of WBCs, which are responsible for killing the body's defective cells, such as tumor cells or virally infected cells. Natural killer cells do not attack pathogens.[4]

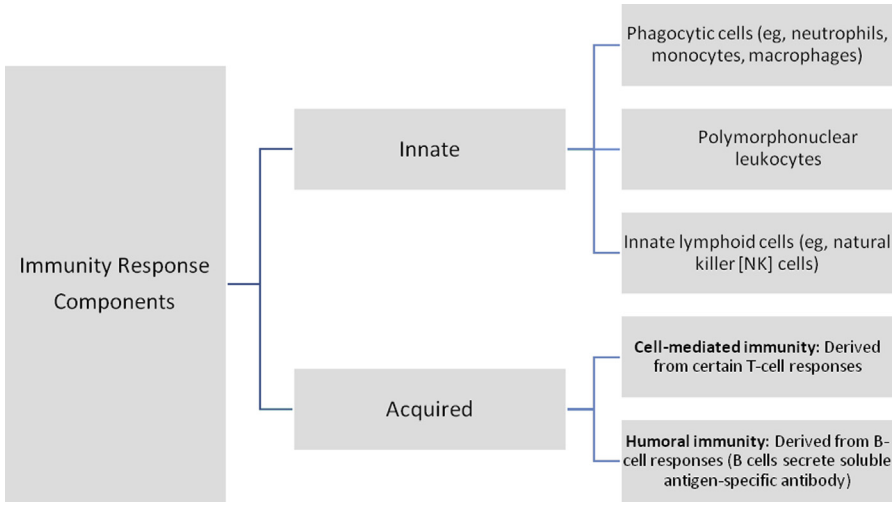

Fig. 1. Types of immunity responses.

The immune system is regulated by regulatory T cells, which secrete immunosuppressive cytokines to help control the immune response.[4] When antigen is eliminated or isolated from the body, the immune response resolves.

RESPIRATORY VIRAL INFECTIONS

Acute respiratory infections (ARIs) are the most common infectious diseases, primarily caused by viruses, and present clinically as upper respiratory tract infections and lower respiratory tract infections (LRIs). In 2014, LRIs were reported as the leading cause of deaths in the United States,[7] and influenza and respiratory syncytial virus (RSV) also are known to cause a high number of deaths.[8] When looking at the influenza virus, a majority of deaths across the world occur in people aged 65 years or older.[9] The United States was estimated to have had up to 62,000 deaths from influenza between October 2019 and April 2020.[10]

Current management for influenza consists of preventative vaccinations and treatment with antivirals. Both approaches have their limitations due to the virus' ability to mutate every year. These leaves the door open to the potential for pandemics of certain strains of the virus.[11] The neuraminidase inhibitors, zanamivir and oseltamivir, used in the treatment of influenza A, both have been found to reduce the duration of the symptoms in some cases but have not been found to be helpful when administered to healthy patients after 2 days of the start of symptoms.[12] There is an increasing amount of evidence to show that influenza viruses are becoming resistant to these neuroaminase inhibitors.[13] As a result of this and the significant possibility of many people losing their lives in the period between the virus mutation and development of a new vaccine for specific strains, which can take many months, the exploration of herbal medication as a means of management of influenza could be deemed reasonable. Many ancient civilizations used herbal medicines in order to both prevent and treat colds and influenza infections.[14]

In Japan, the use of the maoto has been administered traditionally to influenza patients. Maoto is a Kampo medicine, also known as a Japanese herbal medicine, composed of 4 medicinal herbs. A randomized controlled trial showed maoto granules given to patients with influenza had an equal efficacy to the neuraminidase inhibitors, zanamivir and oseltamivir.[15] Another herbal product that has been tested for use in individuals with influenza is echinacea. A randomized controlled trial conducted in the Czech Republic found that Echinacea was an early treatment given patients clinically diagnosed with influenza and was equally as effective as oseltamivir.[16] Traditional Chinese medicine (TCM) long has been studied for its therapeutic effect on influenza, and China continues to be a rich source for the production of novel antiviral medications. The TCM maxingshigan-yingiaosan (composed of 12 different herbal medicines) was studied in comparison to oseltamivir, as well as used in combination with oseltamivir, and both alone and together was found to reduce the time in which fever resolution occurred in comparison to patients receiving no treatment,[17] potentially suggesting that TCMs can be used as an alternative therapy in patients with mild forms of the disease. This study did not make clear whether the effects of the TCM were antipyretic or antiviral, however. Another benefit that was suggested promoted the use of TCMs, which were more economical than the use of Western medicine.[18] In order to consider the use of TCM in the practice of Western medicine, it is fundamental to understand their key ingredients and the effect that they have in order for their use to be evidence based as opposed to experienced based.[19] A recent animal study looking into Bai Shao, a Chinese herb, also known as Radix Paeoniae Alba, the white peony root, identified 3 compounds which it isolated from the herb. These 3 compounds were found to

inhibit the activity of the influenza A virus in Madin-Darby canine kidney cells, leading to evidence for its use in clinical treatment of influenza.[20]

ARIs as a result of viruses are the primary cause of mortality and morbidity in children globally. One of the most major viruses causes ARIs in children is RSV. It is estimated that in the United States alone between 65,000 and 125,000 of children aged 2 years and under are hospitalized with the virus annually, with an estimated number of 65,000 deaths globally.[21] Ribavirin currently is the only approved antiviral used in the treatment of RSV. Currently, cost-effective and easily administered vaccinations and antivirals for the treatment of RSV are unavailable and, therefore, searching for a novel treatment of RSV is vital and herbal medicines provide a rich resource for this. A recent study researching the effects of the herbs, *Plantago asiatica* and *Clerodendrum trichotomum*, demonstrated that they had potential as antivirals in the treatment of RSV.

GASTROINTESTINAL VIRAL INFECTIONS

It is well known that hepatitis B can increase the risk of developing hepatocellular carcinoma, a leading cause of deaths due to cancer worldwide. Although hepatitis B currently is treated with antiviral drugs, its diagnosis often is associated with increased risk of hepatocellular carcinoma. Curcumin is an herbal medicine, derived from the plant turmeric, thought to possess anti-inflammatory and anticancerous activity without toxic side effects, with some studies showing that it may be useful in the prevention of hepatocellular carcinoma development from hepatitis B.[22] Many studies also have found that phytomal curcumin displayed promise in its ability to inhibit the growth of hepatocellular carcinomas through several different mechanisms, including the inhibition of vascular endothelial growth factor expression,[23] the protein associated with triggers the formation of blood vessels in cancer.

In Europe, it has been found that an estimated 52% of children use some form of complementary and alternative medicine (CAM), more specifically, herbal medicine.[24] The management of gastrointestinal disorders in both adults and children is particularly challenging and in more severe cases can lead to hospitalization. Many patients seek help from their practitioners; however, many treatments can be effective but lead to unwanted adverse effects and others may have fewer undesirable outcomes but may be less effective in treatment. A study looking into the reasons as to why parents give their children natural herbal medicine concluded that the primary reason was safety. Parents associated natural health products with being safe and, therefore, parents were more inclined to give them to their children as treatment.[25]

Every year in the United States, on average, norovirus is responsible for 109,000 hospitalizations and approximately 900 deaths (mainly in the ages 65 years and older population).[26] Due to the current lack of a vaccine for prevention of norovirus, preventative measures, such as good personal hygiene for food handlers, currently is recommended, but these have their limitations, such as increased expense of equipment and potential toxic effects from chemical exposure. Therefore, there is an increase in demand for more environmentally friendly chemicals. A study into the effect of 18 phytochemicals on norovirus found that curcumin and resveratrol were the top 2 most effective phytochemicals as antinoroviral agents.[27]

A recent review of herbal medicines and their effect on gastrointestinal disorders showed some positive results in their treatment, but the main limitation continues to be lack of clinical trials and, therefore, a lack of evidence-based information, preventing their use being recommended by medical practitioners and as a result, leading to the use of herbal medicines being primarily patient led.[28]

IDENTIFICATION OF VIRAL VERSUS BACTERIAL INFECTIONS

A major health issue in the United States and globally is antimicrobial resistance, in particular, antibiotic resistance. The primary cause of this antibiotic resistance is over-prescription by health care professionals and, therefore, overuse by patients, when in many cases the infection is not bacterial. It is estimated that antibiotics are prescribed unnecessarily in 30% to 50% of patients in hospital settings.[29]

Earlier detection and a more accurate diagnosis of these infections can allow for the prescription of antibiotics sooner for patients who need them as well as reducing over-prescription where unnecessary. It can be a challenge for health care professionals to distinguish between viral and bacterial infections because many of the symptoms present similarly. Currently, blood cultures, urine cultures, or spinal cultures as well as taking a thorough history can be used in order to diagnose a bacterial infection. The use of cultures enables profiling of pathogens from the blood; however, these tests sometimes can be limited because they are able to detect only a certain number and type of pathogens.[30] One study developed 7 genes as a means of discriminating between viral and bacterial infections, with 94% sensitivity and 59.8% specificity; further clinical authentication is required in order for this to be input into clinical practice.[30] Another recent study identified 11 genetic biomarkers in the blood that were successful in distinguishing between viral and bacterial infection 80% to 90% of the time. Although the main limitation of this study was the small sample size (94 adults), the findings still are significant and identify a potential means of reducing the unnecessary use of antibiotics which, should this move forward, would enable health care professionals to proceed in their treatment plan confidently in not using antibiotics.[31]

ROLE OF ADVANCED PRACTICE NURSE IN THE PRESCRIPTION OF HERBAL TREATMENTS

There still is debate as to whether nurse practitioners and other health care providers should be prescribing herbal medicine. One recent article discussed the points for and against the prescription of CAM, which herbal medicines can be classified as.[32] One argument for nurse practitioners learning about CAM as part of their training and being able to prescribe herbal medicines is that people who are choosing to use them often do so alongside the use of prescribed conventional medicine, often without telling their health care providers that they are doing so. This poses many problems, including the risk of potentially harmful interactions and contraindications. Therefore, it can be argued that it should be a mandatory part of a nurse practitioner's training to have an adequate level of understanding of potential side effects and uses of the herbal medicine or other CAM that patients may be taking, in order to design a safe treatment program with this in mind.[33]

Having said this, there also are many disadvantages to nurses being taught about CAM and prescribing herbal remedies to their patients. Primarily, there is extremely little evidence for CAM, meaning that even if they were to try and attempt to familiarize themselves with side effects and interactions, the lack of evidence would not permit this. As well, there are a huge number of concepts to CAM, making it difficult to make it part of a nurse practitioner's curriculum for training. Some investigators argue that it may be useful for nurse practitioners to refer to CAM practitioners, such as chiropractors or massage therapists, where they feel it would be beneficial.[32] In cases of herbal medicines, however, due to such a lack of evidence, many would agree that prescription of them without first knowing about their mechanism of actions, side effects, and contraindications absolutely should not be permitted and from the researched, discussed previously in this article, many successful findings often are in very early stages of research.

POTENTIAL TREATMENTS ON THE HORIZON

Despite development of various vaccines and therapeutic drugs, novel, mutant and resistant virus strains reduce their effectiveness. In an effort to increase possible interventions, alternative treatment options are important to explore. Herbal medications may provide some antiviral activities and defenses against increased viral load. This exploration also may result in more cost-effective interventions that have the potential to reduce mortality and economic losses.

A stage in the influenza cascade is the fusion of viruses with a host cellular endosomal membrane. This activity is promoted by low endosomal pH.[34] Vacuolar ATPase (V-ATPase) has been identified as a requirement for influenza replication.[35,36] This V-ATPase activity is responsible for pumping protons into endosomal compartments. Endomembrane organelle lumens, such as lysosomes, endosomes, secretory granules, and the Golgi apparatus, are acidified by V-ATPase. This acidification process is required for the influenza virus to enter the cell. It also has been reported that influenza viruses actually enhance V-ATPase function in order to promote infectivity.[37]

Maoto

Maoto is a traditional Japanese herbal medication that has been investigated for its effect on the influenza virus.[38] This herb traditionally is prescribed for upper respiratory infections or febrile diseases of an acute nature.[39] Maoto extract is developed from 4 plants: (1) ephedra herb (ratio 32.3% by weight), (2) apricot kernel (ratio 32.3% by weight), (3) cinnamon bark (ratio 25.8% by weight), and (4) *Glycyrrhiza* root (ratio 9.6% by weight).

It is hypothesized that maoto may have an effect on V-ATPase. The 2 components in maoto identified as having significant antiviral effects are cinnamon bark and ephedra herb. Their effects block the influenza uncoating process. This occurs through V-ATPase inhibition.[38] V-ATPases hydrolyze adenosine triphosphate to drive a proton pump. V-ATPases are key to various vital intracellular and intercellular processes, which include active metabolite transport, homeostasis, and neurotransmitter release.

Diphyllin

Diphyllin has been identified as a V-ATPase inhibitor. It can inhibit lysosomal acidification in osteoclasts.[40] Diphyllin is a natural compound isolated from the leaf extract of the *Cleistanthus collinus* plant. There has been an inhibitory effect of diphyllin against various viruses because research identified that it dose-dependently quenched acidic cytoplasmic vesicles within 20 minutes of incubation time. As a result of this finding, diphyllin could interfere with low pH–dependent membrane fusion that occurs between a specific virus and intracellular endosomes.

Diphyllin alters cellular-demonstrated susceptibility to the influenza virus and may have broad-spectrum antiviral activity, making it capable of addressing various viruses. This V-ATPase inhibitor has a safe therapeutic window. This suggests it as a potential broad-spectrum antiviral agent of high potency and lox toxicity.[41]

KIOM-C

KIOM-C is a total aqueous extract preparation that has shown promise in animal research. KIOM-C consists of the following: *Scutellariae Radix*, *Glycyrrhizae Radix*, *Paeoniae Radix Alb*a, *Platycodon grandiflorum*, and *Ziniberofficinaletc.*[42] Research on mice demonstrated a reduction of viral titers and viral replication. KIOM-C induced antiviral states of significant strength to promote survival in mice against influenza A.[43] The KIOM-C formulation has been shown to have immune-enhancing and immune-regulatory effects.[44,45]

KIOM-C may be a feasible alternative antiviral therapeutic agent. It has demonstrated an ability to disrupt viral infection through type I interferon signaling molecules and proinflammatory cytokine activation. Based on in vivo results, treatment with KIOM-C can reduce influenza-induced mortality. This reduction occurred through its viral replication disruption and viral infection prevention by creation of an antiviral state in the lungs.[43] Additional research could expand identification of specific ingredients that induce antiviral effects as well as specific dose ranges for the best antiviral response. This ability to disrupt viral infection potentially could promote future use of KIOM-C in humans as an antiviral agent.[46]

Several viruses enter target cells based on pH. These include flaviviruses,[47] rhabdoviruses,[48] and coronaviruses.[49] Blocking V-ATPase activity by an intervention of herbal medicines may present an opportunity to impede influenza infections by preventing low pH–dependent membrane fusion. Virus replication also occurs and interfering with this replication could reduce viral load.

As viruses continue to evolve, vaccinations and other treatments based on predicted circulating strains are not as effective. These evolutions can render preexisting antibodies in the circulatory system from any earlier exposure ineffective. It is imperative to continue research to identify natural anti-influenza agents to expand the drug portfolio for clinical application. In addition to the use of herbal medicines in isolation, exploration of combination therapies in antiviral management also is important to investigate.

SUMMARY

The use of herbal medicines is particularly high in developing countries, meaning that a large percentage of the world's population relies on herbal medicine for at least primary health care. The research and evidence of some success in treating viral infections with herbal medicine, discussed previously, brings into question why it is not used more frequently as approved treatments in the developed world. One main reason is the lack of testing and little monitoring of patients' use of these medicines, meaning that their mechanisms of action and reason for sometimes effectively treating viruses, if at all, remains unknown.[33] Having said this, a recent study found that the prevalence of herbal medicine use in the United States is approximately 33%; with patients with more chronic conditions, such as stroke, cancer, and arthritis, found more likely to use them than those without.[50] This study also found that the main consumers of herbal medicine in the United States often use them alongside prescription and nonprescription medications. With this in mind, herbal ingredients appear to be a rich resource for the use of potential antivirals and the need to identify active ingredients, mechanisms of action, and potentially harmful side effects is necessary to move forward with incorporating their use into the health care system. Even if herbal medicines are not a cure, they may buy precious time in protecting and preserving life.

CLINICS CARE POINTS

The immune system becomes less effective with aging in different ways:

- Autoimmune disorders become more common as the immune system's ability in distinguishing self from non-self is reduced.[4]
- The number of lymphocytes that can respond to new antigens decreases—T cells respond more slowly to antigens.[4]
- Aging slows down the macrophages ability to destroy bacteria, cancer cells, and other pathogens. This can be a contributing factor to increased cancer incidence in older adults.[4]

DISCLOSURE

The authors have nothing to disclose.

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