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Antiviral Activities of Polysaccharides from Medicinal Herbs

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Abstract

For thousands of years, medicinal herbs have been a cornerstone of clinical practice, offering a wealth of health benefits. Among these benefits, the antiviral properties of polysaccharides found in these herbs are now gaining recognition. This review provides an in-depth exploration of the antiviral effects of these polysaccharides on viruses affecting humans. It delves into how these polysaccharides inhibit various stages of the viral life cycle, effectively preventing viral infection. Furthermore, the review discusses additional mechanisms through which these polysaccharides exert antiviral effects, such as bolstering immune responses, regulating inflammatory reactions, maintaining gut flora balance, reducing oxidative stress, and inhibiting apoptosis through specific signaling pathways. The article also examines the structure-function relationships of natural polysaccharides, providing critical insights into their antiviral mechanisms and emphasizing the importance of further comprehensive research and analysis. The review underscores the potential of polysaccharides from medicinal herbs as compelling candidates for combatting viral infections in both humans and animals.

Keywords*: Antiviral, Medicinal Plant, Polysaccharides*

Introduction

In recent years, significant progress in science and technology has led to advancements in vaccines and treatments for viral infections [1]. Despite this progress, there has been a surge in viral diseases, causing harm to animal and human health. For instance, the coronavirus disease 2019 (COVID-19) has resulted in a substantial number of cases worldwide, with high infection and mortality rates. Viral diseases in animal farming also pose risks to animals and humans and lead to economic losses. Preventing and treating viral infections is challenging due to viruses' complex life cycle and structure. Immuno-prophylaxis, such as vaccination, has been widely accepted as an effective strategy for controlling viral infections. For example, COVID-19 vaccines have shown efficacy rates ranging from 50% to 95% in clinical trials, with real-world effectiveness ranging from 83.8% to 95.3% across various populations. However, the efficacy of vaccines for diseases like porcine epidemic diarrhea virus (PEDV) depends on multiple factors and has been a cause for concern due to frequent mutant strains [2, 3].

Antiviral medications play a crucial role in managing viral infections. Some antivirals function by preventing viral replication or modifying the immune response, but they may be ineffective against new viruses. Additionally, certain medications initially considered effective for COVID-19 have yet to demonstrate conclusive evidence of their efficacy. Researchers are exploring herbal medicines as potential solutions for preventing and treating COVID-19. Traditional Chinese Medicine (TCM) has shown promising results in treating COVID-19, and herbal remedies may enhance immune function and reduce symptoms [4]. Integrating TCM treatments with

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conventional antiviral therapies could improve efficacy and reduce side effects.

Antiviral Activities of Polysaccharides

Natural products, particularly natural polysaccharides, have gained importance in drug discovery and development. These polysaccharides, derived from various sources such as plants, algae, and fungi, exhibit diverse activities, including antiviral, immune-modulating, antimicrobial, and antioxidant properties with minimal side effects [5]. Some natural polysaccharides have gained approval for clinical use and are used in treating conditions like acute viral myocarditis in children.

Influenza, also known as the flu, is a highly contagious viral infection primarily affecting the respiratory system. It is caused by influenza viruses, with the most common types being influenza A virus strains such as H7N2, H5N1, and H1N1 [6]. These viruses can lead to various symptoms, causing seasonal epidemics and occasional pandemics. The 1968 flu pandemic, caused by the H3N2 strain of the influenza A virus, was a global outbreak, infecting an estimated 500 million people worldwide and resulting in approximately one to four million deaths [7]. A monovalent vaccine containing the A2 Hong Kong strain was developed relatively quickly in September 1968, helping to mitigate the pandemic's impact [8]. However, the virus continues to circulate and causes seasonal flu outbreaks. Supportive care and symptom management were the primary treatments, as specific antiviral drugs were unavailable. Only a few people were given interferon for protection against influenza A viruses. It wasn't until later decades that interferon became more widely studied and used to treat various viral infections and other medical conditions. Researchers are studying natural polysaccharides for their potential therapeutic effects against influenza viruses. *In vitro*, studies have indicated that polysaccharide extracts from *Radix isatidis* exhibit beneficial effects against seasonal influenza virus strains like H3N2 and H1N1[9].

Research has demonstrated that specific polysaccharides, such as Aloe polysaccharides (APS), *Astragalus* polysaccharides (APS), *Houttuynia cordata* polysaccharides (HCP), and *Tamarix chinensis* polysaccharide, have shown promise in mitigating damage and symptoms associated with H1N1 and IAV infections in mouse models. Additionally, Ginseng polysaccharides and Asarum polysaccharides have been found to improve survival rates in mice infected with IAV [10]. Some polysaccharides have resisted H1N1 IV infection, while others have displayed potential antiviral effects against H5 or H7 strains [11]. Respiratory Syncytial Virus (RSV) primarily affects individuals with weakened immunity, and specific polysaccharides have demonstrated excellent anti-RSV activities [12]. Moreover, herbal polysaccharides have been found to inhibit herpes simplex virus (HSV) *in vitro* [13]. Enterovirus 71 (EV71) is responsible for hand, foot, and mouth disease (HFMD), primarily affecting young children [11]. Polysaccharides derived from *Sanguisorba officinalis* (SO) have shown notable antiviral effects by significantly suppressing viral gene expression and preventing Vero cell death induced by EV71. In hSCARB2-transgenic mice, SO polysaccharides were found to alleviate body weight loss and paralysis and enhance survival rates [14]. Additionally, in vitro antiviral testing of GuiQi polysaccharides (GQP) demonstrated effective anti-EV71 activity at a concentration of 31.2 μg/mL [15]. Human Hepatitis B virus (HBV) is a highly infectious pathogen that primarily targets the liver, leading to cirrhosis, hepatocellular carcinoma, and other chronic liver diseases [16]. POP1 extracted from *Platycladus orientalis* (L.) Franco leaves exerted anti-HBV capacity by reducing HBeAg and HBsAg expression and inhibiting HBV DNA proliferation. Similarly, *Radix isatidis* polysaccharide (RIP) demonstrated beneficial effects on HepG2.2.15 cells against HBV infection by suppressing intracellular and extracellular HBeAg and HBsAg, as well as interfering with HBV DNA replication in a dose- and time-dependent manner [17]. Furthermore, RIP could enhance the production of interferon (IFN)-α through activating Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal pathway, as evidenced by elevated protein expressions of p-

Tyrosine kinase (TYK)2, p-JAK1, p-STAT-2, p-STAT-1, Mx, and oligoadenylate synthase (OAS)1 in HepG2.2.15 cells [17]. Human noroviruses are the predominant foodborne etiological agents causing globally widespread acute gastroenteritis, characterized by vomiting and diarrhea [18]. The outcomes of the plaque assay revealed that *Houttuynia cordata* polysaccharide (HCP) effectively reduced murine norovirus-1 (MNV-1), used as a surrogate for human noroviruses, to be undetectable *in vitro* [19]. Studies have found that specific versatile natural polysaccharides can inhibit various human viruses. Purified pumpkin polysaccharides have shown strong inhibitory effects on human immunodeficiency virus (HIV), HSV1, adenoviruses (ADV)7, and hepatitis C virus (HCV). Astragalus polysaccharides (APS), known for their biocompatible, biodegradable, and non-toxic properties, have attracted significant attention in natural polymers due to their therapeutic potential for treating various diseases [20]. In the context of COVID-19 infection, APS extracted from *Astragalus membranaceus* is considered a promising candidate for integration into pharmaceutical formulations and developing novel therapeutic interventions. Additionally, APS has demonstrated notable efficacy in enhancing survival rates and alleviating chronic myocardial fibrosis and dilated cardiomyopathy in viral myocarditis caused by coxsackievirus B3 (CVB3). Furthermore, APS exhibited significant suppression of the expression of Zta, Rta, and early antigen diffuse component (EA-D) during the lytic cycle of Epstein-Barr virus (EBV) (Figure 1).

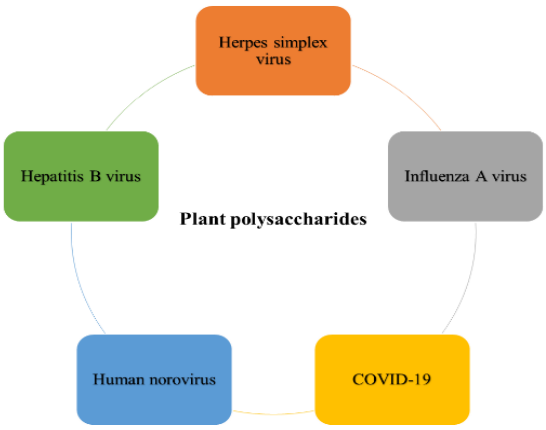

Figure 1. Antiviral Activities of Polysaccharides

Structural Relationship Antiviral Activities of Polysaccharides

The efficacy of natural polysaccharides is contingent upon their stereochemistry, sugar linkages, and composition [21]. Polysaccharides obtained from medicinal herbs typically contain sugars such as arabinose, glucose, galactose, rhamnose, mannose, and galacturonic acid [17, 22]. These polysaccharides often feature a backbone with small branches or remnants, characterized by a porous and uneven surface [23]. An example is the polysaccharide POP1 isolated from *Platycladus orientalis* (L.) Franco leaf, which consists of galactose (6.55%), glucose (64.96%), mannose (10.97%), arabinose (12.58%), and rhamnose (5.74%) with specific linkages and terminal residues [24]. The structural details of these polysaccharides play a pivotal role in their antiviral effectiveness, possibly by impeding the attachment of viruses, bacteria, and protozoa through specific carbohydrate units such as 1,4-linked Galp A [25].

Houttuynia cordata polysaccharide (HCP), primarily composed of xylose, glucose, galactose, and galacturonic acid, is presumed to hinder virus penetration via its core 1,4-linked Galp residues and exhibit anti-inflammatory properties [26]. Additionally, certain polysaccharide compositions, such as mannose-rich polysaccharides, may

effectively modulate immune responses, while high molecular weight and complex branching structures could influence gut flora and oxidative stress (Figure 2). The sulfate content within natural polysaccharides also contributes to their antiviral properties, as evidenced by the sulfate content in PSP-2B, extracted from *Prunellae Spica*. Despite these potential benefits, the complicated nature of these compounds pose significant challenges, warranting further research to identify specific polysaccharides with antiviral properties. Understanding the interaction between polysaccharides and viral proteins or host cell receptors, as well as the impact on immune responses, inflammatory reactions, gut flora, oxidative stress, and apoptosis, is crucial for comprehending their mechanisms of action [27].

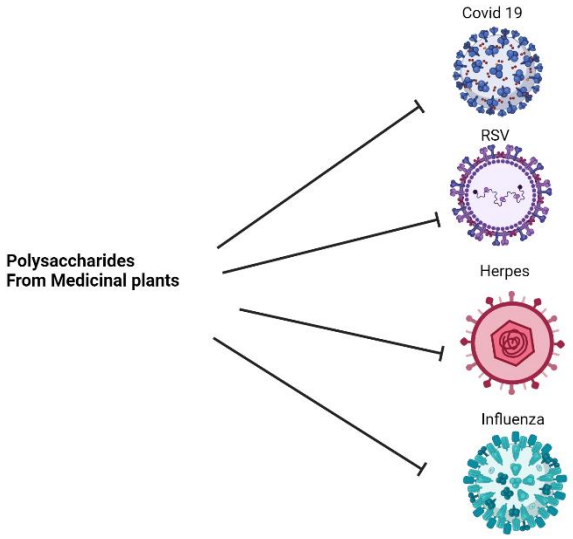

Figure 2. Antiviral Activities of Polysaccharides from Medicinal Plants

Antiviral Drug Development and Challenge

Numerous viral infections have been successfully controlled through widespread vaccination campaigns, exemplified by the global eradication of smallpox [28, 29]. Despite these achievements, vaccines do not guarantee universal protection against all viruses, underscoring the necessity for alternative antiviral treatments [30]. This includes the imperative need to pursue the development of a vaccine for HIV and other challenging viral diseases [31]. Two primary approaches are utilized in developing antiviral drugs: one targeting the viruses directly and the other aiming at host cell factors. Antiviral medications that directly target viruses include inhibitors that hinder virus attachment and entry, uncoating inhibitors, polymerase and protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, and integrase inhibitors. However, challenges exist for molecules affecting internal viral cycle steps, as they must effectively penetrate cells. These challenges include the need for specific delivery systems that can transport the drugs across cell membranes and the potential for off-target effects [32]. An alternative approach involves targeting essential cellular proteins involved in the viral cycle. During the early stages of the antiviral era, antiviral compounds were often discovered without a clear understanding of their specific targets or mechanisms of action [33]. For example, 5-iodo-2′-desoxyuridine (IDU), initially synthesized as a potential antitumor agent, was later identified as a particular inhibitor of certain DNA viruses, particularly the herpes simplex virus, making it the first commercialized antiviral drug used in the topical treatment of herpetic eye infections. Similarly, thiosemicarbazones

demonstrated antiviral properties against the poxvirus vaccinia virus in the 1950s, leading to the development of methisazone in the 1960s to prevent and treat smallpox caused by the variola virus. Another significant example is acyclovir, which functions as a substrate for thymidine kinase encoded by herpes simplex virus (HSV) and inhibits viral DNA synthesis with minimal adverse effects. Over the six decades since the inception of antiviral agents, more than 50 antiviral medications have been developed. Most of these drugs are utilized in HIV treatment, while others target herpesviruses (HSV, VZV, CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), and influenza virus infections. Nucleoside analogs constitute a significant portion of antiviral drugs, enabling competitive inhibition during virus genome replication [34].

Novel antiviral drugs must meet specific ADME (absorption, distribution, metabolism, and excretion) properties and fulfill criteria such as low molecular weight, good solubility, minimal side effects, ease of administration, cost-effective production, and rapid elimination from the body. Unfortunately, many potential therapeutic substances fail during development due to severe adverse effects [35]. The cost-effectiveness of production and commercialization is critical, especially for viral diseases prevalent in developing nations, such as HIV, which accounts for a significant number of deaths. While many compounds demonstrate in vitro antiviral activity, they often impact host cell functions and possess a low therapeutic effect-toxicity ratio, which is a measure of the balance between the therapeutic effect and the drug's toxicity, for humans, preventing them from entering the market. An antiviral substance must achieve a high therapeutic index that balances inhibiting cell functions and blocking viral replication for practical use. Antiviral treatment faces obstacles such as not disrupting normal cellular metabolism, the inability to eliminate latent viral infections, and the genetic variability of viruses leading to resistance against antiviral drugs [36]. The development of resistance is primarily due to the genetic variability of the virus and the specific action of antiviral drugs used, potentially resulting in treatment failures. It is crucial to detect resistance early. One strategy to combat this is using drugs from different therapeutic classes for a single virus to prevent the emergence of resistant mutants. Antiviral drugs targeting viral proteins are more specific but have a narrow spectrum of activity, increasing the likelihood of drug resistance. Conversely, drugs targeting cellular proteins have a broader activity spectrum but higher toxicity levels and reduced chances of resistance development [36].

Conclusion

The escalating incidence of viral diseases in both human and animal populations poses significant health and economic development challenges. Natural polysaccharides derived from medicinal herbs have surfaced as practical tools in combatting viral infections due to their potent antiviral properties with minimal toxicity. These polysaccharides have exhibited the potential to disrupt various stages of the viral life cycle, thereby preventing virus infections in animals and humans. Additionally, they have been shown to bolster immune responses, regulate inflammatory reactions, maintain gut flora balance, minimize oxidative stress, and inhibit apoptosis through associated signaling pathways. Understanding the interaction between polysaccharides and viral entry mechanisms is crucial for identifying effective targets. Shedding light on the specific polysaccharide structures that impede viral attachment and entry into host cells will aid in the discovery of more promising antiviral therapies. Moreover, delving into the role of polysaccharides in modulating immune responses is essential, considering the pivotal role of the immune system in combatting viral infections. Identifying polysaccharide structures that enhance immune responses could hold significant therapeutic benefits. The findings summarized in this review underscore the promising potential of polysaccharides from medicinal herbs as candidates for mitigating viral infections. A thorough investigation into the structure-function relationships of these polysaccharides will deepen

our understanding of their antiviral mechanisms. Further comprehensive research in this field is warranted, and additional *in vitro* and *in vivo* experiments and clinical trials are necessary in the future. Exploring these natural compounds further carries great promise for developing novel antiviral therapies and strategies to safeguard human and animal health against viral threats.

Conflict of Interest

None.

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