



The role of Honeysuckle-derived microRNA2911 in control of viral infections

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ABSTRACT

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MicroRNAs (miRNAs) are non-coding RNA that plays prominent roles in gene regulation mechanisms. Honeysuckle decoction (HD) extract has miRNA-2911 (miR-2911) and may be absorbed into the gastrointestinal (GI) system via SID transmembrane family member 1 (SIDT1) receptors. Several studies have shown inhibitory effects of miR-2911 on NA, PB2, and NS1 proteins of influenza virus (flu), VP1 of enterovirus 71 (EV71), IE62 of varicella-zoster virus (VZV), and SARS-COV-2 (SCOV-2) proliferation. MiRNA-2911 has the potential to change how these viruses are treated and controlled by employing herbal substances instead of chemical medications. This could be a new step in controlling viral infections but requires further studies.

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1. Introduction

Noncoding RNAs (ncRNAs) constitute a sizable portion of the transcriptome that is not translated into a protein. They play critical roles in the regulation of various cellular processes as well as disease progression [1, 2]. Small noncoding RNAs are RNA molecules that are less than 200 nucleotides (nt) in lengths, such as microRNA, tRNA-derived small RNA, small nuclear RNA, and Piwi-interacting RNA [3].

By inhibiting mRNA translation or degradation, microRNAs (miRNAs), which have an average length of 21–23 nucleotides, play a critical role in the control of gene expression and are crucial for processes like evolution, proliferation, and apoptosis [4]. RNA polymerase II (Pol II) largely produces primary miRNA transcripts from canonical miRNAs (pri-miRNAs). The nuclear RNase III Droscha has the ability to split Pri-miRNA into precursor-miRNA (pre-miRNA), which is then cut by the cytoplasmic RNase III Dicer to produce mature miRNAs [5, 6].

Numerous miRNAs have been identified in animals, plants, and viruses and have been found to play significant roles in development and disease since the discovery of the first miRNA (*lin-4*) in 1993 by the collaborative efforts of Victor, Ambros, and Gary Ruvkun's laboratories in *Caenorhabditis elegans* [7, 8]. One of the most powerfully absorbed sRNAs among all plant sRNAs, including miRNAs, has been identified as miRNA-2911 (MiR-2911) [9]. In this section, we will examine the function or effects of miR-2911 in the inhibition of some viral diseases in order to develop novel therapeutic methods.

2. Cross-kingdom RNA interference (RNAi)

Herbal medicines and supplements can be used as an alternative treatment for infectious diseases [10]. Cross-kingdom RNA interference (RNAi) is a biological process that occurs when plants transfer small regulatory RNAs to pathogens, which results in gene silencing in the recipient organism [11]. Recent research has revealed that dietary plant miRNAs can survive in the gastrointestinal (GI) tract, enter the circulatory system, and regulate the expression of endogenous mRNAs [12]. Zhang et al. demonstrated that plant miRNAs could be found in the serum of humans and animals that consume plants and use them to regulate gene expression [13]. Zhou et al. later demonstrated that Honeysuckle-derived microRNA-2911 could be taken up through the GI tract and used to access host cellular targets [14]. Several studies have shown that miR-2911 can play an important role in virus control, including Influenza A virus (IAV), SARS-COV-2 (SCOV-2), varicella-zoster virus (VZV), and enterovirus 71 (EV 71) [14–18]. It's worth noting that HD has been used to treat viral infections in China for over a thousand years [16].

3. Honeysuckle plant

Honeysuckle (*Lonicera caerulea* L) is a member of the Caprifoliaceae family. It contains a high concentration of organic acids, flavonoids, iridoid glycosides, saponins, and volatile oils. These compounds have demonstrated a diverse range of biological and pharmacological activities, including antibacterial, antiviral, antioxidant, and anti-inflammatory properties. The plant is widely used in traditional medicine, particularly in Japan, and is notable for its anti-aging properties as well as its ability to protect against heart disease and gastrointestinal issues. Scientific studies have confirmed the cardioprotective, neuroprotective, anticancer, anti-inflammatory, Antimicrobial, and anti-diabetic properties of honeysuckle. The aforementioned characteristics are mostly associated with primarily phenolic compounds such as anthocyanins, chlorogenic acid, and quercetin. It has also been demonstrated that phenolic extracts can effectively inhibit microbial adhesion and thus prevent a variety of infections, including mouth and urinary diseases [19].

4. MicroRNA 2911 (miR-2911)

MiR-2911 is an atypical miRNA found in honeysuckle decoction (HD) that does not go through traditional miRNA biogenesis and is derived from ribosomal RNA (rRNA). This miRNA self-assembles into exosomes, which are then injected into various organs of mice, containing the spleen, lung, liver, pancreas, and T cells [14, 16].

MiR-2911 is more bioavailable due to three characteristics. 1) A numerous GC content contributes to its digestive stability; 2) a protein complex improves MiR-2911 stability and dietary uptake, and 3) rRNA degradation increases MiR-2911 abundance [14, 16].

5. Influenza virus (Flu)

The four genera of influenza viruses—influenza A virus (IAV), influenza B virus (IBV), influenza C virus (ICV), and influenza D virus—are enveloped viruses that belong to the Orthomyxoviridae family (IDV) [20]. These viruses are enveloped viruses with a single-stranded, negative-sense RNA genome that has been segmented [21]. Influenza viruses are significant human pathogens that cause yearly epidemics and rare pandemics of respiratory tract disease. Despite the availability of vaccines and antivirals, humans experience a wide range of clinical disease severity [22, 23].

Zhou et al. demonstrated that plants containing miR-2911 directly target IAV, including H1N1, H5N1, and H7N9 subtypes, by binding to virus-encoded PB2 and NS1 protein expression and thus inhibiting viral replication [14]. A recent study discovered that HD acids and flavonoid extracts inhibit the NA of the influenza virus H7N9. According to HD's major antiviral active compo-

nents, it has the potential to be developed as an antiviral agent for influenza viruses, particularly those resistant to oseltamivir [17].

6. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

On February 12, 2020, a novel flulike coronavirus (2019-nCoV), named SCoV-2 (lineage B CoV) by the ICTV *Coronaviridae* Study Group, emerged in the city of Wuhan, China, and caused coronavirus disease 2019 (COVID-19) [24]. According to the World Health Organization (WHO), as of March 29, 2022, there are over 481 million confirmed cases worldwide, with over 6 million deaths [25]. Because of the virus's high outbreak and the lack of definitive treatment, herbal medicines can effectively control it [26]. Several studies have shown that HD-miR2911 plays a role in pandemic control [16, 27, 28]. Zhou et al. discovered that SID1 transmembrane family member 1 (SIDT1) in the gastric pit cell membrane mediates dietary HD-miR2911 absorption into cells in an intriguing study. This microRNA forms exosomes, which are then released into the bloodstream and transported to target organs such as the liver, lung, spleen, pancreas, and T cells. MiR-2911-containing exosomes significantly reduced S-protein expression [28].

7. Varicella zoster virus (VZV)

VZV is a member of the Herpesviridae family's Alpha-herpesvirinae subfamily [29]. The virus is extremely contagious and spreads through the respiratory system [30]. Varicella (chickenpox) in childhood and herpes zoster (HZ) in adulthood is caused by VZV infection. When an individual's immune system is suppressed, VZV can remain latent in the cranial nerves and dorsal root ganglions and reactivate, resulting in HZ [31].

VZV's genome is made up of a 125-kbp linear double-stranded DNA molecule with at least 70 annotated open reading frames (ORFs). The VZV IE ORF62 gene functions as a transactivator, controlling the demonstration of other viral genes [32].

Huang et al. found that MiR-2911 targets VZV in vitro (MRC-5) and inhibits VZV replication by targeting the IE62 gene [18]. MiR-2911 could be a new treatment for VZV infections.

8. Enterovirus 71 (EV71)

Enterovirus 71 (EV71) is a human Enterovirus A species in the Enterovirus genus of the Picornaviridae family, with three groups (A, B, and C) and 11 genotypes (A, B1–5 and C1–5). The primary route of transmission is oral-fecal, but it can also be transmitted through contact with virus-infected oral secretions, vesicular fluid, surfaces, and fomites [33]. Infection with the EV71 virus

can cause illnesses that range from mild to severe, with potentially fatal consequences. Hand, foot, and mouth disease (HFMD) is a common exanthematous illness that primarily affects infants and children under the age of five [34]. part from HFMD, EV 71 can cause a variety of neurological disturbances, such as bacterial meningitis, acute flaccid paralysis, encephalitis, and other less common manifestations [35].

A non-enveloped capsid encircles a core of single-stranded, positive-polarity RNA that is approximately 7.5 kb in size [36]. This virus contains several proteins, including structural capsid proteins (VP1-VP4) and non-structural proteins (2A-2C, 3A-3D). The VP1 protein is required for the replication cycle [37]. MiR-2911 was found to have potent antiviral activity against various EV71 strains. Li et al. discovered that miR-2911 blocks EV71 replication by interacting with the VP1 gene [15]. There is currently no approved antiviral treatment for EV71 infection [38]. As a result, miR-2911 could be a future natural remedy for the study of anti-HFMD agents.

9. Conclusion

Human lives are endangered by viral infections and the emergence of novel viral diseases such as SCoV-2. Until now, only a few vaccinations have proven to be effective, and only a few antiviral drugs have been approved for use in clinical practice. Chemical treatments have unexpected effects. Herbal drugs may have antiviral properties as well as defenses against incremented viral load. It is also cost-effective, with the potential to decrease mortality and economic damages. MiR-2911 is an atypical miRNA found in honeysuckle that can be absorbed via SIDT1 receptors in the GI tract. Several studies have shown the inhibitory effects of miR-2911 on NA, PB2, and NS1 proteins in flu, EV71, VZV, and SCoV-2 proliferation. The potential of Honeysuckle decoction effects to restrict viral infection should be investigated oncoming in a clinical environment.

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Authors' contributions

Supervision and conceptualization: ZID, SM, SS, FAJ. Data collection: ZID, NS, IO, HV. Original draft preparation: ZID, NS, IO, HV. Critical revision and editing: SM, SS, FAJ. All authors read and approved the final version of article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical declarations

Not applicable.

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