Slovenian Veterinary Research
DOI 10.26873/SVR-1789-2023
UDC 636.4:578.76:616.2:615.2
Pages: 9–28

Review Article

From Nature's Pharmacy to Swine Health: Harnessing Natural Compounds against PRRSV Infection

Key words

antiviral agents;
natural compounds;
PRRSV;
swine industry

Fredmoore L. Orosco[1,2,3]

[1]Virology and Vaccine Institute of the Philippines Program, Industrial Technology Development Institute, [2]S&T Fellows Program, Department of Science and Technology, Bicutan, Taguig City, 1634, [3]Department of Biology, College of Arts and Sciences, University of the Philippines Manila, Ermita, Manila, 1000, Philippines

***Corresponding author:** orosco.fredmoore@gmail.com

Abstract: Porcine reproductive and respiratory syndrome virus (PRRSV) is a significant viral pathogen that causes substantial economic losses to the swine industry worldwide. The limited efficacy of current therapeutic approaches and emergence of new PRRSV strains highlight the urgent need for novel antiviral strategies. Natural compounds derived from plants, animals, bacteria, and fungi have attracted increasing attention as potential antiviral agents. This comprehensive review focuses on natural compounds with antiviral activity against PRRSV and explores their mechanisms of action, efficacy, and potential applications. These compounds exhibit diverse antiviral mechanisms such as viral attachment and entry inhibition, replication suppression, and modulation of host immune responses. This review also highlights challenges and future directions in this field. Research gaps include the need for further elucidation of the precise mechanisms of action, comprehensive evaluation of safety profiles, and exploration of combination therapies to enhance efficacy. Further research and translational studies are warranted to harness the full potential of these natural compounds and pave the way for the effective control and management of PRRSV infections in the swine industry.

Received: 11 June 2023
Accepted: 22 December 2023

Introduction

Porcine reproductive and respiratory syndrome virus (PRRSV) is the etiological agent responsible for the pathological condition observed in swine, which was initially documented within the borders of the United States (U.S.) in 1987 and subsequently in Europe in 1990 (1). These outbreaks were characterized by detrimental effects on reproduction, post-weaning pneumonia, and elevated mortality rates in growing swine. In the early stages, attempts to identify the causative agent responsible for this novel syndrome proved to be futile, leading to its provisional designation as a mystery swine disease (MSD) in North America. However, in 1991, Koch's postulates for MSD were eventually satisfied through the discovery of a hitherto unidentified RNA virus in Europe, which was subsequently named the Lelystad virus (LV) (2). Shortly after this significant finding, the virus was successfully isolated in North America and was initially referred to as swine infertility and respiratory syndrome virus (SIRSV) (3).

PRRSV has emerged as a pervasive pathogen in most swine-producing nations, posing substantial economic repercussions to the swine industry. PRRSV can infect pigs across all age groups; however, its clinical manifestations are particularly pronounced in pregnant sows and young pigs (4). In pregnant sows, PRRSV infection during the final trimester of gestation may lead to adverse outcomes, such as abortion, characterized by the delivery of stillborn, partially autolyzed, and mummified fetuses. Conversely, young pigs infected with PRRSV commonly display clinical signs, including elevated body temperature, severe dyspnea, diminished appetite, lethargy, eyelid edema, and ear discoloration, appearing either blue or red (5).

The term PRRSV encompasses two distinct genotypes: PRRSV-1, comprising genotypes initially isolated in Europe, and PRRSV-2, which consists of genotypes first identified in North America (6). Presently, both virus types have

achieved global distribution, with PRRSV-1 primarily prevalent in Europe, whereas PRRSV-2 exhibits a wider geographic range, including North America, Asia, and South America (7). Recent investigations into multiple arteriviral nucleotide sequences in nonhuman primates have prompted the reclassification of PRRSV into two separate entities: PRRSV-1 and PRRSV-2 (8). This classification was substantiated by the recognition of remarkable genetic variability within both PRRSV-1 and PRRSV-2, as evidenced by phylogenetic analysis based on ORF5 (9). The extensive genetic diversity exhibited by PRRSV poses a significant challenge for the development of effective antiviral therapeutics. This review aims to discuss the molecular biology, clinical characteristics, transmission, and different natural compounds with antiviral activity against PRRSV, and their respective molecular mechanisms.

Molecular Biology of PRRSV

Taxonomy and Structure

PRRSV is an enveloped RNA virus characterized by a single positive strand (Figure 1) (10). Taxonomically, it belongs to the order *Nidovirales* and family *Arteriviridae*, which also encompasses other viruses such as the lactate dehydrogenase-elevating virus of mice, equine arteritis virus, and simian hemorrhagic fever virus (11). The arterivirus genome is enclosed within a lipid envelope and associated with a singular N protein comprising 110-128 amino acids, forming a core structure. Furthermore, the viral particles exhibited an approximately spherical or oval shape with diameters ranging from 50 to 60 nm. The reported buoyant densities of PRRSV virions in sucrose range from 1.13 to 1.17 g/cm^3 (12). The enveloped surface of the virions appears relatively smooth, which can be attributed to the limited size of the ectodomains of the two major envelope proteins, GP5 and M.

Genome Organization

The complete genome of PRRSV spans approximately 15 kb, featuring a cap structure at the 5' end during mRNA processing and a poly A tail structure at the 3' end (Figure 2) (13). PRRSV isolates can be categorized into two distinct genotypes based on their genomic and antigenic variations: North American (NA), PRRSV-2, and European (EU), or PRRSV-1. These genotypes exhibit an approximate sequence identity of 65% (14).

The PRRSV genome comprises 12 open reading frames (ORFs) designated as ORF1a, ORF1a', TF, ORF1b, ORF2a, ORF2b, ORF3, ORF4, ORF5a, and ORF5–ORF7 (15). Among these, ORF1a and ORF1b encode polyproteins pp1a and pp1ab, which undergo processing to yield 17 nonstructural proteins (NSPs) (NSP1α, NSP1β, NSP2, NSP2N, NSP2TF, and NSP3-14), which play a pivotal role in virus replication (16). Recently, a novel ORF known as the ORF trans-frame (TF) was discovered within the nsp2 region (17). This ORF, expressed through both −1 and −2 ribosomal frameshifting, gives rise to two additional nsps: nsp2N, a truncated version of nsp2; and nsp2TF, a fusion protein formed by the N-terminal two-thirds of nsp2 and a C-terminal region encoded by the TF ORF spanning 169 amino acids (18). The major envelope proteins GP5 and M are encoded by ORF5 and ORF6, respectively. These proteins interact with each

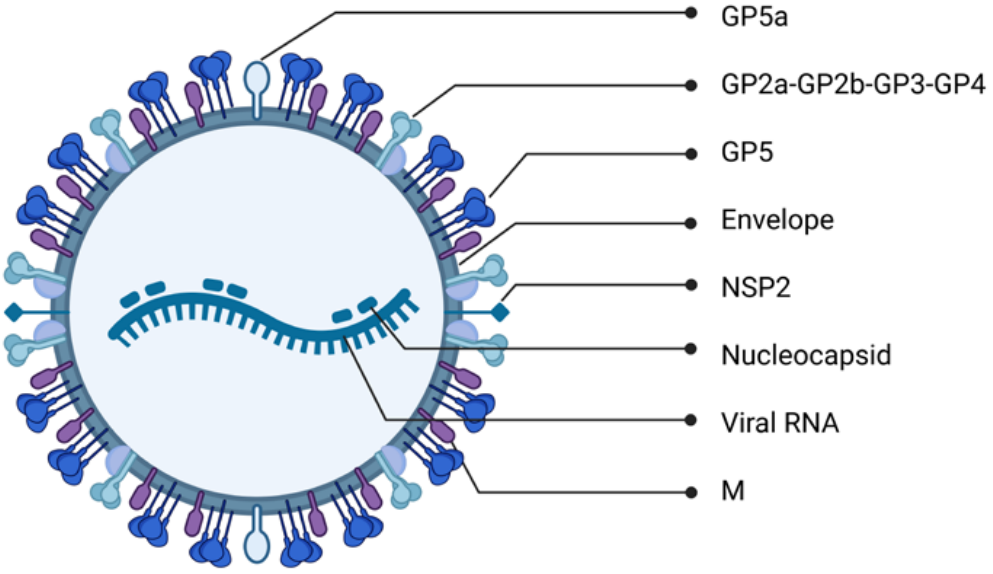

Figure 1: Schematic representation of PRRSV structure

PRRSV mature viral particle, composed of a lipid bilayer envelope with viral receptor glycoproteins involved in infection and cell internalization. Single-stranded positive RNA is associated with nucleocapsid protein in the internal layer of the virus.

other to form heterodimers on the surface of viral particles. Notably, GP5 exhibits substantial variability among structural proteins in the PRRSV genome, making it a commonly employed target for phylogenetic analyses (19). ORF2, ORF3, and ORF4 encode the minor envelope proteins GP2a, GP3, and GP4, respectively, forming noncovalent heterodimers. In addition, two small non-glycosylated proteins, E and GP5a, are encoded by ORF2b and ORF5a, respectively. The highly conserved nucleocapsid protein (N protein) is encoded by ORF7 (20).

Clinical Characteristics

PRRSV infections are characterized by several distinctive clinical features, including elevated body temperature, pronounced contagiousness, and substantial morbidity and fatality rates. Following infection, pigs often experience a rapid increase in body temperature, reaching 41-42°C within a span–1-2 days (21). This heightened contagiousness results in infection spreading throughout the entire pig population within 3-5 days, with a disease duration typically lasting 1-3 weeks. Notably, the highly pathogenic PRRSV (HP-PRRSV) demonstrated a particularly high fatality rate in suckling pigs (100%) and nursery pigs (approximately 70%). Furthermore, adult pigs exhibit an increased mortality rate, with finishing pigs experiencing a mortality rate of 20% and pregnant sows experiencing a minimum of 10% mortality (22). Additionally, PRRSV infections are frequently associated with an elevated incidence of abortions, ranging from 40% to 100%. Furthermore, affected pigs often display signs, such as skin erythema and severe respiratory symptoms, including coughing, dyspnea, and tachypnea. Some pigs may also exhibit neurological signs, such as limping, and gastrointestinal manifestations, such as constipation or diarrhea (21).

PRRSV infection induces a wide array of pathological changes in affected pigs. Among the prominent gross lesions, multifocal hemorrhages are particularly notable, affecting various tissues and organs, such as the skin, lungs, lymph nodes, kidneys, and heart (22). Another significant observation was the presence of lymphadenopathy accompanied by pronounced interstitial pneumonia, characterized by severe pulmonary edema and consolidation. In certain instances, edema and congestion can be observed within the brain. Additionally, severe thymus atrophy is frequently encountered, especially in piglets infected with HP-PRRSV (21).

Secondary bacterial infections are a significant and frequently encountered issue in the context of HP-PRRSV infections. Among the commonly detected bacterial pathogens, *Escherichia coli*, *Streptococcus suis*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae* are frequently implicated (22). Furthermore, PRRSV-infected pig populations often exhibit the presence of various viral pathogens, including classical swine fever virus (CSFV), pseudorabies virus (PRV), and porcine circovirus type 2 (PCV2). The potential synergistic effects of these coinfections on PRRSV pathogenesis have garnered substantial attention within the PRRSV research community, prompting intensive investigation (21).

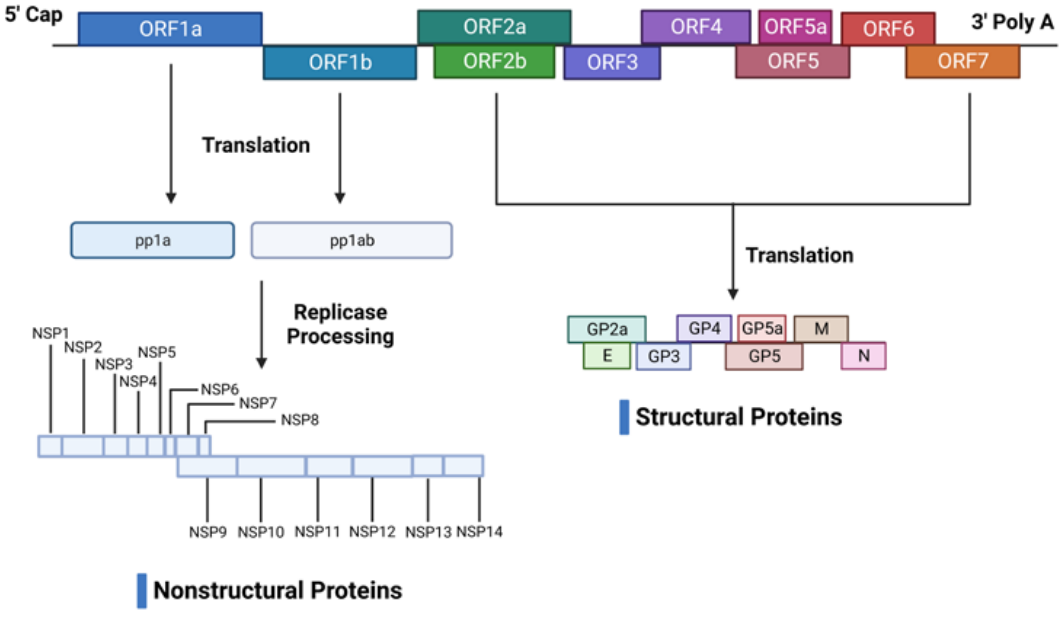

Figure 2: Genome organization of PRRSV virus

Non-structural proteins are located in the 5' end of the genome, coding for two different polyproteins pp1a and pp1ab that is cleaved into at least 14 nsps. Structural proteins near the 3' end are associated with the viral envelope and RNA packaging.

Transmission of PRRSV

Transmission Routes

PRRSV transmission in pigs can occur through various routes, including direct contact and indirect transmission via fomites. Exposure to PRRSV primarily occurs through respiratory and oral routes as well as through mucosal or percutaneous routes. The modes of transmission encompass aerial transmission, either over short or longer distances, as well as transmission through coitus or insemination, ingestion, contact, and occasionally through inoculation, often arising from iatrogenic factors. Vertical transmission during the later stages of gestation is particularly noteworthy. The minimum infectious dose (MID) of PRRSV depends on the specific route of exposure. For instance, infectious dose 50 (ID_{50}) through oral and nasal exposure has been previously evaluated. Notably, variations in infectivity have been observed among different PRRSV isolates via various transmission routes (23). In terms of sexual transmission, the ID_{50} for exposure via artificial insemination is 103.3 $TCID_{50}$ (24).

Based on available data, percutaneous exposure is associated with the lowest MID. Within the farm environment, parenteral exposure is likely to occur frequently, involving routine practices, such as ear notching, tail docking, teeth clipping, and the administration of drugs and vaccines. During the peak viremia stage, infected animals typically exhibit a viral load of at least 103–104 $TCID_{50}$/mL (25). Regular pig behavior can also contribute to parenteral exposure, such as bites, cuts, scrapes, and abrasions, during instances of inter-pig fighting. Aggressive interactions between infected sows and susceptible contacts may play a significant role in PRRSV transmission (26).

PRRSV is notably susceptible to inactivation by various means, including lipid solvents, heat, desiccation, and extreme pH conditions (27). Notably, LV was shown to undergo inactivation after 6 min at 56°C or 3 h at 37°C. However, it displays stability for up to 140 hours at 4°C and remains viable for several months when maintained in a cell culture medium at pH 7.5 and temperatures ranging from -70°C to -20°C (28). In terms of disinfection, iodine (0.0075%) and quaternary ammonium compounds (0.0063%) achieve complete inactivation of the virus within 1 min (29). Chlorine can also completely inactivate PRRSV, although higher disinfectant concentrations (0.03%) and longer exposure times (10 min) are required. Additionally, a 10-minute exposure to ultraviolet light effectively leads to the complete inactivation of the virus on commonly encountered farm surfaces and materials (30).

Development of Viremia and Viral Persistence

Following exposure to PRRSV, viral replication initially occurs within permissive macrophages located in lymphoid tissues at the entry portal. Subsequently, the virus rapidly disseminates throughout the body via the lympho-haematic route. In a genotype 2 model, detectable viremia was observed as early as 12 hours post-infection (hpi) (31). The viral load in the serum peak around 7-10 days post-infection (dpi). The duration of viremia can vary depending on factors such as the specific PRRSV strain and age of the infected animal (32). Various studies have indicated that the viremic period ranges from a few weeks, typically less than four weeks, in adult or grower-finisher pigs, to as long as three months in very young piglets (33). In the case of adult sows infected with genotype 1 PRRSV, viremia may be limited to just one week (34).

During the initial phase of infection, the lungs and various lymphoid organs, including tonsils, Peyer's patches, thymus, and spleen, exhibit the highest viral loads (35). In the lungs, viral detection can typically be observed from 1 to 28 dpi (36). Notably, in young pigs, the virus has been reported to persist in the lungs for up to 49 dpi (37).

Subsequent to the viraemic phase, viral infection enters a stage characterized by the sequestration of the virus within secondary lymphoid tissues, leading to a decline in viral replication. Over time, contagiousness diminishes, although transmission remains feasible for up to three months in horizontally infected pigs. However, in congenitally infected animals, the period of contagiousness may extend beyond this time frame (38). Several situations inducing stress, such as farrowing or regrouping, can trigger reactivation of viral replication and shedding (39).

Viral Shedding

The presence of viremia and the distribution of susceptible macrophages within the body contribute to PRRSV shedding through various routes. In particular, nasal shedding appears to exhibit strain-dependent characteristics, particularly in genotype 1 PRRSV. For instance, nasal shedding of genotype 1 was limited, with only four out of eight pigs showing isolation of the virus at 3 dpi and one out of eight pigs at 7 dpi, always at low titers (25). In the case of genotype 2, nasal secretion was reported in only 1.9% (2/105) of nasal swabs collected from experimentally inoculated pigs during a 28-day observation period (40). Additionally, no virus has been isolated from the nasal secretions of experimentally infected pigs (31).

The shedding of PRRSV in oral fluids appears to be relatively consistent, although most of the available data focus on genotype 2 viruses. The presence of the virus in oral fluids and the steady nature of its shedding over time have important implications for PRRSV transmission. With regard to viral shedding in the semen of infected boars, the detection of the viral genome using RT-PCR has been reported as early as 3 dpi and persisted up to 92 dpi in 1 out of 4 boars inoculated with the VR-2332 isolate (41). PRRSV has also been found in the urine (40) and mammary gland secretions (42). In experimentally infected sows, genotype

2 PRRSV was detected using RT-PCR on the first day of lactation (42). Lastly, infected pigs have been observed to generate aerosols contaminated with the virus during respiratory activities, such as breathing, sneezing, or coughing, although the extent of aerosol transmission can vary depending on the strain (43).

Anti-PRRSV Agents

Natural compounds derived from plants, animals, fungi, and bacteria have received significant research attention because of their potent antiviral activities *in vitro* and *in vivo*. These compounds possess different molecular mechanisms, such as activation of TLR signaling, activation of interferon signaling, downregulation of receptors, and blocking of virus attachment, fusion, replication, translation, assembly, maturation, and release (Figure 3). The compounds are discussed in detail in this section.

Plant-derived Compounds

Tea polyphenols

Tea polyphenol (TPP) refers to the collective group of polyphenols found in tea leaves, with catechins and their derivatives being the primary constituents (44). TPP exhibits a wide range of physiological activities, including antioxidant, anti-radiation, anti-aging, blood lipid-lowering, blood sugar-lowering, and inhibition of bacteria and enzymes (45). Structurally, TPP possesses polyphenolic characteristics such as catechins and anthocyanins (46). Green tea, which serves as a primary source of TPP, exerts notable antiviral and antifungal effects (47). Notably, epigallocatechin gallate (EGCG) has demonstrated antiviral properties against

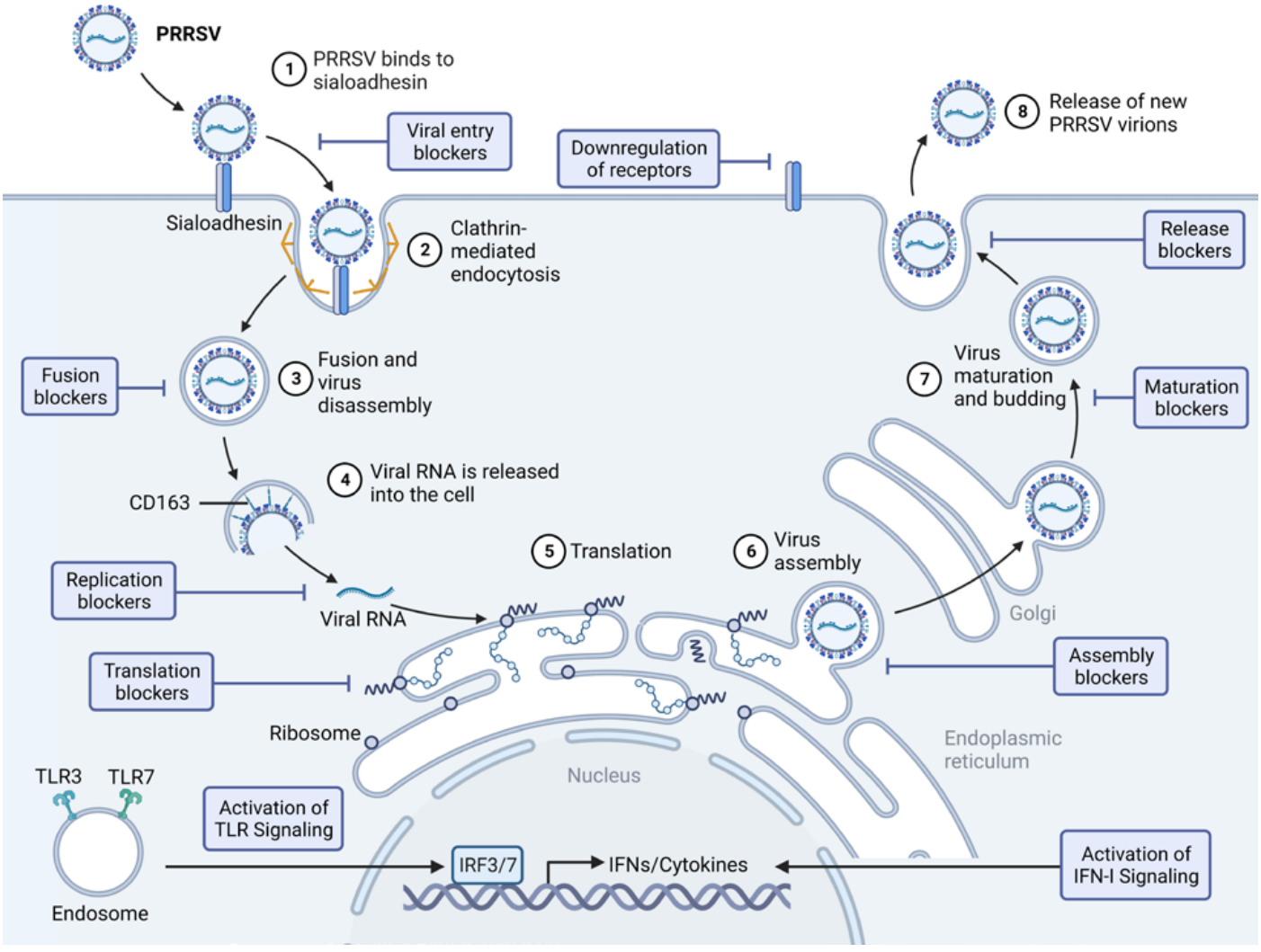

Figure 3: Life cycle and molecular targets of antiviral compound

The life cycle of PRSSV begins with binding of PRRSV with sialoadhesin (1) that will trigger clathrin-mediated endocytosis (2) to fuse with an endosome (3). The virus is then disassembled and the viral RNA is released (4) for translation in the endoplasmic reticulum (5). Translated viral proteins are assembled into new progeny virions (6) followed by maturation and budding in the Golgi body (7). This new progeny virions are released outside of the cell via exocytosis (8).

various viruses, including hepatitis C (HCV), chikungunya (CHIKV), hepatitis B (HBV), and Zika (ZIKV) viruses (48).

TPP potently inhibited PRRSV infection in Marc-145 cells in a dose-dependent manner. TPP exerts its inhibitory effects across multiple stages of the PRRSV life cycle, including attachment, internalization, replication, and release. Mechanistically, TPP impeded the transport of p65 into the nucleus, thereby suppressing the activation of the NF-κB signaling pathway, which ultimately resulted in the downregulation of inflammatory cytokine expression induced by PRRSV infection. Additionally, TPP can interfere with the synthesis of viral nsp2, a crucial component of replication transcription complexes (RTC), leading to inhibition of viral protein translation and assembly (49).

Matrine

Matrine, a prominent quinolizidine alkaloid derived from the dried roots of *Sophora flavescens* Ait, as described in the Chinese Pharmacopeia 2005, exhibits a range of pharmacological effects, including antiviral, anti-inflammatory, and immunoregulatory properties (50). Previous studies have revealed the inhibitory effects of matrine on PRRSV infection in Marc-145 cells, suggesting that matrine can directly inactivate PRRSV and disrupt viral replication within host cells. Furthermore, an indirect immunofluorescence assay and western blot analysis demonstrated that matrine is capable of inhibiting the expression of N protein in Marc-145 cells. Additionally, matrine impedes PRRSV-induced apoptosis by inhibiting the activation of caspase-3 (51).

Moreover, matrine exhibits antiviral activity against both PRRSV and PCV2 (51). The antiviral mechanisms underlying the effects of matrine are thought to involve partial regulation of the TLR3/TLR4/NF-κB/TNF-α pathway (50). Notably, matrine treatment has been shown to improve pneumonia symptoms in PRRSV/PCV2 co-infected mice and has shown efficacy in attenuating inflammation in mice with LPS-induced acute lung injury. Furthermore, matrine directly hindered PRRSV replication by inhibiting the activity of Nsp9. Recent studies have also revealed that matrine can inhibit IL-1β secretion in primary porcine alveolar macrophages (PAMs) by acting on the MyD88/NF-κB pathway and the NLRP3 inflammasome. This inhibition is associated with downregulated expression of MyD88, NLRP3, and caspase-1 as well as suppression of ASC speck formation, IκBα phosphorylation, and hindered translocation of NF-κB from the cytoplasm to the nucleus (52).

Rottlerin

Rottlerin, a polyphenolic ketone compound derived from the Indian Kamala tree (*Mallotus philippensis* Muell. Arg), has gained prominence as a selective PKCδ inhibitor (53). Historically, rottlerin has been used in traditional Indian medicine to treat tapeworm, scabies, and herpetic ringworm infections, implying its long-standing safety record. Notably, several prior studies have documented the antiviral properties of rottlerin against various viruses, including rabies, influenza, human immunodeficiency virus, and PRRSV (54).

Earlier investigations have highlighted the significant impact of rottlerin pretreatment on diminishing both viral RNA synthesis and titer. More recently, it has been demonstrated that the administration of rottlerin during the early stages of PRRSV infection effectively impedes viral replication. PRRSV infection is known to induce phosphorylation of protein kinase C-δ, a process that is specifically counteracted by rottlerin (55). Treatment with rottlerin disrupts the entry pathway of PRRSV by impeding endocytosis of virions. Moreover, *in vivo* studies involving the administration of rottlerin-liposomes to PRRSV-infected pigs, specifically those infected with LMY or FL12 strains, revealed a notable dose-dependent reduction in blood viral load, interstitial pneumonia, and clinical scores when compared to untreated pigs (55).

Sanguinarine

Sanguinarine, a quaternary benzo[c]phenanthridine alkaloid found in various plants such as *Macleaya cordata* (Wild.) R.Br., *Bocconia frutescens* L., *Chelidonium majus* L., *Fumaria officinalis* L., and *Sanguinaria canadensis* L., has been extensively studied for its anti-inflammatory, anti-tumor, and antimicrobial properties (56). While its antiviral activity has rarely been reported, there have been observations of moderate antiviral effects of sanguinarine against tobacco mosaic virus (57). Furthermore, a derivative of sanguinarine, 8-hydroxydihydrosanguinarine, has recently emerged as a potential drug candidate for combating COVID-19 (58).

Regarding its effects on PRRSV, sanguinarine demonstrates potent antiviral activity by targeting multiple stages of the virus life cycle, including internalization, replication, and release (59). Network pharmacology and molecular docking studies identified potential anti-PRRSV targets of sanguinarine, including ALB, AR, MAPK8, MAPK14, IGF1, GSK3B, PTGS2, and NOS2. Additionally, the combination of sanguinarine and chelerythrine, another bioactive alkaloid derived from *Macleaya cordata*, has shown improved antiviral effects (59).

Platycodin D

Platycodon grandiflorum A. DC is a widely recognized Chinese herb that is used to treat pulmonary and respiratory diseases. Notably, saponins have been identified as the primary bioactive constituents of P. grandiflorum roots (60). Among these saponins, platycodin D (PD), an oleanane-type triterpenoid saponin with sugar chains attached at the C-3 and C-28 positions of the aglycone, is the most potent in terms of biological activity (61). Previous investigations have demonstrated the diverse pharmacological effects of PD, including its antitumor properties (62), anti-inflammatory effects (63), and immunological adjuvant activities (60). Moreover, PD has been shown to possess hepatoprotective properties and anti-hepatitis C virus (HCV) activity (64).

PD demonstrated remarkable efficacy against PRRSV infection in both Marc-145 cells and primary PAMs (65). Its inhibitory effects extend across various strains of PRRSV, including the highly pathogenic type 2 strains GD-HD and GD-XH, as well as the classical strains CH-1a and VR2332. Notably, PD displayed dose-dependent inhibition of PRRSV RNA synthesis, viral protein expression, and production of progeny viruses, with significant effects observed at concentrations ranging from 1 to 4 μM. The EC_{50} values of PD against the four tested PRRSV strains in Marc-145 cells ranged from 0.74 to 1.76 μM (65).

The antiviral mechanism of PD involves direct interaction with PRRSV virions, thereby affecting multiple stages of the viral life cycle, including viral entry and release of progeny virus. Furthermore, PD exhibited the ability decreases the production of cytokines (IFN-α, IFN-β, IL-1α, IL-6, IL-8, and TNF-α) induced by both PRRSV and LPS in PAMs (65).

Cryptotanshinone

Cryptotanshinone (CPT) is a natural compound derived from the roots of *Salvia miltiorrhiza* Bunge (Danshen). The roots of *S. miltiorrhiza* have long been used in traditional oriental medicine to treat various circulatory disorders, liver diseases, coronary heart disease, hepatitis, and chronic renal failure (66). Notably, CPT exhibited remarkable antibacterial activity, surpassing the effectiveness of the other tested tanshinones. Furthermore, its anti-inflammatory properties have been attributed to the inhibition of cyclooxygenase II activity and endothelin-1 expression (67).

CPT has demonstrated notable efficacy in impeding the infection of diverse PRRSV strains in PAMs, which serve as primary targets of PRRSV *in vivo*. The underlying mechanism involves the inhibition of signal transducer and activator of transcription 3 (STAT3) activation, the blockade of interleukin 10 (IL-10)-stimulated CD163 expression, and the basal level of CD163 expression in PAMs (68). Remarkably, CPT was effective in both pre- and post-PRRSV infection treatment, with the combined application resulting in substantial dose-dependent inhibition of PRRSV infection. Moreover, CPT displays inhibitory effects against both type I and type II PRRSV infections in PAMs (68).

Allicin

Garlic (*Allium sativum* L.) and its organosulfur compounds (OSC) have been extensively studied for their pharmacological properties, including antibacterial, antiviral, anti-inflammatory, anticancer, and antioxidant effects (69). Allicin, an OSC present in garlic, onion, and other Allium plants, has been recognized for its significant antiviral activity against herpes simplex virus-1 and 2, parainfluenza-3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus-2 (70). Previous investigations have also demonstrated the antiviral potential of allicin against respiratory viruses, such as influenza, SARS-CoV, and rhinovirus (71). In a recent study, allicin was found to alleviate SARS-CoV-2 infection *in vitro* and restore host cellular pathways disrupted by viral infections (72). Furthermore, allicin has shown efficacy as an antiviral agent against the reticuloendotheliosis virus by reducing inflammation and oxidative damage, primarily through inhibition of the ERK/MAPK pathway (73). Additionally, allicin exhibits anti-inflammatory properties by inhibiting the P38 and JNK pathways as well as the TLR4/NF-κB signaling pathway (74).

Supplementation of garlic botanicals in the nursery basal diet has been shown to have beneficial effects on PRRSV-infected pigs, including reduction of viral loads and improvement of immune responses (75). Allicin demonstrated a dose-dependent inhibitory effect on both HP-PRRSV and NADC30-like PRRSV. It exerts its antiviral activity by interfering with various stages of the viral life cycle, including entry, replication, and assembly. Additionally, allicin alleviates the expression of pro-inflammatory cytokines (such as IFN-β, IL-6, and TNFα) induced by PRRSV infection. Treatment with allicin effectively restores dysregulated pro-inflammatory signaling pathways, including the TNF and MAPK signaling pathways, which are upregulated during PRRSV infection (76).

Curcumin

Curcumin, a natural polyphenolic compound isolated from *Curcuma longa* L. rhizomes, has been extensively studied for its various biological and pharmacological effects. It is the major component of *C. longa* and accounts for its immunomodulatory, antitumor, anti-inflammatory, antioxidant, antimutagenic, antibacterial, antifungal, and antiviral activities associated with this plant (77). Among its antiviral properties, curcumin has been shown to inhibit the entry of several viruses into cells, including HCV, CHIKV, and vesicular stomatitis virus (VSV) (78). In the context of PRRSV infection, curcumin has been found to effectively inhibited the infection of both Marc-145 cells and PAMs by four different genotype 2 PRRSV strains. Interestingly, curcumin did not affect the levels of major PRRSV receptor proteins on the cell surface or PRRSV binding to cells. Instead, it specifically targets two crucial steps in the PRRSV infection process: virus internalization and virus-mediated cell fusion (79).

Aloe vera extracts

Aloe vera is known for its remarkable inhibitory effect on a wide range of viruses, including herpes simplex virus type 1, influenza virus, and pigeon paramyxovirus type 1 (80). Notably, this antiviral property has been attributed not only to the whole extract of Aloe vera but also to its isolated compounds. Emodin (1, 3, 8-trihydroxy-6-methylanthraquinone), an anthraquinone compound found in the roots and bark of pharmaceutical plants, such as Chinese rhubar (*Rheum palmatum* L.) and *Aloe vera* L. (81), has demonstrated significant inhibitory effects against various viruses. These include Cyprinid herpesvirus 3 (CHV3) (82), coxsackieviruses (CV) (83), ZIKV (84), enterovirus 71 (EV71) (85), Epstein-Barr virus (EBV) (86), HCoV-OC43 (87), herpes simplex virus (HSV) (88), HBV (89), and SARS-CoV

(90). Emodin exerts its antiviral activity through multiple mechanisms, including blockade of virus-receptor interactions, inhibition of viral protein translation, suppression of viral maturation, and inhibition of viral release (90).

Aloe extract (Ae) has been found to exhibit potent inhibitory effects against PRRSV *in vitro*, specifically in Marc-145 cells and PAMs (91). Emodin demonstrated an inhibitory effect by targeting various stages of the PRRSV infection cycle. Emodin was able to directly inactivate PRRSV particles. Additionally, emodin treatment significantly upregulated the expression of Toll-like receptor 3 (TLR3) ($p < 0.01$), IFN-α ($p < 0.05$), and IFN-β in iPAMs. This suggested that the anti-PRRSV effect of emodin may be attributed to the induction of antiviral agents through TLR3 activation (91).

Cepharanthine

Cepharanthine (CEP) is an alkaloid derived from *Stephania cepharantha* Hayata, which has a long history of use in Japanese medicine for various conditions, including radiation-induced leukopenia and certain skin and ear disorders (92). The therapeutic potential of CEP extends beyond its traditional applications, as it possesses diverse properties such as anti-inflammatory, antioxidant, immunomodulatory, and antiparasitic effects, making it an attractive candidate for treating viral diseases such as COVID-19 (93).

Notably, CEP has demonstrated antiviral activity against HCoV-OC43, a mildly pathogenic human coronavirus (94), and severe acute respiratory syndrome coronavirus (SARS-CoV) (95). Moreover, in a comprehensive drug screening study involving 2406 clinically approved drugs, CEP emerged as the most effective compound against pangolin coronavirus closely related to SARS-CoV-2, the virus responsible for the COVID-19 pandemic (96). This discovery is particularly significant considering the high genomic similarity between SARS-CoV and SARS-CoV-2 (97). Given these promising findings, CEP has garnered significant attention as a potential therapeutic option for the treatment of COVID-19 by exploiting its established antiviral properties and favorable activity against related coronaviruses (96).

In recent investigations, CEP has demonstrated superior inhibitory effects on PRRSV infection compared to tilmicosin, as evidenced by reductions in both RNA and protein levels. Notably, CEP treatment led to a 5.6-fold decrease in $TCID_{50}$, providing substantial protection against PRRSV infection in Marc-145 cells (98). Mechanistically, detailed analyses involving western blot assessments of Marc-145 cells and PAMs subjected to CEP treatment and PRRSV infection at various time points revealed the ability of CEP to suppress the expression of integrins β1 and β3, integrin-linked kinase (ILK), RACK1, and PKCα. These effects culminated in the suppression of NF-κB signaling, ultimately alleviating PRRSV infection. These findings underscore the potential of CEP as a valuable intervention strategy against PRRSV infection, offering new insights into its antiviral mechanisms and therapeutic implications (98).

Glycyrrhizin

Glycyrrhizin, a triterpene saponin found in licorice root (*Glycyrrhiza glabra* L.), possesses a diverse range of biological activities, including antibacterial, antiviral, anti-inflammatory, anticancer, antioxidant, liver protection, neuroprotection, skin whitening, hypoglycemic, and memory-enhancing properties (99). These characteristics highlight the promising potential of licorice in cosmetic production and therapeutic applications for various conditions such as liver disease, diabetes, ischemia-reperfusion injury, Alzheimer's disease, Parkinson's disease, epilepsy, depression, and cancer (100).

Numerous studies have documented the potent antiviral effects of glycyrrhizin against a range of viruses, including the hepatitis B virus (HBV) (101), HCV (102), herpes simplex virus (HSV) (103), SARS coronavirus (104), and influenza viruses (105). Recent studies have revealed dose-dependent inhibitory effects of glycyrrhizin on the proliferation of PRRSV. Treatment with glycyrrhizin effectively reduced PRRSV proliferation and PRRSV-encoded protein expression, which primarily targeted the penetration stage of the PRRSV life cycle, exerting minimal influence on the processes of viral adsorption or release (105).

Flavaspidic acid AB

Flavaspidic acid AB (FA-AB) is a naturally occurring compound derived from *Dryopteris crassirhizoma* Nakai, a semi-evergreen fern with a rich history in traditional Chinese medicine (106). The rhizome of *D. crassirhizoma* has traditionally been employed as an anti-infection agent, particularly for respiratory ailments such as the common cold and flu. Notably, it has been utilized in combination with other Chinese herbal medicines, including Astragalus, Atractylodes, Red Atractylodes, Pogostemon, Adenophora, and Lonicera, in a prescription formula to prevent SARS (106).

FA-AB belongs to the phloroglucinol derivative family (107). Extensive investigations have demonstrated the antibacterial, antitumor, and antioxidant properties of phloroglucinol derivatives (107). Additionally, dimeric phloroglucinols have shown inhibitory effects against HIV-1 reverse transcriptase, highlighting their potential for antiviral intervention (108).

FA-AB inhibits the internalization and intercellular transmission of PRRSV, although it does not interfere with the initial binding of PRRSV to host cells (109). Remarkably, when FA-AB treatment was initiated 24 hours after viral infection, it effectively suppressed PRRSV replication, as evidenced by kinetic analysis of viral replication. Moreover, FA-AB can induce the expression of important antiviral cytokines, including IFN-α, IFN-β, and IL1-β, in PAMs (109).

***Caesalpinia sappan* (CS) heartwood**

Caesalpinia sappan L. 1753 (CS), derived from the *Leguminosae* family, is a renowned medicinal plant that is

widely distributed and cultivated in various tropical Asian regions such as Southern China, India, Myanmar, Vietnam, Sri Lanka, and Thailand (110). CS dried heartwood has been utilized in traditional medicine practices, including Indian Ayurveda and Traditional Chinese Medicine (111). CS heartwood exhibits a diverse range of biological activities, including antioxidant (112), antibacterial (113), anti-inflammatory (114), hypoglycemic (115), and hepatoprotective (116) properties, as reported in previous studies. Moreover, CS extract constituents have demonstrated significant activity against the H3N2 strain of influenza virus (117). Additionally, CS showed promising antiviral activity against PRRSV replication in MARC-145 cells, with a significant reduction in the viral titer observed at 72 hpi. Notably, this antiviral effect was attributed to the presence of specific compounds such as byakangelicin, brazilin, naringenin, and brazilein (118).

Saponin Components

Saikosaponin A (SSA), Saikosaponin D (SSD), Panax notoginseng saponins (PNS), Notoginsenoside R1 (SR1), and Anemoside B4 (AB4) have gained significant attention in recent research because of their diverse bioactivity (119). Specifically, its antiviral potential against PRRSV was investigated. In a study involving 132 healthy piglets, saponin components were evaluated for their effects on PRRSV-induced immunopathological damages (120). Piglets were divided into 22 groups, with each group consisting of six animals. The control group received an intramuscular injection of PRRSV solution, while the low-, middle-, and high-dose treatment groups were administered PRRSV solution followed by intraperitoneal injections of AB4, PNS, SR1, SSA, or SSD at varying doses. The results demonstrated that all five saponin components reduced the incidence and severity of PRRSV-induced immunopathological damage, including symptoms, such as elevated body temperature, weight loss, anemia, and internal inflammation. Furthermore, these saponin components exhibited the ability to enhance protein absorption and immune responses (120).

Isobavachalcone

Isobavachalcone (IBC) is a prenylated chalcone compound belonging to the flavonoid subclass that was originally derived from *Psoralea corylifolia* L. (121). Extensive research has revealed that IBC exhibits a broad range of biological activities, including antibacterial, antifungal, anticancer, antireverse transcriptase, antitubercular, and antioxidant properties (121). Notably, IBC demonstrated inhibitory effects on PRRSV replication at the post-entry stage of infection. This suggests that IBC may serve as a promising therapeutic candidate for the treatment of PRRSV infection in swine (122).

Ursolic acid derivatives

Ursolic acid (UA) and its derivatives are widely recognized as prominent examples of pentacyclic triterpenoids (PTs), which possess diverse biological activities, including antiviral and antibacterial properties. UA has exceptional anti-HIV activity, which is attributed to its ability to inhibit HIV-1 proteases (123). Both oleanolic acid (OA) and UA possess anti-HCV activity by suppressing the enzymatic activity of HCV NS5B RNA-dependent RNA polymerase, acting as non-competitive inhibitors (124).

Recent investigations have revealed that the amidation of the 17-carboxylic acid group of UA yields notable improvements in both anti-PRRSV efficacy and cytotoxicity attenuation in MARC-145 cells. This modified derivative potently inhibited PRRSV infection not only in MARC-145 cells but also in PAMs and PRRSV-infected cells *in vivo* (125). Moreover, it displayed broad-spectrum inhibitory activities against various PRRSV strains, including the highly pathogenic NADC30-like and GD-XH strains, as well as the classical CH-1a and VR2332 strains *in vitro*. Mechanistically, the compound exerted its antiviral effects by directly inactivating PRRSV virions, thereby disrupting multiple stages of the viral life cycle, including viral entry, replication, and release, while leaving cellular susceptibility to PRRSV unaffected (125).

Xanthohumol

Xanthohumol (Xn), a prenylated flavonoid originating from the hop plant *Humulus lupulus* L., emerges as a natural compound with diverse bioactive properties, (126). Notably, Xn has garnered attention for its anti-inflammatory potential, as demonstrated by its ability to counteract lipopolysaccharide (LPS)-induced acute lung injury and ischemia reperfusion-induced liver injury in murine models (127). Additionally, Xn exhibits anti-proliferative effects in various cancer cell lines, including breast, colon, and ovarian cancers (128). The antiviral activity of Xn has also been documented against human immunodeficiency virus (HIV), bovine viral diarrhea virus (BVDV), and HSV-1 and -2 (129).

Xn, a prenylated flavonoid compound, displays potent inhibitory effects against various sub-genotype strains of PRRSV when tested on PAMs (130). Notably, Xn exhibited a low half-maximal inhibitory concentration (IC_{50}), emphasizing its efficacy in combating PRRSV infections *in vitro*. Furthermore, Xn treatment led to a reduction in the expression levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, in PAMs infected with PRRSV and those treated with LPS. Animal challenge experiments using highly pathogenic PRRSV infections have shown that Xn effectively mitigates clinical signs, lung pathology, and inflammatory responses in the lung tissues of infected pigs (130).

Toosendanin

Toosendanin (TSN) is a tetracyclic triterpene derived from the bark and fruit of *Melia toosendans* Sieb. et Zucc. Traditionally, it has been used as an agricultural insecticide and digestive tract parasiticide in China (131). Notably, TSN has demonstrated significant efficacy in combating botulism, as evidenced by *in vivo* and *in vitro* studies (132). Subsequent studies have highlighted its potential as an anticancer agent with the ability to induce apoptosis in diverse

cancer cell types (133). Recently, TSN has garnered attention for its antiviral properties, exhibiting activity against influenza A virus (IAV) (134), HCV (135), severe fever with thrombocytopenia syndrome virus (SFTSV), and SARS-CoV-2 (136).

TSN exhibited robust inhibitory effects on the replication of type 2 PRRSV both *in vitro*, using Marc-145 cells, and ex vivo, using PAMs, even at sub-micromolar concentrations (137). Transcriptomic analyses further elucidated that TSN treatment upregulated IFI16 expression in Marc-145 cells. Additionally, we demonstrated that TSN induces the activation of caspase-1 and maturation of IL-1β through an IFI16-dependent pathway (137).

Iota-Carrageenan

Carrageenan (CG), a sulfated galactan derived from marine red algae (*Rhodophyta*), has garnered significant attention because of its various biological activities (138). It is widely recognized as a safe compound by regulatory authorities and has extensive applications in the food, cosmetic, and pharmaceutical industries as a stabilizer, emulsifier, or thickener (139). Previous studies have demonstrated the anticoagulant, antitumor, and immunomodulatory properties of carrageenan (140). Notably, carrageenan exhibits potent inhibitory effects against a range of viruses including IAV, dengue virus-2 (DENV-2), human rhinovirus (HRV), and HSV-1 (141).

Recent investigations have revealed the effectiveness of CG in inhibiting replication of the CH-1a strain of PRRSV at both the mRNA and protein levels in Marc-145 cells and PAMs (142). The antiviral mechanism of CG primarily occurs during viral attachment and entry into the viral life cycle. Moreover, CG hampered viral release in Marc-145 cells and mitigated CH-1a-induced apoptosis during the late stages of infection. Furthermore, CG inhibits CH-1a-induced NF-κB activation, thereby interfering with cytokine production in both Marc-145 cells and PAMs (142).

Griffithsin

Griffithsin, a lectin derived from marine red algae of *Griffithsia* spp., is a small protein consisting of 121 amino acids (143). Griffithsin effectively inhibits viral infectivity through its interaction with glycan moieties associated with the glycoproteins of various enveloped viruses (144). Extensive studies have demonstrated the remarkable antiviral activity of Griffithsin against several human enveloped viruses, including HIV (143), Middle East respiratory syndrome coronavirus (MERS-CoV) (145),SARS-CoV (146), HCV (147), HSV-2 (148), and Japanese encephalitis virus (JEV) (149).

An exceptional characteristic of Griffithsin is its impressive thermostability, as it remains stable even at temperatures as high as 80°C (150). Griffithsin displays resistance to organic solvents (143) and protease degradation (151), further emphasizing its potential as a therapeutic agent. Moreover, extensive cytotoxicity studies have revealed the superior safety profile of Griffithsin (152). No cytotoxic effects were observed against various cell types, and it demonstrated minimal impact on peripheral blood mononuclear cell activation as well as cytokine and chemokine production (152).

Griffithsin demonstrated potent antiviral activity against PRRSV, which was likely mediated by its specific interactions with glycans present on the surface of the virus, thereby impeding viral entry. Notably, Griffithsin effectively blocked viral adsorption while leaving viral penetration unaffected. Additionally, Griffithsin exhibited the ability to hinder cell-to-cell spread, thereby interrupting virus transmission (153).

Proanthocyanidin A2

Proanthocyanidins, a class of naturally occurring polyphenolic bioflavonoids abundant in various plant sources, such as fruits, vegetables, nuts, seeds, and bark, including grape seeds, have garnered attention for their diverse array of bioactive properties, including antioxidant, cardioprotective, anticancer, antibacterial, antiviral, and anti-inflammatory activities (154). Notably, grape seed-derived proanthocyanidins have demonstrated significant bioactivity *in vitro* (155).

Of particular interest is Proanthocyanidin A2 (PA2), a dimeric form of proanthocyanidin that results from the condensation of catechins (156). The antiviral potential of PA2 and its analogs has been highlighted against various viruses, including HSV, Coxsackie B virus (CBV), and canine distemper virus (CDV) (157).

PA2 showed remarkable antiviral activity against PRRSV infection both *in vitro* (158). Notably, PA2 exhibited broad-spectrum inhibitory effects against traditional genotype II PRRSV strains, such as CH-1a, GD-XH, and GD-HD strains, with comparable potency and EC_{50} values ranging from 2.2 to 3.2 μg/ml. Treatment with PA2 results in a dose-dependent reduction in viral RNA synthesis, viral protein expression, and progeny virus production in PRRSV-infected Marc-145 cells (158).

Furthermore, PA2 exerted immunomodulatory effects by suppressing the expression of key cytokines (TNF-α, IFN-α, IL-1β, and IL-6) induced by PRRSV infection in PAMs. This highlights the potential of PA2 in mitigating the inflammatory response associated with PRRSV infection. Mechanistically, PA2 exhibits multifaceted antiviral mechanisms by targeting various pathways, including inhibition of viral entry and blocking progeny virus release (158).

Bacterial Compounds

Tilmicosin

Tilmicosin, a chemically modified macrolide antibiotic derived from tylosin, is an essential veterinary antimicrobial agent used to treat bacterial infections in animals. Originally synthesized in *Streptomyces fradiae*, tilmicosin

has specifically been formulated for veterinary use in cattle, sheep, and swine. It is available in injectable form for cattle and sheep, whereas a premix feed formulation is utilized for swine (159). The antimicrobial activity of tilmicosin is effective against a wide range of gram-positive and gram-negative bacteria. Additionally, tilmicosin demonstrates efficacy against intracellular bacteria such as *Rhodococcus* sp. and *Mycoplasma* sp., making it a valuable therapeutic option in veterinary medicine (160).

Limited research has explored the antiviral properties of tilmicosin against PRRSV; however, promising findings have emerged. Previous investigations have demonstrated the dose-dependent inhibitory effects of tilmicosin on PRRSV replication in cultured PAMs (160). Additionally, tylvalosin, a macrolide derivative, exhibits inhibitory activity against both European and North American strains of PRRSV in cultured cells (161). In an experimental setting using PRRSV-infected pigs, the administration of tilmicosin as a feed additive resulted in noticeable reductions in lymph node hypertrophy, lung lesions, and viremia compared with non-medicated infected controls (162).

Tilmicosin has demonstrated significant potential for mitigating the severity of PRRSV infections in various experimental settings. In a study involving experimentally PRRSV-infected nursery pigs, tilmicosin treatment yielded notable improvements in disease outcomes, as evidenced by reduced clinical signs, improved feed consumption, and enhanced weight gain, compared to non-medicated challenged pigs. Furthermore, there was a tendency towards lower virus titers in the lungs and serum of tilmicosin-treated pigs (163).

Field evaluations of tilmicosin in sows have yielded promising results (164). In one study, the administration of an aqueous form of tilmicosin to nursery pigs in a controlled environment resulted in a 50% reduction in mortality, lower body temperature, a significant increase in average daily gain, and reduced lung lesions in the medicated group compared to the non-treated group (165,166). These findings highlight the potential of tilmicosin in improving both clinical outcomes and performance indicators in PRRSV-infected pigs. The accumulation of tilmicosin in macrophages, the primary target cells for PRRSV replication, may provide a mechanistic explanation for the observed reduction in clinical severity (167).

Tulathromycin

Tulathromycin (TUL), a triamide compound, possesses unique structural features characterized by a lactone ring containing three polar amine groups. This antimicrobial agent is commonly employed for the treatment and prevention of swine respiratory diseases associated with *Actinobacillus pleuropneumoniae* (App), a gram-negative bacterium frequently found in PRRSV-infected pigs (168).

Recent investigations have revealed additional properties of tulathromycin beyond its antimicrobial effects. Studies have demonstrated its ability to inhibit the production of CXCL-8 and LTB4, the key mediators of inflammation, in stimulated neutrophils and macrophages (169). Moreover, tulathromycin promotes apoptotic death of neutrophils and facilitates their phagocytic clearance by macrophages, a crucial process known as efferocytosis, which contributes to the resolution of inflammation (170). TUL also exhibited potent immunomodulatory properties in the absence of any direct antiviral effects against PRRSV. TUL has exhibited an additive effect with PRRSV in inducing macrophage apoptosis and effectively inhibiting virus-induced necrosis (171).

Actinobacillus pleuropneumoniae

Porcine pleuropneumonia, a significant disease affecting the swine industry worldwide, is caused by *Actinobacillus pleuropneumoniae* (App). In recent years, *in vitro* models using St. Jude Porcine Lung (SJPL) cell line, an immortalized epithelial cell line, have been developed to investigate host-pathogen interactions (172). These models have been instrumental in studying co-infections involving App and porcine viral pathogens. Interestingly, during App-PRRSV coinfection of SJPL cells, it was unexpectedly observed that App culture supernatants exhibited robust antiviral activity against PRRSV (173). This finding was further supported by another study that confirmed the antiviral effect of App culture supernatant (174). Antiviral activity of App against PRRSV has also been observed in PAMs (174). Moreover, App inhibits PRRSV replication by inducing cell cycle arrest in the G2/M phase of SJPL cells (175).

Fungal Compounds

Cryptoporus volvatus

The utilization of mushrooms in medical applications has a rich history in Asian countries, and its usage has slightly increased in the Western hemisphere over the past few decades (176). Antiviral properties have been attributed not only to whole mushroom extracts but also to isolated compounds (177). *C. volvatus*, a member of the Order *Aphyllophorales* and genus *Cryptoporus* (178), is found in specific regions of China. The fruiting body of this mushroom has been traditionally employed in the treatment of asthma and bronchitis, with references dating back to the 15th century in the "Materia Medica of Yunnan" (178).

Extracts of *C. volvatus* obtained from various separation processes exhibit differing degrees of inhibitory activity against PRRSV (179). A specific anti-PRRSV component, CM-H-L-5, was isolated from a water-soluble fraction of *C. volvatus*. The inhibitory effect of CM-H-L-5 against PRRSV was dose-dependent. Chemical analysis revealed that CM-H-L-5 is a low-molecular-weight polyol fragment containing amide and carboxylic acid groups (179).

Deoxynivalenol (DON) Mycotoxin

Deoxynivalenol (DON), a trichothecene mycotoxin, is produced by various *Fusarium* spp. molds that are commonly found in feed and other organic substrates. Cereal grains such as wheat, barley, and corn are major sources of DON contamination (180). Pigs, owing to their high grain-based diets, are particularly susceptible to DON toxicity, making them frequently exposed to this mycotoxin (181).

In the context of PRRSV infection, it has been observed that DON concentrations ranging from 140 to 280 exert a significant impact on cell survival (182). Specifically, these DON concentrations remarkably increased the survival rate of PRRSV-infected cells. Furthermore, DON at these concentrations led to a substantial reduction in PRRSV replication. This inhibitory effect is attributed to the induction of pro-inflammatory cytokines and the early activation of apoptosis. These mechanisms appear to interrupt the viral replication cycle and impede PRRSV propagation within the host (182).

Animal-Derived Compounds

Honeybee Venom

Honeybee (*Apis mellifera* Linnaeus 1758) venom (HBV) is recognized as an alternative medicine owing to its therapeutic properties, particularly in the management of pain, inflammation, and immune-related conditions such as rheumatoid arthritis and multiple sclerosis (183). Notably, HBV has demonstrated immunomodulatory effects on the Th1 immune response. Administration of HBV leads to the differentiation of CD4+ T lymphocytes into Th1 cells, thereby enhancing the production of interferon-gamma (IFN-γ) in mouse models (184). Furthermore, HBV phospholipase plays an important role in the maturation of dendritic cells and subsequent activation of dendritic cell-associated immune responses (185,186).

Investigations have been conducted to explore the potential antiviral activity of HBV against PRRSV. In a recent study, HBV was administered to healthy pigs via nasal, neck, and rectal routes, followed by intranasal inoculation with PRRSV (187). Significantly increased levels of CD4+/CD8+ cell ratio, IFN-γ, and IL-12 were observed in HBV-administered pigs via nasal and rectal administration. In pigs experimentally challenged with PRRSV, the viral genome load in the serum, lung, bronchial lymph nodes, and tonsils was significantly reduced, accompanied by mitigation of interstitial pneumonia severity in the nasal and rectal administration groups. Moreover, HBV administration leads to a substantial elevation in the levels of Th1 cytokines (IFN-γ and IL-12) and upregulation of pro-inflammatory cytokines (TNF-α and IL-1β) (187).

Caprylic Monoglyceride

Medium-chain fatty acids (MCFAs), including caprylic monoglycerides (CMG), are a class of fatty acids with carbon chain lengths ranging from 8 to 10 carbon atoms. While MCFAs are present in small quantities in nature, they are primarily derived from milk and breast milk and can also be found in palm kernel oil and coconut oil (188). Notably, MCFAs possess antimicrobial properties and their effects on animal productivity vary depending on the dosage employed (189).

One significant application of MCFAs is their ability to mitigate the transmission of the porcine epidemic diarrhea virus (PEDV) through feed and ingredients (190). Additionally, MCFAs have been demonstrated to influence the growth performance of animals by serving as readily available energy substrates, modulating gastrointestinal morphology, and exerting antimicrobial effects (191). MCFAs as a feed additive can also suppress African swine fever virus (ASFV) infection(192).

In light of the potential antiviral and antimicrobial effects of MCFAs, we investigated their antiviral activity against PRRSV. Recently, a study evaluated the cytotoxicity of four MCFAs, namely caprylic acid, CMG, decanoic monoglyceride, and monolaurin, along with their inhibitory effects on PRRSV. The results demonstrated that CMG exhibited the lowest toxicity towards cells among the four MCFAs, while displaying the highest inhibition rate against PRRSV (193).

To further assess the impact of CMG on PRRSV infection, piglets were treated with varying concentrations of CMG, revealing a significant decrease in mortality and viral load following PRRSV infection in piglets administered higher CMG concentrations ($p < 0.05$). Additionally, the pulmonary pathology in piglets was ameliorated by CMG treatment. Notably, CMG administration resulted in a significant downregulation of pro-inflammatory cytokines, including IL-6, IL-8, IL-1β, IFN-γ, and TNF-α, while upregulating the levels of the anti-inflammatory cytokine IL-10 in comparison to the positive control group ($p < 0.05$) (193).

Protegrin-1

Antimicrobial peptides (AMPs), including protegrin-1 (PG-1), are polypeptides of less than 100 amino acids (194). AMPs are found in both plant and animal kingdoms and exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and viruses involved in the innate immune response to infection (195). PG-1, originally isolated from porcine leukocytes (196), is considered to be an antibiotic agent against Gram-positive and Gram-negative bacteria and fungi *in vitro* (197). Furthermore, previous studies have shown that PG-1 inhibits dengue NS2B-NS3 serine protease and viral replication in MK2 cells (198).

PG-1 also strongly inhibits PRRSV infection and replication by suppressing viral RNA and protein synthesis, virus progeny production, and viral particle release. Furthermore, during the PRRSV life cycle, PG-1 mainly blocked viral attachment in Marc-145 cells. However, in PAMs, PG-1 neither inhibits PRRSV replication nor elevates antiviral cytokine expression (199).

Porcine Plasma Ficoline

Ficolins are proteins that activate the complement system and exhibit the ability to bind N-acetyl groups in various saccharides, particularly N-acetylglucosamine (GlcNAc) (200). This suggests that ficolins may also have the capacity to bind certain viruses that display host glycans on their surfaces (201).

Viral glycoproteins often possess complex-type oligosaccharides that are characterized by two terminal GlcNAc residues (202). Similar collagenous lectins have been shown to bind glycoproteins in IAV, HIV, HSV, and non-enveloped rotavirus (RV) (203). In a recent study, the antiviral activity of plasma-purified and recombinant ficolin α was assessed against PRRSV. The results revealed a reduction in the cytopathic effect of PRRSV-infected Marc-145 cells and inhibition of viral replication in the presence of ficolin α, which is dependent on GlcNAc recognition. Additionally, plasma ficolin α and recombinant ficolin α bind to PRRSV-coated wells in a GlcNAc-dependent manner (204).

Cecropin P1

Cecropin P1 (CP1) is a small antimicrobial peptide originally derived from the intestine of pigs, and it has demonstrated antiviral activity against various viruses, including infectious hematopoietic necrosis virus, viral hemorrhagic septicemia virus, snakehead rhabdovirus, and infectious pancreatic necrosis virus, in *in vitro* studies (205). CP1 exhibits significant antiviral effects against PRRSV, both as an extracellular virucidal agent and as an inhibitor, when administered prior to, simultaneously with, or following viral inoculation. The inhibitory mechanism of CP1 primarily targets viral attachment rather than viral entry into Marc-145 cells (206). Moreover, CP1 effectively impeded viral particle release and mitigated virus-induced apoptosis during the late stages of infection. The inhibitory action of CP1 against PRRSV was also extended to PAMs *in vivo*. Additionally, CP1 upregulates the expression of IL6 in PAMs, which could potentially contribute to its ability to inhibit PRRSV infection (206).

Cecropin D

Cecropin D (CD) is an antimicrobial peptide originally derived from Hyalophora cecropia Linnaeus 1758 pupae, and it has been previously demonstrated to possess antibacterial activity against both Gram-positive and Gram-negative bacteria, including *Escherichia coli* DH5α, K88, K99, *Streptococcus zooepidemicus* C55138, and *Staphylococcus aureus* Cowan I (207). In the context of PRRSV infection, CD exerted inhibitory effects during viral attachment and the early stages of viral entry into Marc-145 cells. Furthermore, CD effectively suppressed virus-induced apoptosis during the late phase of PRRSV infection and attenuated viral release within cells. These observations collectively contribute to the inhibition of PRRSV infection by CD. Importantly, similar inhibitory effects against PRRSV infection are evident when CD is utilized in PAMs during *in vivo* infection in pigs (208).

Conclusions

This comprehensive review highlights the potential of natural compounds derived from plants, animals, bacteria, and fungi as effective antiviral agents against PRRSV. These compounds exhibit diverse mechanisms of action targeting various stages of the PRRSV replication cycle (attachment, entry, fusion, replication, translation, maturation, and release). These compounds have shown promising broad-spectrum antiviral activities both *in vitro* and *in vivo*.

Although significant progress has been made in the field of natural compounds with antiviral activity against PRRSV, several research gaps still need to be addressed. First, further studies are needed to elucidate the precise mechanisms by which these natural compounds exert their antiviral effects. Understanding the molecular interactions between these compounds and PRRSV components will provide valuable insights for the development of more targeted interventions. Second, comprehensive investigations on the safety, pharmacokinetics, and toxicity profiles of these natural compounds are essential. These studies will help determine the optimal dosage and administration routes as well as evaluate potential side effects, ensuring their safe use in veterinary medicine. Finally, there is a need for more comprehensive studies to evaluate the efficacy of combination therapies using natural compounds. Investigating the synergistic effects of combining different compounds or combining them with existing antiviral drugs may enhance overall antiviral efficacy and reduce the emergence of drug-resistant viral strains.

Future research should explore the application of advanced technologies, such as nanotechnology and targeted delivery systems, to enhance the bioavailability and therapeutic potential of these natural compounds. These innovative approaches may improve compound stability, increase tissue specificity, and enhance the antiviral efficacy. Further research addressing the aforementioned research gaps and exploring new avenues, combined with rigorous preclinical and clinical trials, will accelerate the translation of these natural compounds into effective antiviral therapies for the control and prevention of PRRSV infections in swine.

Acknowledgments

The author would like to thank the DOST S&T Fellows Program, the Philippine Council for Agriculture, Aquatic and Natural Resources Research and Development (DOST-PCAARRD) for funding this research project, and the Industrial Technology Development Institute (DOST-ITDI) for hosting this research project.

Conflict of Interest. The author declares that there are no conflicts of interest.

Author Contributions. Fredmoore Orosco: Conception and design of the study, wrote the first draft of the manuscript, critically revised the manuscript, funding acquisition.

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Od naravne lekarne do zdravja prašičev: Izkoriščanje naravnih spojin proti okužbi z virusom PRRSV

F. L. Orosco

Izvleček: Virus prašičjega reprodukcijskega in respiratornega sindroma (PRRSV) je pomemben virusni patogen, ki povzroča znatne gospodarske izgube v prašičereji po vsem svetu. Zaradi omejene učinkovitosti obstoječih terapevtskih pristopov in pojavov novih sevov PRRSV so nujno potrebne nove protivirusne strategije. Naravne spojine, pridobljene iz rastlin, živali, bakterij in gliv, so vse bolj poznana kot potencialna protivirusna sredstva. Ta izčrpen pregled se osredotoča na naravne spojine s protivirusnim delovanjem proti PRRSV ter raziskuje mehanizme njihovega delovanja, učinkovitost in morebitno uporabo. Te spojine imajo različne protivirusne mehanizme, kot so zaviranje pritrjevanja in vstopa virusa, zaviranje razmnoževanja in modulacija gostiteljevega imunskega odziva. Pregled izpostavlja tudi izzive in prihodnje usmeritve na tem področju. Raziskovalne vrzeli vključujejo potrebo po nadaljnjem pojasnjevanju natančnih mehanizmov delovanja, celoviti oceni varnostnih profilov in raziskovanju kombiniranih terapij za povečanje učinkovitosti. Potrebne so nadaljnje raziskave in translacijske študije, da bi izkoristili celoten potencial teh naravnih spojin in utrli pot učinkovitemu nadzoru in obvladovanju okužb z virusom PRRSV v prašičereji.

Ključne besede: protivirusna sredstva; naravne spojine; PRRSV; prašičereja