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Review article

Recent progress in plant-derived antiviral compounds against African swine fever virus

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Abstract

African Swine Fever Virus (ASFV) poses a significant threat to the global swine industry, necessitating the development of effective therapeutic strategies. Through a detailed exploration of ASFV biology, pathogenesis, and replication cycle, critical targets for intervention were identified. The aim of this review was to evaluate the antiviral activity of different plant-derived compounds against ASFV, discuss research gaps, and highlight future perspectives. Key findings from the literature highlight the diverse mechanisms by which plant-derived compounds exert their antiviral effects on ASFV. Notably, flavonoids, alkaloids, and terpenoids exhibit promising antiviral potential via distinct modes of action. However, research gaps persist in the understanding of the precise mechanisms of action, strain-specific effects, and potential toxicity. With a growing understanding of ASFV biology and its intricate replication cycle, these compounds offer a promising avenue for intervention. Addressing research gaps and optimizing formulations are vital for translating these findings into effective therapeutic solutions. Interdisciplinary collaborations in virology, pharmacology, and plant science present an opportunity to combat ASFV, ensuring the security of the food supply and animal health on a global scale.

Keywords: African swine fever virus, Antiviral agents, Plant-derived compounds, Swine industry

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INTRODUCTION

African swine fever virus (ASFV) is the causative agent of African swine fever (ASF), a highly lethal viral disease in swine, with mortality rates near 100%. ASFV was initially identified in Kenya in 1921 and subsequently spread to Europe, the Americas, and Asia. Notably, commercial vaccines and antiviral drugs for ASFV remain to be developed (Golnar et al., 2019; Simbulan et al., 2024). In China, the first ASFV outbreak in August 2018 led to substantial economic losses exceeding billions of dollars, jeopardizing the pig industry and economic progress (Zhao et al., 2019).

ASFV is profoundly transmissible and is categorized as a notifiable pathogen by the World Organization for Animal Health (OIE). The virus is predominantly transmitted through direct contact with infected animals, consumption of infected animal products, and indirect transmission through contaminated gear, vehicles, footwear, feed, and attire. Furthermore, specific ticks and biting flies are also under scrutiny for their potential roles in virus transmission (Sánchez-Cordón et al., 2018).

ASFV is the sole member of the *Asfarviridae* family and represents the singular identified DNA arbovirus. This sizable double-stranded DNA virus comprises a linear genome measuring 170–190 kb, hosting over 150 open reading frames (ORFs) (de Villiers et al., 2010). ASFV exhibits an enveloped structure composed of five layers: the outer membrane, capsid, inner membrane, core-shell, and nucleoid, as illustrated in Figure 1 (Wang et al., 2019). The intricacies of ASFV infection and pathogenesis mechanisms remain incompletely understood, primarily due to its complex viral architecture, which is a challenge impeding vaccine advancement (Rock, 2017). The absence of a viable commercial vaccine underscores the need for innovative antiviral approaches.

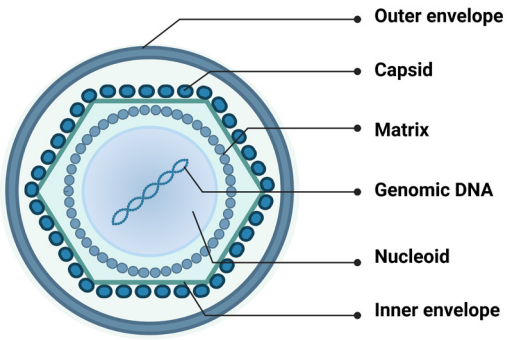

Figure 1 Schematic representation of ASFV structure.

In recent decades, various strategies and substances such as nucleoside analogs (Goulding et al., 2022), interferons (Muñoz-Moreno et al., 2016), antibiotics (Mottola et al., 2013), small interfering RNAs (Keita et al., 2010), CRISPR/Cas9 (Hübner et al., 2018), and plant-derived compounds (Y. Chen et al., 2022; Orosco, 2023a), have demonstrated *in vitro* efficacy against ASFV. Among these are plant-derived compounds, which present a range of targets and bioactivities while maintaining low toxicity (Table 1). This class of compounds has constituted over 50% of approved drugs or candidates in the last 30 years (Adhikari et al., 2021).

This comprehensive review aimed to explore different plant-derived compounds with antiviral activity against ASFV. The ASFV biology, pathogenesis, replication cycle, research gaps, and future perspectives for developing anti-ASFV compounds are also discussed.

Table 1 Plant-derived compounds and extracts with anti-ASFV activity.

Compound/ Extract	Chemical Class	Experiment	Mode of Action	Reference
Apigenin	Flavonoid	*In vitro*	Inhibition of protein synthesis and viral factory formation	(Hakobyan et al., 2016)
Genistein	Flavonoid	*In vitro*	Disruption of viral DNA replication, inhibition of late viral gene transcription and protein synthesis	(Arabyan et al., 2018)
Genkwanin	Flavonoid	*In vitro*	Reduction of late and early protein synthesis, DNA synthesis; Inhibition of virion entry and egress	(Hakobyan et al., 2019)
Toosendanin	Terpenoid	*In vitro*	Inhibition of virus internalization; upregulation of IRF1	(Liu et al., 2022)
Myricetin and derivatives	Flavonoid	*In vitro*	Inhibition of viral DNA synthesis; regulation of the TLR4/MyD88/MAPK/ NF-κB signaling pathway; inhibition of protease	(Jo et al., 2020) (Chen et al., 2023)
Berbamine hydrochloride	Alkaloid	*In vitro*	Inhibition of viral entry	(Zhu et al., 2023)
Luteolin	Flavonoid	*In vitro*	Inhibition of ASFV replication by regulation of NF-κB/STAT3/ATF6 signaling pathway	(Chen et al., 2022)
Theaflavin	Flavonoid	*In vitro*	Inhibition of ASFV replication, upregulation of AMPK signaling, downregulation of genes associated with lipid synthesis	(Chen et al., 2023)
Emodin and rhapontigenin	Anthraquinone/ Stillbene	*In vitro*	Inhibition of early ASFV replication stages, reduction of Rab 7 protein expression, elevated free cholesterol accumulation in endosomes hindering virus escape and late endosomal release	(Guo et al., 2023)
Aloe-emodin	Anthraquinone	*In vitro*	Inhibition of ASFV replication, early activation of the NF-κB pathway, apoptosis pathway later in infection, suppressed expression of MyD88, phosphor-NF-κB p65, pIκB proteins, and IL-1β and IL-8 mRNA levels, promotion of apoptosis	(Luo et al., 2023)
Kaempferol	Flavonoid	*In vitro*	Inhibition of ASFV entry and post-entry stages, inhibition of viral protein and DNA synthesis, induction of autophagy,	(Arabyan et al., 2021)
Natural oil blend formulation	Various	*In vivo* (pigs)	Reduced viral replication, high IgG levels, low IgM levels	(Babikian et al., 2021) (Truong et al., 2021)
Peppermint Extract	Various	*In vitro*	Not determined in the study	(Juszkiewicz et al., 2021)
Ancistrocladus uncinatus	Various	*In vitro*	Not determined in the study	(Fasina et al., 2013)

AFRICAN SWINE FEVER VIRUS BIOLOGY

ASFV, a large DNA virus enveloped in intricate layers, is an exclusive member of the *Asfarviridae* family and *the Asfivirus* genus (Arias et al., 2018). Within its genetic framework, 150–165 pivotal proteins are crucial for replication and circumventing the host immunity (Dixon et al., 2013). Prior research has delineated a comprehensive proteomic blueprint for ASFV (Alejo et al., 2018). It is noteworthy that approximately 54 of these proteins play a dual role in both structure and infection processes (Dixon et al., 2013; Orosco, 2023b), orchestrating strategies for host immune evasion. This includes dampening host transcription factors that are vital for viral replication. ASFV infiltrates host cells by engaging cell surface receptors, often traveling through tonsils neighboring lymph nodes during infection (Reis et al., 2017; Orosco, 2023c).

Post-viremia, ASFV migrates to tissue organs with primary transmission involving direct contact with infected pigs, contaminated objects, or swill (Guinat et al., 2016). *Ornithodoros* ticks contract the virus during their consumption by infected pigs; within the ticks, viral replication unfolds in gut tissues before relocating to the salivary glands. These infected ticks, which serve as vectors, transmit the virus through bites to other pigs. The virus accesses pig cells through endocytosis pathways encompassing clathrin-mediated and receptor-mediated mechanisms (Galindo and Alonso, 2017).

In new swine herds, ASF manifests as widespread animal mortality accompanied by heightened fever, diminished appetite, restricted mobility, and pig clustering. In severe cases, death might occur prior to the appearance of additional clinical signs over a span of up to four days. The initiation of clinical manifestations can be affected by various factors including viral genotype, animal lineage, environmental conditions, incubation duration, and route of exposure (Jori and Bastos, 2009).

Milder instances of ASF are distinguished by petechial hemorrhage, mucoid diarrhea, and skin reddening near the ears, abdomen, and limbs (Pikalo et al., 2019). Post-mortem evaluations revealed hemorrhages within internal organs, including the lungs, lymph nodes, intestines, heart, kidney, and liver. The spleen exhibits an augmented size and anomalous darkened appearance (Sánchez-Cordón et al., 2018). The effect of scavenging pigs, wild hosts, and convalescent pigs on the epidemiology of the virus remains uncertain, although some studies have proposed their potential involvement in transmission (Probst et al., 2019).

ASFV PATHOGENESIS

ASF is characterized by marked leukopenia, particularly lymphopenia, and a pervasive condition of immunodeficiency (Patil et al., 2020). Primary pig infection originates from the oral-nasal pathways or bites from infected soft ticks. Initially, the virus proliferates in tonsils or nearby lymph nodes (Pikalo et al., 2019) and then spreads through the lymph and blood to secondary replication sites within 2–3 days (Colgrove et al., 1969) before disseminating to various organs, facilitating replication across different cell types (Heuschele, 1967).

Monocytes and macrophages are the predominant targets of ASFV (Dixon et al., 2019). Although ASFV is a DNA virus, its replication occurs within the cytoplasm rather than the nucleus (Coelho and Leitão, 2020; Mahedi et al., 2023). Infected monocyte-macrophages display enlargement, nuclear chromatin repositioning, and harbor intracytoplasmic juxtanuclear inclusion bodies. Transmission electron microscopy revealed that these bodies were viral factories. Viral replication leads to host cell necrosis, with virions released via budding and detected freely in the blood, lymph, and interstitial tissues (Salguero, 2020).

The destruction of monocyte macrophages induced by ASF is associated with ASFV-triggered apoptosis or necrosis (Afe et al., 2023). Genes within the ASFV genome play roles in modulating programmed cell death, featuring both inhibitory and inducible functions (Netherton et al., 2019). Specific genes may promote the survival of infected cells, whereas apoptosis is considered less likely to cause cell death within the infected monocyte-macrophage group (Dixon et al., 2017).

ASF is characterized by substantial degradation of lymphoid organs including the spleen, lymph nodes, thymus, and tonsils (Sánchez-Cordón et al., 2021). During acute ASFV infection, notable fractions of B and T lymphocytes, along with macrophages, undergo cell death (Schäfer et al., 2022). Replication of the virus within monocyte-macrophages triggers their activation, resulting in an increased release of proinflammatory cytokines during early disease stages (Gómez-Villamandos et al., 2013). The amplified expression of proinflammatory cytokines, notably IL-1, TNF-α, and IL-6, recognized as a "cytokine storm," contributes to substantial lymphocyte apoptosis close to activated/infected monocyte-macrophages within tissues (Machuka et al., 2022).

ASFV REPLICATION CYCLE

ASFV proliferates within the mononuclear phagocyte system of infected pigs, primarily in monocytes and macrophages. The replication cycle initiates viral attachment and entry into the cell. While specific cellular receptors for ASFV entry remain unidentified, receptor-dependent mechanisms, such as clathrin-mediated endocytosis, have been documented (Galindo et al., 2015). Evidence also suggests that ASFV uses an alternative mechanism, macropinocytosis, to enter the Vero cells (Sánchez et al., 2012). Following endocytosis, ASFV undergoes conformational changes due to acidic conditions in the endosome. Uncoating occurs within multivesicular late endosomes, leading to inner membrane fusion, core release into the cytosol, and viral factory formation near the nucleus (Hernáez et al., 2016).

The four classes of ASFV transcripts linked to accumulation kinetics include immediate early, early, intermediate, and late genes. Immediate early and early genes are transcribed immediately after infection, until viral DNA synthesis begins. Intermediate and late gene transcription occurs after the initiation of DNA replication (Rodríguez and Salas, 2013). ASFV particles migrate from the factory to the cell surface via microtubule-mediated transport depending on the capsid protein pE120R and kinesin motor protein (Wang et al., 2021). They exit the cell by budding at the membrane, acquiring an additional lipid membrane. At late infection stages, ASFV prompts cell lysis, potentially

constituting an alternative viral egress mechanism (Breese and DeBoer, 1966). Categorized by their anti-ASFV mechanisms, potential antiviral compounds fall into two categories: (1) direct-acting antivirals targeting viral proteins and (2) host-targeting antivirals, inhibiting cellular factors implicated in ASFV replication. Advancing anti-ASFV drug development hinges on deeper insights into the roles of viral enzymes and host elements, underlining the necessity for further research (Arabyan et al., 2019). The scope of this review is limited to inhibitors that directly act on ASFV by targeting proteins.

PLANT-DERIVED ANTIVIRAL AGENTS

Apigenin

Apigenin (Figure 2), a flavonoid isolated from *Ocimum basilicum*, is a consumable compound (4′,5,7-trihydroxyflavone) that has distinctive effects on normal and cancer cells, distinguished from structurally related flavonoids (Gupta et al., 2001). Its low intrinsic toxicity and robust antioxidant and anti-inflammatory properties contribute to its cancer preventive potential (Singh et al., 2012). Particularly noteworthy is the role of apigenin in cancer prevention via the induction of apoptosis in diverse cell lines and animal models (Kaur et al., 2008). Additionally, apigenin exhibits potent antiviral activity against adenoviruses and hepatitis B virus (Chiang et al., 2003), and subsequent research highlights its capacity to hinder the translation of viral genes, including in the post-treatment stage of foot-and-mouth disease virus (Qian et al., 2015).

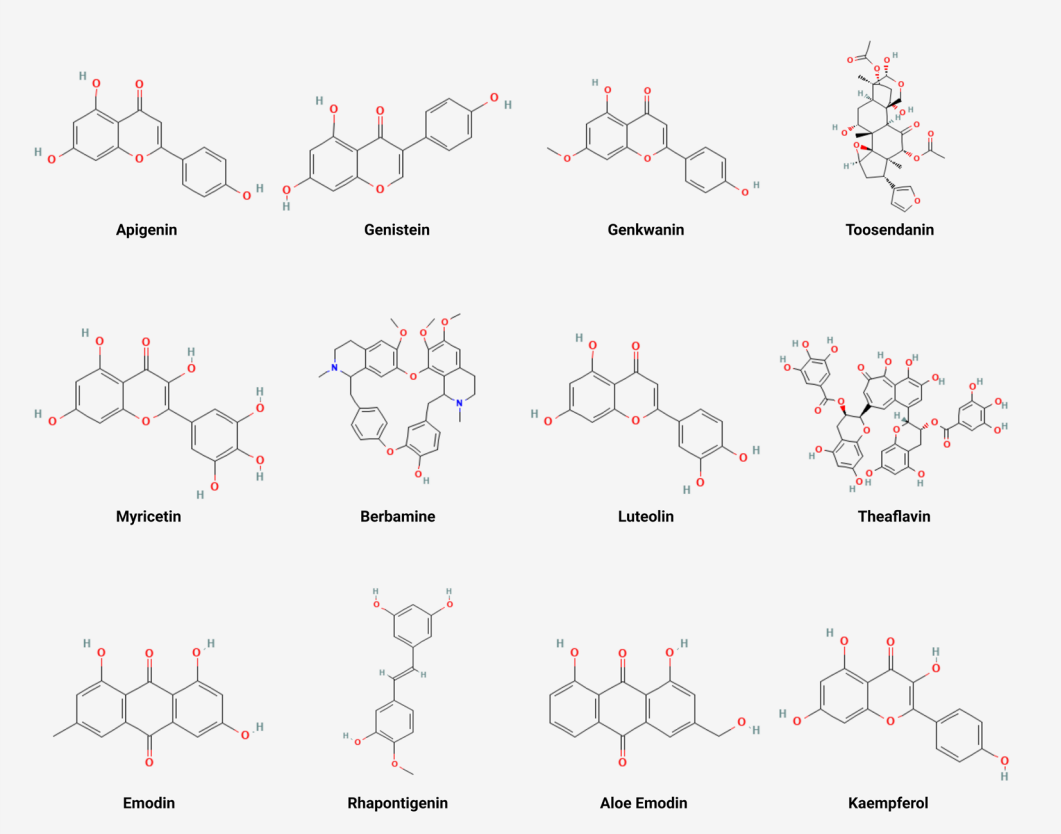

Figure 2 Chemical structures of plant-derived compounds with antiviral activity against ASFV.

Consequently, the antiviral potential of apigenin extends to other viruses, demonstrating substantial *in vitro* anti-ASFV efficacy in a dose-dependent manner (Hakobyan et al., 2016). Time-of-addition trials revealed the pronounced effectiveness of apigenin during early ASFV infection stages, resulting in over 99.99% reduction in ASFV yield when administered at 1 hpi. Subsequent investigations into ASFV protein synthesis and viral factories underscored the inhibition of ASFV-specific protein production and viral factory formation by apigenin (Figure 3). Continuous apigenin treatment of ASFV-infected cells prevented the cytopathic effect, emphasizing its potential as an antiviral agent (Hakobyan et al., 2016).

Genistein

Genistein (Figure 2), an isoflavonoid derived from *Genista tinctoria*, has demonstrated its potential to inhibit the replication of diverse viruses through distinct mechanisms. Notably, it hampers human cytomegalovirus replication by targeting the viral immediate-early protein function (Evers et al., 2005). In the case of Pichinde virus, genistein disrupts the activation of viral transcription factor-2 in Vero cells (Vela et al., 2008). Moreover, genistein impedes replication of avian leukosis virus subgroup J by obstructing viral transcription (Qian et al., 2014). Its antiviral effect extends to HIV infection, where it interferes with viral protein U, which contributes to ionic channel formation in infected cells (Sauter et al., 2014).

A notable study revealed that genistein effectively inhibited ASFV infection at non-cytotoxic levels in both Vero cells and porcine macrophages (Arabyan et al., 2018). This isoflavone, known for its role as a eukaryotic topoisomerase II inhibitor, demonstrated its highest antiviral efficacy when introduced during the mid-infection phase (8 hpi). Genistein disrupts viral DNA replication, inhibits late viral gene transcription and protein synthesis, ultimately constraining viral progeny production (Figure 3). Additionally, single-cell electrophoresis analysis revealed fragmented ASFV genomes in genistein-exposed cells, highlighting its role as an ASFV-topo II poison rather than a reversible inhibitor (Arabyan et al., 2018).

Genkwanin

Genkwanin (Figure 2), an O-methylated flavone that is highly present in *Alnus glutinosa* seeds, exhibits a range of biological functions, including antioxidant (Sroka et al., 2015) and anti-inflammatory (Z. Chen et al., 2022), neuroprotective (Li et al., 2021), anticancer (El-Wassimy et al., 2019; Orosco, 2023d), antibacterial (Lucarini et al., 2015), and antidiabetic effects (Mohammed et al., 2017). Notably, genkwanin demonstrated potential as an anti-inflammatory agent by effectively targeting proinflammatory mediators such as TNF-α, IL-1β, IFNγ, and IL-6. This is accomplished by inhibiting reactive oxygen species (ROS) generation (Sun et al., 2020) or by modulating the microRNA-101, p38-, and JNK-mediated AP-1 signaling pathways (Gao et al., 2014).

Mohammed et al. identified genkwanin-6-C-beta glucopyranoside as a promising antiviral candidate against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (Mohammad et al., 2021). It displayed notable binding affinity for nsp10, with a higher affinity (−37.4±1.3 Kcal/mol), and exhibited potent bioactivity without inducing toxicity. The compound

effectively obstructed the nsp10-nsp16 interaction, with a low IC_{50} (0.029–0.035 M), implying its potential as a robust target protein inhibitor. These characteristics position genkwanin-6-C-beta glucopyranoside as a naturally derived substance capable of disrupting the nsp10-nsp16 complex interaction interface of SARS-CoV-2 (Mohammad et al., 2021).

Studies have demonstrated the significant inhibitory impact of genkwanin on ASFV, yielding a dose-dependent decline in viral titer from 6.5 ± 0.1 to 4.75 ± 0.25 log TCID/ml (with IC_{50} at 2.9 µM and SI at 205.2) (Hakobyan et al., 2019). This is achieved by decreasing ASFV early and late protein levels along with viral DNA synthesis (Figure 3). Further investigations revealed the capability of genkwanin to impede both ASFV entry and egress phases. Moreover, genkwanin showed efficacy against highly virulent ASFV strains circulating in Europe and China, underscoring its potential as a candidate for antiviral drug development (Hakobyan et al., 2019).

Toosendanin

Toosendanin, or TSN (Figure 2), is a triterpenoid saponin isolated from *Melia toosendan* Sieb. et Zucc in 1950, has long been used as an agricultural insecticide and has historically been employed as an ascarifuge in China (Ma et al., 2013; Orosco & Quimque, 2024). TSN exhibits diverse activities, including analgesic, anti-inflammatory, anti-botulism, and antimicrobial effects (Jin et al., 2017). Notably, TSN exhibited anti-proliferative and apoptosis-inducing effects *in vitro* in several human cancer cell lines. For instance, TSN hampers colorectal cancer cell growth by inhibiting the AKT/GSK-3 β/β-catenin pathway, leading to apoptosis (Wang et al., 2015). In human gastric cancer cells, TSN induces caspase-dependent apoptosis by activating the p38 MAPK pathway (Zhou et al., 2018). Furthermore, TSN curtails adipogenesis by activating Wnt/β-catenin signaling (Chen et al., 2018).

Nonetheless, limited investigations have been conducted regarding the antiviral potential of TSN. In 2011, Watanabe et al. demonstrated TSN's capacity, alone or combined with IFNα, to hinder hepatitis C virus (HCV) infection in a human hepatoma cell line (Watanabe et al., 2011). A subsequent study by Jin et al. (2019) indicated that TSN inhibits early stage influenza A virus infection through alteration of PA protein nuclear localization (Jin et al., 2019). Building on this, Li et al. uncovered TSN's expansive antiviral effects of TSN against bunyaviruses and emerging SARS-CoV-2 in 2021 (S. Li et al., 2021).

Recent studies have investigated the antiviral efficacy of TSN against ASFV. These findings underscore its potent dose-dependent inhibitory effect on the ASFV GZ201801-38 strain within porcine alveolar macrophages (PAMs) (EC_{50} = 0.085 µM, SI = 365) (Liu et al., 2022). TSN exhibited robust antiviral activity across varying ASFV infection doses, manifesting as reduced ASFV p30 protein transcription and translation levels, decreased viral genomic DNA quantity, and lowered viral titers at both 24 and 48 h post-infection (Figure 3). Notably, TSN did not affect virion attachment and release but intervened in its internalization within PAMs. Further investigations revealed TSN's antiviral mechanism of TSN, attributed to the upregulation of the host IFN-stimulated gene (ISG) IRF1, as opposed to direct virus particle inactivation. Collectively, these findings suggest that TSN has a promising role as an effective antiviral agent against ASFV replication *in vitro*, highlighting its potential clinical application (Liu et al., 2022).

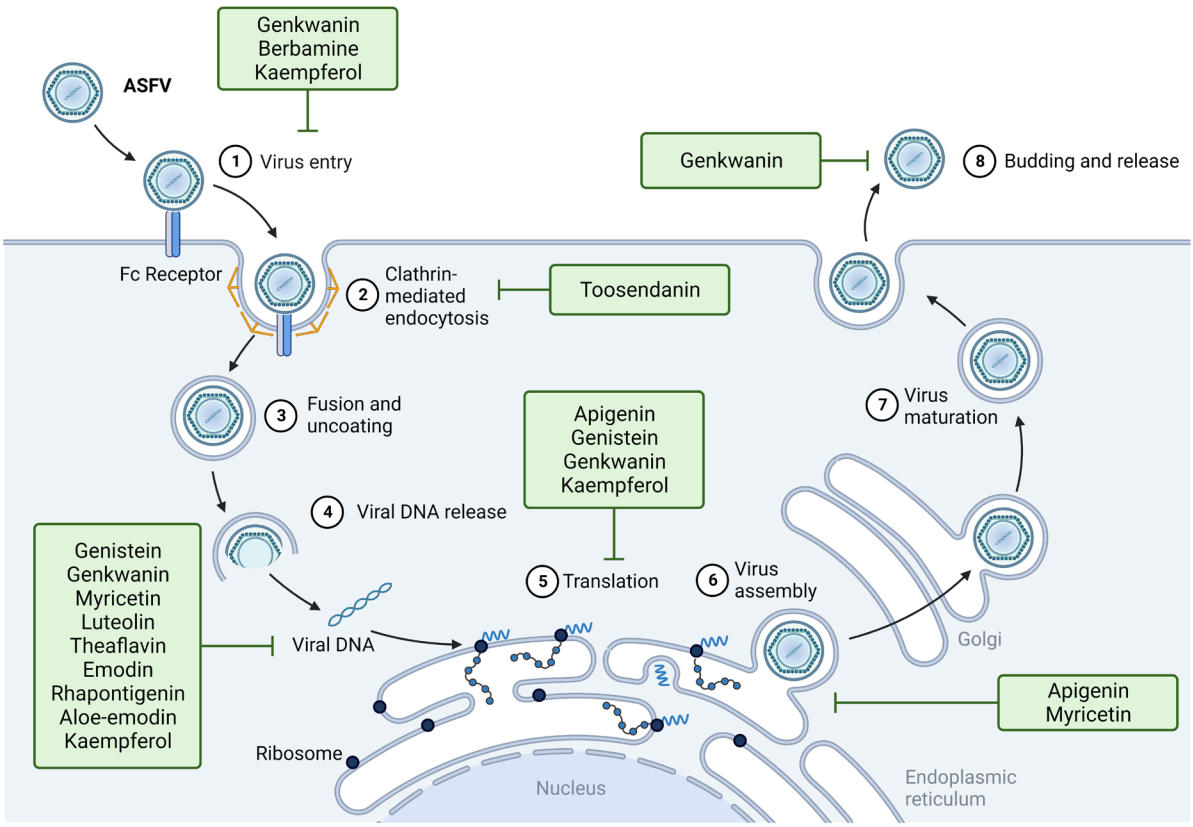

Figure 3 Chemical structures of plant-derived compounds with antiviral activity against ASFV.

Myricetin and its derivatives

Myricetin (Figure 2), a polyhydroxyflavonoid, was originally discovered in bayberry bark during the late 18th century and was subsequently isolated from various plants, including *Myricaceae, Vitaceae, Fabaceae, Ericaceae,* and *Euphorbiaceae* (Taheri et al., 2020). This natural flavonoid is used in medicine, food, health products, and cosmetics. Its antioxidant properties are well established, and it effectively scavenges free radicals and ions such as DPPH, NO, and ROS (Zhang et al., 2011). Functioning both as an antioxidant and pro-oxidant depending on ascorbic acid and Fe3+ involvement (Duthie and Morrice, 2012), myricetin guards organisms against oxidative damage. Myricetin also has diverse anti-cancer effects, is cytotoxic towards various cancer cells, and inhibits cancer-associated enzymatic activity (Xie et al., 2020). The anti-inflammatory activity of this compound has been demonstrated in multiple trials, modulating different signaling pathways (Kan et al., 2019). Myricetin exhibits inhibitory potential against both bacteria and viruses (Naz et al., 2007; Orosco & Wong, 2023). Studies have shown that myricetin targets the viral gD protein to suppress HSV replication by downregulating the cellular EGFR/PI3K/Akt pathway (Li et al., 2020). Myricetin also hampers HIV infection through SEVI fiber suppression and direct killing effects (Ren et al., 2018). Moreover, it inhibits the activation of reverse transcriptase in murine leukemia virus (RLV) and HIV, as well as the activation of the SARS-CoV helicase protein. Additionally, myricetin shows anti-allergic, anti-acid, antihypertensive, and analgesic activities (Yu et al., 2012).

Recent studies have revealed the anti-ASFV properties of myricetin and its derivatives. Using a fluorescence resonance energy transfer (FRET)

assay, myricetin exhibited robust anti-ASFV protease activity, with the lowest IC_{50} at 8.4 μM (Jo et al., 2020). Likewise, its derivative myricitrin, containing a rhamnoside moiety, demonstrated significant inhibitory effects on ASFV protease. These flavonols offer a promising foundation for the development of anti-ASFV agents that utilize their structural framework (Jo et al., 2020).

In a recent study, dihydromyricetin (DHM) emerged as a potent anti-ASFV agent (Chen et al., 2023a). DHM treatment effectively inhibited ASFV replication in a dose-dependent manner Notably, DHM exhibited a broad-spectrum antiviral effect by inhibiting replication of porcine reproductive and respiratory syndrome virus and swine influenza virus (Orosco, 2024). Mechanistically, DHM's impact of DHM on ASFV replication was observed across various treatment stages (pre-, co-, and post-treatment) in the time-to-addition assay (Figure 3). Additionally, DHM's anti-ASFV effect of DHM extended to the regulation of the TLR4/MyD88/MAPK/NF-κB signaling pathway, which contributed to the reduction of ASFV-induced inflammatory mediators. Moreover, DHM intervention led to a decrease in reactive oxygen species accumulation induced by ASFV, resulting in suppression of NLRP3 inflammasome activation and subsequent pyroptosis (Chen et al., 2023a). These findings collectively underscore DHM's efficacy of DHM against ASFV and elucidate its underlying mechanism, offering a potential avenue for antiviral drug development against ASFV.

Berbamine hydrochloride

Berbamine hydrochloride (Figure 2), derived from *Berberis amurensis*, a traditional Chinese herb, is a bis-benzylisoquinoline alkaloid with documented antiviral properties against various viruses, including the bovine viral diarrhea virus (BVDV) (Wang et al., 2022), Japanese encephalitis virus (JEV) (Huang et al., 2021), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhang et al., 2022). Furthermore, berbamine hydrochloride exhibits the capacity to modulate cellular processes; it interferes with lysosomal acidification in human lung carcinoma cells and mitigates inflammation by modulating the NF-κB and MAPK signaling pathways (Zhan et al., 2022).
Berbamine hydrochloride showed notable antiviral efficacy against ASFV. In a dose-dependent manner, it demonstrated inhibition of ASFV with a reduction of 4.14 log $TCID_{50}$ in viral titer without inducing cytotoxicity (Zhu et al., 2023). Its antiviral action remained consistent for 48 h and was effective against various multiplicities of infection (MOI) levels (0.01, 0.1, and 1). Detailed time-of-addition analysis revealed its inhibitory influence throughout the viral life cycle (Figure 3), and subsequent experiments focusing on viral entry confirmed its ability to block the initial phase of ASFV infection (Zhu et al., 2023).

Luteolin

Luteolin (Figure 2), a flavonoid compound, is derived from green peppers, celery, broccoli, and parsley (Taheri et al., 2021). Luteolin displays a range of biological activities, including anti-inflammatory, anti-cancer, and anti-allergic effects (Punia Bangar et al., 2023). Additionally, luteolin modulates signaling pathways, such as NF-κB, JAK-STAT, and ER stress (Huang et al., 2023). It is noteworthy that its antiviral activity against respiratory syncytial, dengue, and Epstein-Barr viruses (Wang et al., 2020). Moreover, molecular docking studies have emphasized luteolin's stronger binding affinity to the main protease of SARS-CoV-2 than to a control molecule (Yu et al., 2020).

In a recent investigation, the potent antiviral efficacy of luteolin against ASFV in PAMs was elucidated, along with its mechanism of action (Chen et al., 2022). Notably, luteolin exhibited dose-dependent inhibition of ASFV replication, remaining effective for 24–72 h (Figure 3). Subsequent assays revealed its ability to impede various ASFV replication phases, particularly at 6–9 h and 12–15 h post-infection, without direct ASFV interactions. Interestingly, ASFV triggered phosphorylated NF-κB, IL-6, and phosphorylated STAT3 expression, but luteolin countered these effects. Notably, the NF-κB agonist, CU-T12–9, weakened luteolin's NF-κB and STAT3 inhibition, partially restoring its ASFV inhibitory effect. Similarly, luteolin reduced ASFV-induced ATF6 expression, with CU-T12–9 mitigating its inhibitory impact (Chen et al., 2022). These findings suggest that luteolin inhibits ASFV via NF-κB/STAT3/ATF6 modulation, thereby offering insight into potential anti-ASFV drug development.

Theaflavin

Theaflavin (TF) (Figure 2), derived from black tea, has a range of biological functions, including antioxidant, anti-inflammatory, and anticancer properties (O'Neill et al., 2021). Furthermore, TF have demonstrated antiviral activity. A recent study highlighted the *in vitro* effectiveness of a TF-enriched tea extract against the influenza A virus (IAV), although the specific active compound remains unidentified (Mohamed et al., 2022). Additionally, TF has shown potential in inhibiting hepatitis C virus (HCV) replication, although the exact mechanism underlying its antiviral action remains unclear (Chowdhury et al., 2018).

In a recent study, TF potently inhibited ASFV replication in PAMs at non-cytotoxic concentrations (Chen et al., 2023b). Notably, TF's antiviral mechanism was mediated through host cells rather than through direct interaction with ASFV. This study also revealed that TF activated the AMPK signaling pathway in both infected and uninfected cells. The AMPK agonist MK8722 mirrored TF's effects of TF by upregulating AMPK signaling and inhibiting ASFV proliferation in a dose-dependent manner (Figure 3). Conversely, the AMPK inhibitor dorsomorphin partially reversed the effects of TF on AMPK activation and ASFV inhibition. Furthermore, TF downregulated the genes associated with lipid synthesis, concurrently decreasing intracellular total cholesterol and triglyceride accumulation in ASFV-infected cells. These findings suggest that TF's inhibition of ASFV replication by TFs involves disruption of lipid metabolism (Chen et al., 2023b). Thus, this study provides valuable insights into TF's role of TF as an ASFV inhibitor, shedding light on its mechanism of action and its potential as an anti-ASFV drug candidate.

Emodin and rhapontigenin

Emodin (EM) is a naturally occurring anthraquinone derivative (Figure 2) found in sources such as rhubarb, Japanese knotweed, and fleeceflower. Its therapeutic potential extends beyond antitumor effects, encompassing properties such as antiulcer, anti-inflammatory, hepatoprotective, neuroprotective, muscle relaxant, antibacterial, immunosuppressive, and antifibrotic activities (Stompor-Gorący, 2021). Conversely, rhapontigenin (RHAG), a stilbene derivative (Figure 2), has antiallergic, antiangiogenic, anticoagulant, hypoglycemic, and laxative effects (Park et al., 2002). RHAG has demonstrated notable antiviral

efficacy against a wide spectrum of viruses both *in vitro* and *in vivo*, including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), coxsackievirus B (CVB), hepatitis B virus (HBV), influenza A virus (IAV), severe acute respiratory syndrome coronavirus (SARS-CoV), viral hemorrhagic septicemia rhabdovirus (VHSV), enterovirus 71 (EV71), dengue virus type 2 (DENV-2), and Zika virus (ZIKV) (Kausar et al., 2021).

A recent investigation revealed that both EM and RHAG exhibited a dose-dependent inhibitory effect on the ASFV GZ201801 strain within the PAMs (Guo et al., 2023). The inhibitory effects persisted at 24, 48, and 72 h. Beyond impacting virion attachment and internalization, EM and RHAG demonstrated robust inhibition of the early ASFV replication stages (Figure 3). Molecular insights indicated decreased Rab 7 protein expression due to EM and RHAG treatments. Moreover, EM and RHAG induced elevated free cholesterol accumulation in endosomes while inhibiting endosomal acidification, hindering viral escape and late endosomal release. This investigation underscores the potential of EM and RHAG to counter ASFV replication *in vitro*. Their targeting of Rab 7 in the viral endocytosis pathway, promotion of cholesterol accumulation in endosomes, and inhibition of endosomal acidification collectively obstruct viral uncoating and infection (Guo et al., 2023).

Aloe-emodin

Aloe vera has notable inhibitory activity against influenza virus, herpes simplex virus type 1, and other pathogens (Dziewulska et al., 2018). Apart from the holistic antiviral effect of the entire aloe extract, individual compounds also displayed antiviral properties. One such compound is aloe-emodin or Ae (Figure 2), a natural anthraquinone derivative (C15H10O5) found in Chinese herbs such as *Cassia occidentalis*, *Rheum palmatum* L., *Aloe vera*, and *Polygonum multiflorum* Thunb (Dong et al., 2020). Recent research highlights the potential of Ae as an antiviral, anticancer, and anti-inflammatory agent, with involvement in immunomodulation and apoptosis induction (Ma et al., 2022). The impact of Ae on inflammation includes inhibition of inducible nitric oxide synthase expression, IκBα protein degradation, and phosphorylation of ERK, p38, JNK, and Akt proteins under inflammatory stress. Furthermore, Ae downregulates proinflammatory factors within the NF-κB pathway to counteract inflammation (Xian et al., 2021). Additionally, Ae markedly elevated intracellular reactive oxygen species levels, hindered cell proliferation, and triggered apoptosis (Byun et al., 2018).

Numerous studies have highlighted the antiviral effectiveness of Ae against pathogens, such as porcine reproductive and respiratory syndrome virus (PRRSV) (Xu et al., 2021), influenza virus (Gansukh et al., 2018), and SARS-CoV (Ho et al., 2007). Given this, its potential antiviral effect on ASFV has been explored. The findings indicated significant inhibition of ASFV replication by Ae (Figure 3). Transcriptomic analysis revealed ASFV activation of the NF-κB pathway early and the apoptosis pathway later during infection (Luo et al., 2023). Ae notably suppressed the expression of MyD88, phospho-NF-κB p65, and pIκB proteins, and IL-1β and IL-8 mRNA levels in ASFV-infected PAMs, thereby curbing the ASFV-induced NF-κB signaling pathway. Flow cytometry and western blot assays demonstrated the role of Ae in augmenting the ASFV-induced apoptotic cell percentage. Ae achieves this by elevating cleaved-

caspase3 and Bax protein levels and reducing Bcl-2 protein levels, thereby promoting apoptosis. This suggests that Ae induces apoptosis by modulating the NF-κB pathway, ultimately inhibiting ASFV replication (Luo et al., 2023). These findings hold promise for enhancing therapeutic strategies against ASF and for bolstering prevention and treatment approaches.

Kaempferol

Kaempferol (Figure 2), known chemically as 3, 5, 7-trihydroxy-2-(4-hydroxyphenyl) -4H-1-benzopyran-4-one, is a natural flavonol primarily sourced from ginger rhizomes and found in various plants such as tea, broccoli, and purple cabbage (Imran et al., 2019). As a tetrahydroxy flavone with hydroxy groups at positions 3, 5, 7, and 4', it has garnered attention for its multifaceted properties, including anticancer, anti-inflammatory, antioxidant, antibacterial, and antiviral effects, as well as its potential in treating diabetes and osteoporosis (Lei et al., 2019). This phytoestrogen has been shown to inhibit pathogens such as the main protease of SARS-CoV-2 (3CLpro) (Zhao et al., 2021), herpes simplex virus (HSV) type-1, rotavirus, and pseudorabies virus (Li et al., 2021) replication, underscoring its diverse antiviral capabilities among other biological activities.

Recently, kaempferol has demonstrated robust anti-ASFV activity, characterized by dose-dependent inhibition, primarily exerting a virostatic effect (Arabyan et al., 2021). Time-of-addition experiments revealed that kaempferol influenced both the entry and post-entry stages of the ASFV replication cycle, impeding vital protein and DNA synthesis (Figure 3). Moreover, induction of autophagy was observed in ASFV-infected Vero cells following kaempferol treatment, contributing to its antiviral effect; this autophagy induction was partially reversible with an autophagy inhibitor. Kaempferol displayed dose-dependent inhibition of the virulent ASFV Arm/07 isolate in porcine macrophages (Arabyan et al., 2021). These outcomes collectively underscore the potential of kaempferol as a promising anti-ASFV agent, distinguished by its unique antiviral mechanism compared to other flavonoids targeting ASFV.

Natural oil blend formulation

Natural oils are recognized for their established role as antiviral agents and serve as vital constituents of standardized antiviral compounds (Juergens, 2014). A noteworthy formulation harnesses the synergistic potential of three natural oils with proven antiviral properties: *Eucalyptus globulus, Pinus sylvestris,* and *Lavandula latifolia*. Eucalyptus oil, enriched with cineole as its principal component, has remarkable anti-inflammatory and antimicrobial capabilities, and is particularly effective against respiratory viral infections (Wang et al., 2020). Lavender oil, prominently containing linalool, is known for its antiviral efficacy (Probst et al., 2019). Isobornyl acetate, extracted from pine oil, contributes to its antimicrobial properties (Choi, 2018). *In vitro* trials of the formulated blend revealed that NOBF at dilution 13 (0.000625 mL) neutralized a lethal dose of 10^5 HAD_{50} ASFV (Truong et al., 2021). Remarkably, NOBF at a dilution of up to 12 (0.00125 mL) exhibited no HAD (Rosetta formation). In real-time PCR analysis at 96 h post-infection, the NOBF group displayed consistent or reduced Ct values (≤ 25), while positive controls showed substantial Ct value increments (17.84), demonstrating the potential of NOBF as an effective antiviral compound against ASFV (Truong et al., 2021).

In a separate investigation utilizing NOBF, both challenged (three) and cohoused (three) pigs in the positive control group exhibited clinical signs of ASFV infection (Babikian et al., 2021). This was evident through RT-PCR detection in the blood samples, oral swabs, and feces. Tragically, the positive control group experienced 100% cumulative mortality, with both challenged and co-housed pigs succumbing to infection by day 20. In contrast, the NOBF-incubated group remained free from infection and mortality. Among the challenged pigs, those directly exposed to NOBF displayed clinical symptoms and mortality, whereas cohoused pigs did not exhibit signs of infection. Notably, immunoglobulin G (IgG) levels in contact pigs were highest in the treatment group and lowest in the positive control group. Conversely, IgM levels were the lowest in the contact pigs of the treatment groups, whereas they were the highest in the positive control group. RT-PCR analysis confirmed the deactivation of ASFV in the NOBF-treated group. High Ct values were observed in the challenged and contact pigs in the positive control group. Challenged pigs in the NOBF group also displayed high Ct values, whereas contact pigs in the same group, along with those in the negative control group, tested negative for ASFV in all samples via PCR. A comparative analysis between the challenged groups revealed that the onset of viral appearance was delayed by a minimum of 2 days in the NOBF group compared to the positive control group (Babikian et al., 2021).

The results of these studies indicate that NOBF can impede the dissemination of ASFV within a population. Furthermore, NOBF has the potential to augment porcine humoral immune response by elevating IgG levels and diminishing IgM levels. This investigation underscores the role of NOBF as an anti-ASFV agent, effectively curbing horizontal transmission and bolstering humoral immunity in pigs. However, additional testing is required to validate these findings.

Peppermint Extract

In a recent investigation, 14 plant extracts were screened for their virucidal effects on ASFV using a suspension test based on the PN-EN 14675:2015 European Standard protocol (Li et al., 2017). The results indicated that the majority of the tested plant extracts displayed limited effectiveness against ASFV. Notably, certain extracts suspended in the hydroglycolic medium exhibited substantial virus titer reduction, although this effect was ascribed to the composition of the medium. However, a peppermint extract at 1.05% concentration demonstrated pronounced efficacy against ASFV, achieving a virus titer reduction of ≥4 log10 despite ASFV being an enveloped virus (Lelešius et al., 2019). This aligns with prior studies showing the virucidal efficacy of peppermint against enveloped viruses. Considering the established inactivating effect of menthol against herpes simplex virus infection (HSV-1 and HSV-2) and the composition analysis of the peppermint extract, it can be hypothesized that the high menthol content (42.8%) contributes to its antiviral effectiveness against ASFV (Juszkiewicz et al., 2021). This distinctive menthol abundance sets it apart from the other Lamiaceae family members. These findings highlight the potential use of natural compounds as virucidal agents in disinfection procedures, offering both efficacy and safety for humans and animals.

Ancistrocladus uncinatus Extract

Ancistrocladus uncinatus is one of the plants administered to ASF-infected pigs in West Africa, reportedly leading to unverified reductions in morbidity and mortality. There are even claims of complete recovery from illness upon oral administration of *A. uncinatus* preparations. This particular Liana plant species was initially documented in southeastern Nigeria by Hutch and Dalziel, as cited by Cheek (Cheek, 2000), whereas a related plant was recently characterized by Thomas and Gereau (1993). Although the geographic distribution of *A. uncinatus* has been generally outlined, A. korupensis is situated within the tropical swamp of Korup National Park in Cameroon and the contiguous Cross River National Park in Nigeria.

The antimalarial and anti-HIV attributes of the *Ancistrocladus liana* plant (Schwikkard and van Heerden, 2002). Several naphthylisoquinoline alkaloids (such as korundamine, yaoundamine, and korupensamine) exhibit diverse biological activities, including anti-HIV, antimalarial, fungicidal, larvicidal, and molluscicidal effects (Hallock et al., 1998). Moreover, michellamine B, another alkaloid present in this plant, has shown anti-HIV potential by impeding viral replication, syncytium formation, enzymatic activity, and cell-killing functions (McMahon et al., 1995).

In a separate investigation, the utilization of GC-MS methodology identified 35 compounds, and specific extracts and fractions of the plant exhibited significant reduction of the ASF virus (NIG 99) (Fasina et al., 2013). However, water-based extraction yielded poor results and the plant extracts displayed cytotoxicity, posing a notable challenge because they also affected the primary cells used in the assay. This study confirms the antiviral potential of the plant against the ASF virus, corroborating farmers' claims to a certain extent (Fasina et al., 2013). Nevertheless, optimizing strategies to harness the potential of the plant while mitigating its *in vitro* and *in vivo* cytotoxic effects is imperative.

CONCLUSIONS

In conclusion, extensive exploration of plant-derived compounds as potential antiviral agents against ASFV has yielded promising results. A variety of compounds from different plant sources have demonstrated inhibitory effects at various stages of the ASFV replication cycle, demonstrating their potential as novel therapeutic strategies. The intricate understanding of ASFV biology, pathogenesis, and the replication cycle has provided valuable insights into potential targets for intervention.

Through this comprehensive review, it is evident that plant-derived compounds are a rich source of antiviral agents with diverse mechanisms of action against ASFV. Notably, flavonoids, such as quercetin, myricetin, and kaempferol, display potent antiviral activities by interfering with the critical stages of viral replication. Moreover, alkaloids and terpenoids have shown promise for targeting ASFV's unique characteristics of ASFV. Essential oils and crude plant extracts have also displayed virucidal activity against ASFV, offering potential applications in disinfection.

Despite the progress made in understanding the potential of plant-derived compounds against ASFV, several research gaps remain to be addressed. The

precise mechanisms of action of these compounds require further elucidation, along with their effects on ASFV variants and strains. In-depth studies exploring the synergistic interactions between different compounds and their potential adverse effects on non-target organisms are essential for safe and effective applications.

The future of anti-ASFV compounds lies in a multidisciplinary approach combining virology, pharmacology, and plant science. Further investigations into optimal formulations, delivery systems, and dosage regimens are necessary to ensure efficacy and minimize cytotoxicity. Innovative strategies, such as nanotechnology and gene editing, have the potential to enhance the antiviral activity of these compounds.

In the realm of ASFV research, the development of effective antiviral compounds remains an urgent priority for mitigating the devastating impact of ASF outbreaks on the global swine industry. By harnessing the power of nature through plant-derived compounds, we are on the cusp of a new era of combating ASFV infections, thereby safeguarding food security and animal health. The collective efforts of researchers, industries, and policymakers will drive the translation of these promising findings into practical solutions that address the pressing challenges posed by ASFV.

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AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

The authors declare that they hold no competing interests.

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