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REVIEW

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Advances in research on the efficacy of traditional Chinese herbal medicine in combating African swine fever

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Abstract

African swine fever (ASF) is a highly contagious disease of domestic and wild pigs caused by African swine fever virus (ASFV). The mortality rate associated with ASF is remarkably high, almost approaching 100%. Since the introduction of ASF into China in 2018, its rapid spread has caused marked economic losses in the country's swine industry. To date, there are no safe and effective commercial vaccines or antiviral drugs against ASF; thus, there is an urgent need to develop novel prevention and control strategies. Traditional Chinese medicine (TCM), which comprises various herbs that are abundant in various potential functional components, holds great promise for the prevention and control of ASF. Here, we provide a comprehensive review of the advancements in TCM and the effects of its compound formulas against ASF, including the antiviral abilities, immunoregulatory activities, and practical application of these formulas for the prevention and control of ASF. We specifically examined the potential and constraints of natural product-derived extracts and TCM formulas in combating ASFV. This review aims to offer insights and ideas for the holistic management and containment of ASF.

Keywords African swine fever, Traditional Chinese medicine, Herbal medicine, Pig farming, Disease prevention

Introduction

African swine fever (ASF), caused by African swine fever virus (ASFV), is a highly contagious and deadly infectious disease in pigs and is clinically characterized by acute clinical signs such as fever and hemorrhage (Zhang et al. 2022). ASFV is a large and complex enveloped double-stranded DNA virus, and it is currently the only known DNA virus transmitted by arthropods (Teklue et al. 2020). Due to the abundance and structural complexity of viral proteins and enzymes encoded by ASFV, the mechanisms by which these viral proteins and enzymes participate in genome transcription, replication, pathogenesis, and antagonism of innate immune responses remain poorly understood (Alejo et al. 2018). ASF was first identified in Kenya (Wang et al. 2018a, b), after which the introduction of ASFV to Georgia marked the onset of its expansion into various EU countries, including Russia, Ukraine, Belarus, Poland, Lithuania, Latvia, Estonia, Romania, the Czech Republic, and Hungary. This spread in a sequence from 2007, initially hitting Eastern Europe and progressively affecting other regions over the following years up to 2018 (Zheng et al. 2022). It has severely impacted China's pig farming industry since it was first reported in 2018, notably diminishing production capacity (Song and Xie 2020). Currently, in the absence of safe and highly effective commercial vaccines and effective drugs, biosecurity management

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remains the primary strategy for epidemic prevention and control on pig farms (Duan and Yang 2020). To control ASF outbreaks, Chinese authorities have implemented various strategies, such as culling pigs within a 3 km radius of detected infections, enforcing pig movement restrictions, enhancing surveillance in containment and protection zones, and mandating the destruction of pig-related products (Ferdousi et al. 2019). In recent years, various natural mutations have been identified in ASFV, some of which have led to increased transmissibility and virulence, as well as a more diverse clinical presentation, making prevention and control efforts more challenging (Gallardo et al. 2019) and leading to substantial economic losses (Huang et al. 2021).

Traditional Chinese medicine (TCM), long valued in the medical field for its natural origin, diverse components, and minimal side effects, has shown broad-spectrum antiviral effects against various infectious diseases (Adhikari et al. 2021; Sithisarn et al. 2013), such as severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19). *Isatidis* Radix is a TCM used to drain heat, resolve fire toxicity, relieve swelling, disperse stagnation and cool the blood. It is a powerful herb with anti-inflammatory, antipyretic and antibacterial properties. During the SARS outbreak in 2003, herbs such as is *Isatidis Radix* and *Lonicerae Japonicae* Flos were widely used and played a positive role in epidemic prevention and control. In the treatment of COVID-19, several classic formulas are known to significantly alleviate clinical signs and enhance immunity (Li et al. 2022), with treatments involving Chinese medicine demonstrating a cure rate of up to 90% (Xu et al. 2020). Pharmacological research has shown that Chinese medicines target a variety of pathways, providing antiviral, anti-inflammatory, and immunomodulatory benefits in the fight against COVID-19. Among these, Lianhua-Qingwen Prescription (LHQW) stands out for its ability to address viral infections through the modulation of PTGS2, IL6, CASP3, MAPK1, EGFR and ACE2. The active components of LHQW are involved in T-cell activation, viral receptor interaction, and inflammatory response modulation, supporting its antiviral and anti-inflammatory effects (Shen and Yin 2021). Similarly, Huoxiang Zhengqi oral liquid (HXZQ), a widely used prescription for clearing dampness, not only helps to relieve symptoms and balance the stomach but also plays a crucial role in blocking the entry and replication of viruses, in addition to curbing inflammation and cytokine storms (Dai et al. 2020).

TCM has also shown potential for preventing and treating various veterinary diseases in veterinary medicine. In line with the "Comprehensive Antibiotic Reduction" initiative proposed by the Ministry of Agriculture and Rural Affairs in 2021, there has been a growing focus on the use of Chinese herbal medicines for the prevention and treatment of animal diseases. Herbal feed additives containing ingredients such as *Codonopsis Radix*, *Atractylodis Macrocephalae R* Rhizoma and *Poria* have been shown to enhance the immunity of weaned piglets by increasing their serum immunoglobulin and cytokine levels (Zhou et al. 2022). Additionally, formulas such as San Wu Huangqin decoction (SWHD), LHQW, and Fufang Yinhua Jiedu (FFYH) granules have shown antiviral effects against avian influenza, potentially owing to their ability to block virus particle proliferation and replication, thereby significantly reducing viral damage to the lungs (Li et al. 2020; Ma et al. 2021; Zhang et al. 2021). Our previous research contributed to this field by extracting glycyrrhizin (GA) from *Glycyrrhizae* Radix et Rhizoma to synthesize highly dispersible carbon dots (CDs), which possess enhanced water solubility and demonstrate significantly improved anti-influenza virus activity (IVA) compared to that of GA alone. GA-CDs inhibit IVA through various mechanisms, including impeding viral internalization, viral genome replication, neuraminidase activity, and the host inflammatory response. In a mouse model, GA-CDs significantly alleviated clinical signs, reduced mortality, and lowered lung viral titers (Li et al. 2023). Chinese herbal medicine not only treats various diseases but also enhances the antiviral capabilities and immunity of animals. This is evident in the stress-relieving and appetite-enhancing effects of Chinese medicinal formulations and feed preservatives, each of which exhibit unique preventive and therapeutic effects (Zhou 2021).

TCM has also shown promise for the prevention and control of ASF. Moreover, regarding the prevention and control of ASF, the TCM preparation "Xin Wen Kang" has been shown to enhance immunity, thereby successfully reducing ASF incidence (Li et al. 2019). Natural extract has also demonstrated significant antiviral effects against ASFV (Juszkiewicz et al. 2021). The specific contents of the TCM and prescriptions mentioned above can be found in Tables 1 and 2. Here, this article aims to comprehensively review the research progress on the use of TCM for preventing and treating ASF and explore the development of related antiviral drugs.

ASFV and its current research status

Since its first identification in Kenya in 1921, ASFV has become endemic to Africa. It subsequently spread to Europe, the Caribbean, and South America from the 1950s to the 1980s and subsequently extended to countries such as Spain and Italy (Gaudreault et al. 2020). The complexity and severity of the global ASF epidemic have recently increased, with outbreaks reported in

Table 1 Overview of traditional Chinese medicine (TCM)

Name/Latin name	Place of origin	Source	Active ingredient	Treatment approach	References
Isatis Root/*Isatidis* Radix	Henan, Hebei, Anhui, Jiangsu, Northeast China et al.	From the dried root of the Cruciferous plant *Isatis indigotica* Fort.	Isatis root polysaccharide (IRPS)	Anti-inflammatory, antipyretic and antibacterial properties	Li et al. 2022; Wang et al. 2020a, b
Honeysuckle/*Lonicerae Japonicae* Flos	Henan, Shandong et al.	From the dried flower buds or flowers just beginning to open of the *Caprifoliaceae* plant *Lonicera japonica* Thunb.	Chlorogenic acid, flavonoid, caffeoylquinic acid, and iridoid glycoside	Inhibit herpes simplex keratitis, influenza virus pneumonia, influenza A virus, porcine reproductive and respiratory syndrome virus, Newcastle disease virus, respiratory syncytial virus, influenza virus, human cytomegalovirus et al.	Li et al. 2015
Pilose Asiabell Root/*Codonopsis* Radix	Gansu, Shanxi, Shaanxi, Sichuan et al.	From the dried roots of the plant *Codonopsis pilosula* (Franch.) Nannf., belonging to the *Campanulaceae* family	Alkaloids, alkynes and polyacetylenes, flavonoids, lignans, steroids, terpenoids, organic acids, volatile oils, saccharides and other components	Safeguarding the gastrointestinal mucosa and preventing ulcers, modulating immune system function, exhibiting anti-cancer properties, influencing endocrine system balance, enhancing blood formation capabilities, providing cardiovascular benefits, and offering anti-aging and antioxidant advantages	Dong et al. 2023
Swordlike Atracylodes Rhizome/*Atractylodis Macrocephalae* Rhizoma	Zhejiang, Hubei, Jiangsu, Henan et al.	From the dried rhizome of the *Atractylodes lancea* (Thunb.) DC., belonging to the *Asteraceae* family	Volatile oil, lactones, polysaccharides, amino acids, vitamins and resins	Inhibit tumor growth, protective effects on neural tissues, counteracting liver toxicity, supporting both immune function and anti-inflammatory responses	Ruqiao et al. 2020
Indian Buead Tuckahoe/*Poria*	Anhui, Jiangxi, Jiangsu, Zhejiang et al.	From the dried sclerotium of the fungus *Poria cocos* (Schw.) Wolf, belonging to the *Polyporaceae* family	Polysaccharides and triterpenoids	Triterpenoids have a pivotal influence on certain diseases such as rheumatoid arthritis, psoriasis, autoimmune uveitis, septic shock, and possibly bronchial asthma, while polysaccharides can potentiate the immune response	Ríos et al. 2011
Liquorice Root/*Glycyrrhizae* Radix et Rhizoma	Neimeng, Shanxi, Gansu, Xinjiang, Ningxia et al.	From the dried roots and rhizomes of the *Glycyrrhiza uralensis* Fisch., belonging to the legume family	Glycyrrhizin, glycyrrhizic acid	Glycyrrhetic acid inhibits the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) and exhibits effects similar to corticosteroids, mitigate inflammation, enhance antioxidant levels, reduce allergic reactions, and resist microbial infections	Kwon et al. 2020

Table 2 Overview of the Chinese herbal formulas

Name	Composition	Treatment approach	Active ingredient	References
Lianhua Qingwen Prescription (LHQW)	*Isatidis* Radix, Fructus *Forsythiae*, *Lonicerae Japonicae* Flos, Rhizoma *Dryopteridis Crassirhizomatis*, Herba *Ephedrae*, Semen *Armeniacae Amarum*, Herba *Houttuyniae*, Herba *Pogostemonis*, Radix et Rhizoma *Rhodiolae Crenulatae,* Radix et Rhizoma *Rhei and* Radix et Rhizoma *Glycyrrhizae* and *Gypsum Fibrosum*	Affect PTGS2, IL6, CASP3, MAPK1, EGFR, and ACE2; Involved in T cell activation, viral receptor interaction, and inflammatory response modulation; anti-inflammatory actions	Quercetin, kaempferol, luteolin, β-sitosterol, indigo, wogonin, tryptanthrin, [E]-4-phenyl-3-buten-2-one, 1-methyl-2-nonyl-4(1H)-quinolone, stigmasterol, naringenin, 18β-glycyrrhetinic acid	Shen et al. 2021; Dai et al. 2020
Huoxiang Zhengqi Oral Liquid (HXZQ)	*Perilla frutescens* (L.) Britton, *Atractylodes macrocephala* Koidz., *Platycodon grandiflorum* (Jacq.) A.DC., *Pogostemon cablin* (Blanco) Benth., *Glycyrrhiza uralensis Fisch.*, *Citrus reticulata* Blanco, *Magnolia officinalis Rehd*. et Wils., *Angelica dahurica* (Fisch.ex Hoffm.) Benth.et Hook.f., *Poria cocos* (Schw.) Wolf., *Areca catechu* L., and *Pinellia ternata* (Thunb.) Breit.	Clearing dampness, relieving symptoms and balancing the stomach, blocking the entry and replication of viruses, in addition to curbing inflammation and cytokine storms	Liquiritin, narirutin, hesperidin, ammonium glycyrrhetate, honokiol and magnolol	Dai et al. 2020; Guo et al. 2021; Yu et al. 2013
San Wu Huangqin decoction (SWHD)	the dried root of *Sophora flavescens* Aiton, the dried root of *Scutellariae* Radix, and the dried root tuber of *Rehmannia glutinosa* (Gaertn.) DC.	Anti-inflammatory, anti-swelling, and anti-itching effects, bacteriostasis in vitro, and large-dose diuretic effects	Matrine in *Sophora flavescens* Aiton; the baicalein in *Scutellaria* Radix	Ma et al. 2021
Fufang Yinhua Jiedu (FFYH) granules	*Artemisia annua* L., *Lonicerae japonica* Thunb., *Schizonepeta tenuifolia* (Benth.) Briq., *Mentha haplocalyx* Briq., *Chrysanthemum indicum* L., *Isatidis tinctorial* L., *Forsythia suspensa* (Thunb.) Vahl., *Commelina communis* L., *Peucedanum praeruptorum* Dunn, and *Glycine* max (L.) Merr.	Displayed extensive antiviral properties against multiple strains of influenza A viruses including H1N1, H3N2, H5N1, H7N9, and H9N2. It significantly suppressed the production of inflammatory cytokines such as TNF-α, IL-6, IFN-γ, IP10, IL-10, and IL-1β, both mRNA and protein levels, by blocking the TLR7/MyD88/NF-κB pathway in vivo	Neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, isochlorogenic acid B, isochlorogenic acid A, 4,5-Dicaffeoylquinic acid, forsythoside A, forsythoside, buddleoside, and praeruptorin A	Zhang et al. 2021

numerous countries. ASF outbreaks began in Poland in 2014, initially affecting wild boars near the Belarus border, followed by a wider spread in wild populations and pig farms. In 2020, ASFV emerged among wild boars in eastern Germany. Genome analysis revealed that the strain was akin to those in western Poland and had a notable mutation in the O174L gene, indicating greater genetic variability in strains at the German–Polish border (Forth et al. 2023). The ASF reappeared in continental Italy in 2022. That same year, initial cases were documented in North Macedonia and Thailand in January and in Nepal by March. More recently, ASF was detected on domestic pig farms for the first time in Bosnia and Herzegovina, Croatia, and Kosovo, as well as in wild boars and imported live pigs in Singapore (Juszkiewicz et al. 2023). Since August 2018, China has faced multiple ASF outbreaks, and by 2019, 160 outbreaks across various provinces and cities resulted in the culling of approximately 1.193 million pigs (Duan and Yang 2020). ASF control relies primarily on stringent biosecurity measures, including limiting interregional pig contact and controlling the import and export of pork products (Wang et al. 2021a, b).

ASFV belongs uniquely to the Asfarviridae family and genus and is the sole DNA virus transmitted by insects in the NCLDV family (Wang et al. 2021a, b). The virus exhibits icosahedral symmetry and possesses a multilayered structure, including a core genome, core shell, inner membrane, capsid, and outer membrane, with an average diameter of approximately 200 nm (Alejo et al. 2018). The ASFV genome is complex, spanning approximately 170–193 kb and encoding 150–167 proteins, with viral strain-dependent variability (Zheng et al. 2022). ASFV primarily targets porcine macrophages and monocytes (Andres 2017), completing its life cycle within the cell. This cycle encompasses attachment, cell entry, uncoating, intracellular replication, assembly, and the release of new viral particles (Peng et al. 2022). The virus triggers severe inflammatory responses (Lv et al. 2022), can induce a type I IFN cascade and encodes several proteins that suppress host immune responses (Garcia-Belmonte et al. 2019).

Studies have revealed the evolution of multiple mechanisms by which ASFV evades host immunity, thus complicating epidemic control (Razzuoli et al. 2020; Wang et al. 2020a, b). Despite extensive research, the complexity of the viral genome and the mechanisms of the host immune response are still not fully understood, posing significant challenges to the development of safe and effective vaccines against ASFV. Existing vaccine candidates, such as inactivated and subunit vaccines, have shown limited efficacy, with only a few live attenuated vaccines providing effective protection but carrying inherent risks (Zhang et al. 2023). Therefore, the development of safe and effective commercial vaccines remains a critical goal. Additionally, research should focus on vaccine development, as well as understanding the infection mechanisms and immune evasion strategies of ASFV and exploring new control strategies to manage and prevent this significant animal disease more effectively.

Traditional Chinese veterinary perspective on ASF

According to traditional Chinese veterinary concepts, ASFV is perceived as a “pestilence qi”, akin to the “heat pathogen” in TCM, characterized by intense heat and damp-toxic properties. ASFV invades through the respiratory tract, initially lurking in the throat, and then spreads to the body’s Sanjiao (triple energizer), triggering heat toxins and damaging organs such as the lungs, spleen, and kidneys, causing blood circulation disorders, thereby leading to acute clinical signs such as edema and hemorrhage and severely affecting organ function and fluid metabolism (Han et al. 2021). The occurrence of ASF is related to the principle of “where heat pathogen gathers, qi is deficient”, reflecting the struggle between the body’s healthy energy and pathogenic factors (Zhang 2019).

Understanding ASF from a traditional Chinese veterinary perspective in better comprehending disease progression and clinical signs. Following the “holistic” concept, various clinical signs of externally contracted warm-heat diseases are classified into four categories: defense (wei) level syndrome, qi level syndrome, nutritive (ying) level syndrome, and blood (xue) level syndrome, where defense, qi, nutrition, and blood are seen as the body’s four defensive barriers against warm pathogens. This theory can discuss the depth of the disease location, severity, and patterns of disease progression and transformation of ASF, guiding the selection of TCM prescriptions at different stages (Mao et al. 2021). Therefore, different prescriptions should be chosen at various stages of the disease or during different stages of the struggle between healthy energy and pathogenic factors. In the early stages of infection with high fever, which is associated with heat toxins and significant clinical signs, supportive and detoxifying medicines should be used. The use of antibiotics at this stage may continuously weaken the immunity of the pig, making it easier for pathogenic factors to invade; as the disease further worsens into the pathogen entering the “pathogen-entering-the-nutritive-level”, pigs show clinical signs of qi and blood deficiency and lack strength; finally, when the disease progresses to the “pathogen-entering-the-blood”, exhibiting clinical signs such as loss of appetite and deficiency of both qi and blood, Chinese medicines that nourish yin and produce blood and activate blood to dispel stasis should be used for the final rescue (Mao et al. 2021; Li et al. 2020).

Overall, the primary strategy for the prevention and treatment of African swine fever should prioritize preventive measures, adhering to the traditional Chinese medicine principle of preventing illness before it occurs. This involves employing strategies such as clearing heat and detoxifying to reduce inflammation and control infection, strengthening the constitution to enhance the physiological functions and resistance of the animals, and promoting diuresis to regulate internal conditions by facilitating the excretion of wastes and toxins. Together, these methods aim to increase animal resistance and constitute a comprehensive approach for the prevention and control of this disease (Li et al. 2019).

Different types of TCMs against ASF

Although vaccines are deemed the most cost-effective method for controlling infectious diseases in animals and improving production efficiency, the development of safe and effective vaccines against ASF faces numerous challenges (Urbano and Ferreira 2022). This has led researchers to explore various alternative therapeutic methods, among which natural product extracts and TCM formulations have demonstrated significant potential for prevention and control. These naturally derived medicines and formulas exhibit direct antiviral activity against ASFV as well as beneficial regulation of the host immune system (Fig. 1).

Extracts derived from natural products

In recent years, groundbreaking studies have been conducted on natural product extracts and their potential roles in combating ASFV. In a pioneering effort, Zhu et al. extracted berbamine hydrochloride from the TCM *Berberis amurensis* Rupr. and revealed its substantial direct antiviral activity against ASFV. They discovered that berberine chloride hindered ASFV proliferation in a dose-dependent manner, particularly by targeting the early stages of viral infection, such as attachment and internalization. This marked a significant milestone in antiviral research (Zhu et al. 2022). Furthermore, Chen demonstrated the effectiveness of luteolin, a compound prevalent in broccoli and apple skin, against ASFV in pulmonary alveolar macrophage (PAM) cells. These findings indicate considerable viral suppression during critical postinfection phases, attributed to the ability of luteolin to inhibit several stages of the ASFV replication cycle by downregulating the NF-κB/STAT3/ATF6 signaling pathway, revealing a novel mechanism for viral inhibition (Chen et al. 2022).

In another notable study, Hakobyan extracted apigenin from celery, which is renowned for its medicinal properties. When applied to Vero cells infected with the BA71V strain, apigenin demonstrated dose-dependent antiviral effects, particularly at 1 h post infection. This led to a significant reduction in viral activity at the early stage, which was attributed to the suppression of ASFV protein synthesis and virus factory formation (Hakobyan et al. 2016). Furthermore, aloe-emodin (Ae), found in TCMs such as *Cassia occidentalis, Rheum palmatum L., Aloe vera, and Polygonum multiflorum Thunb*, significantly suppressed ASFV-induced inflammation by downregulating the mRNA expression of NF-κB pathway-related proteins, promoting ASFV-induced cell apoptosis, and thereby inhibiting viral replication (Luo et al. 2023). Similarly, Juszkiewicz conducted extensive tests on extracts from 14 medicinal plants, including *Citrus aurantifolia* (Christm.) Swingle and Menthae Haplocalycis Herba. While most extracts showed limited virucidal effects in Vero cells, the 1.05% peppermint extract was a notable exception, exhibiting remarkable antiviral activity and substantially reduced ASFV titers (Juszkiewicz et al. 2021).

In a study by Qian tetrandrine (TET) was extracted from the Chinese herb *Stephania tetrandra* Radix, and TET inhibited the currently prevalent genotype II ASFV strain in various cell types, including PAMs, bone marrow-derived macrophages, and MA104 cells, in a dose-dependent manner. Time of addition (TOA) analysis confirmed that TET mainly inhibited ASFV during internalization. Macropinocytosis is the primary method by which ASFV enters host cells, and TET inhibits this process by blocking the PI3K/Akt pathway, thereby preventing ASFV entry and replication (Qian et al. 2023). Jo extracted myricetin and its derivative myricitrin from Myrica, which significantly inhibited the ASFV protease. The 3,4,5-trihydroxyphenyl ring of myricetin was confirmed to play an essential role in the development of anti-ASFV drugs based on its flavonol skeleton (Jo et al. 2020). DHM has also been shown to inhibit ASFV-induced NLRP3 inflammasome activation in vitro, reduce cell apoptosis, and target TLR4 to impair ASFV replication (Chen et al. 2023). PolX, an ASFV DNA polymerase, plays a crucial role in the repair and mutation of the ASFV genome. Virtual screening targeting the DNA-binding region of this polymerase revealed several natural products, including components of Dolichousnea longissima, wallflower, horseradish, broccoli and Litophyton erectum, as potential antiviral drugs (Wang et al. 2018a, b). The details and comparisons of the natural extracts mentioned can be found in Table 3.

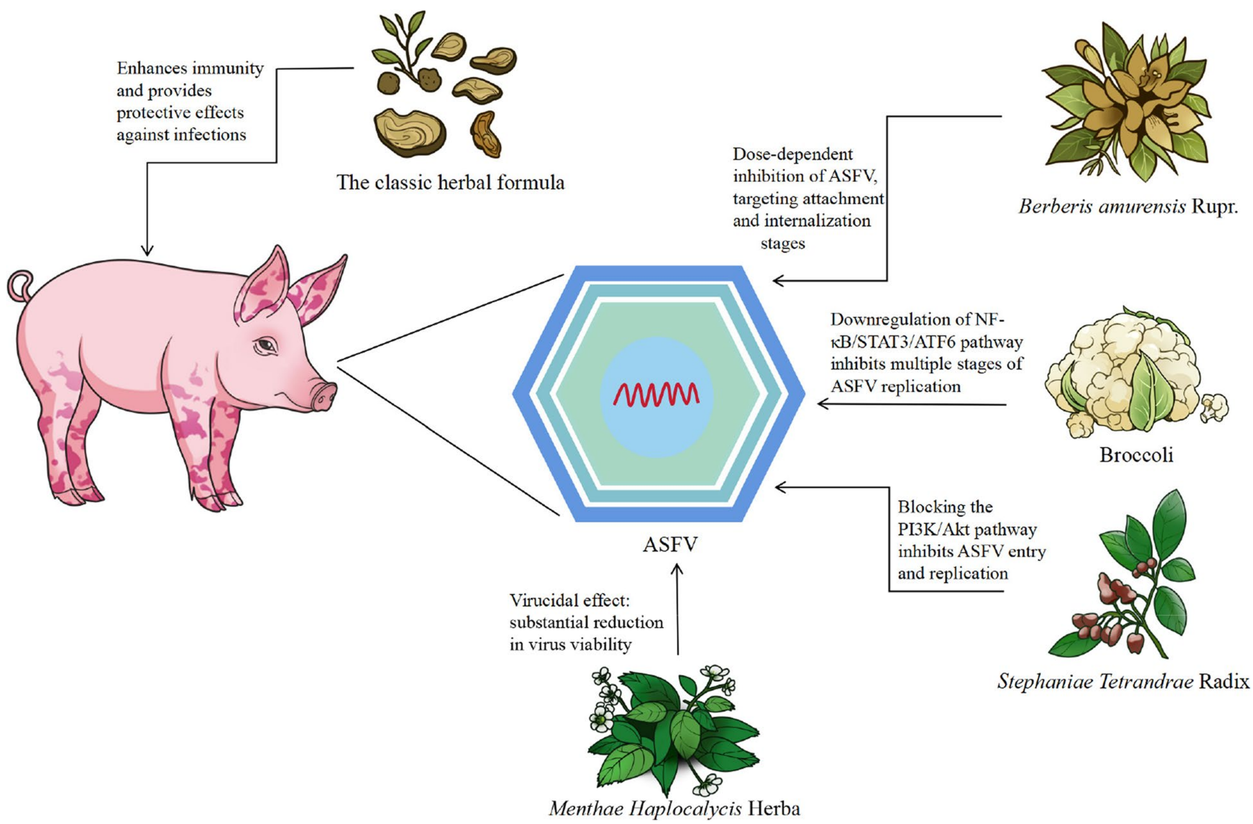


Fig. 1 Different pathways associated with the protective effects of traditional Chinese herbs against African swine fever

Chinese herbs and their active components have also been confirmed to regulate animal immune functions. For example, Astragaloside IV, an extract from *Astragali* Radix, can significantly increase γ-interferon levels in myocarditis model mice, significantly enhancing mucosal immunity and thereby helping to strengthen resistance to ASFV, whereas high doses of total ginsenoside (16 μg/ml) have been shown to inhibit ASFV-induced cytotoxicity in LAK (lymphokine-activated killer) cells (Zhang et al. 2019). These results indicate that the mechanism of action of Chinese herbal medicines against ASFV involves multiple pathways and targets. In addition to their direct antiviral effects, they enhance defense against viruses by adjusting the immune system. This includes boosting interferon production, reducing inflammatory factors, and neutralizing endotoxins (Table 3).

The exploration of natural product extracts as potential agents against ASFV holds theoretical promise for the development of anti-ASFV drugs. However, the practical feasibility and effectiveness of these extracts require rigorous and thorough research and validation. The current research findings are predominantly constrained by the limitations of animal models and the requirements of biosafety level 3 laboratories, with validations primarily conductedin vitro using PAM and Vero cell cultures. Further studies in live animal models and pig herds are needed to obtain more comprehensive and applicable results. A critical aspect to consider is the high variability of ASFV, which implies that single herbal extracts may not uniformly combat all viral strains. Moreover, as highlighted by Zhang, focusing solely on single natural product extracts may disregard the complex interactions and synergistic effects inherent to Chinese herbal formulas (Zhang 2019). These interactions can result in the formation of new compounds and may also involve antagonistic and restrictive dynamics between different herbal components, potentially mitigating toxicity and hindering drug efficacy.

Transitioning from single herbal extracts to marketable products for anti-ASF applications introduces additional challenges, including the intricacies of production technology, the costs associated with extraction processes, and the looming threat of drug resistance. Consequently, determining the antiviral mechanisms of these natural product extracts and pursuing the development of multicomponent combination drugs are of

Table 3 Natural active ingredients for ASFV

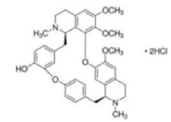
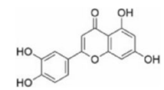
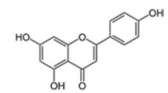
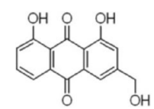
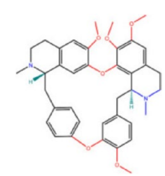
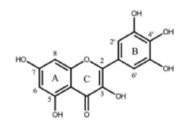
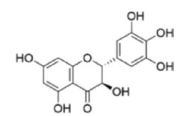
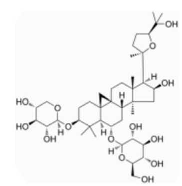
Name/Latin name	Place of origin	Source	Extracts of natural products	Chemical structure	Chemical composition	Pathways against ASFV	References
Berberis amurensis/*Berberis amurensis* Rupr.	Gansu, Hebei, Heilongjiang, Henan, Jilin, Liaoning, Shaanxi, Shandong, Shanxi et al.	Berberis amurensis	Berbamine hydrochloride		Bis-benzylisoquinoline alkaloid	Hindered ASFV proliferation in a dose-dependent manner, particularly by targeting the early stages of viral infection, such as attachment and internalization	Zhu et al. 2022
Onion, Broccoli, Apple et al.	Nationwide	Onion leaves, carrots, broccoli, and apple skin (belonging to ordinary plants)	Luteolin		Flavonoid compound	Inhibit several stages of the ASFV replication cycle by downregulating the NF-κB/STAT3/ATF6 signaling pathway	Chen et al. 2022
Celery/*Apium graveolens* L.	Nationwide	Celery	Apigenin		Flavonoid compound	Lead to a significant reduction in viral activity of early stage, which was attributed to the suppression of ASFV protein synthesis and virus factory formation	Hakobyan et al. 2016
Peppermint/*Menthae Haplocalycis Herba*	Anhui, Jiangsu, Jiangxi, Sichuan et al.	The dried aerial parts of the *Lamiaceae* plant *Mentha haplocalyx* Briq.	Possibly menthol	Unclear	Unclear	1.05% peppermint extract was a notable exception, exhibiting remarkable antiviral activity and substantially reduced ASFV titers	Juszkiewicz et al. 2021
Sickle Senna Seed, Rhubarb/*Cassia occidentalis, Rheum palmatum* L. et al.	Anhui, Jiangsu, Sichuan et al./Gansu, Qinghai, Tibet, Sichuan et al.	The dried mature seeds of *Cassia obtusifolia* L. or *Cassia tora* L., leguminous plants/The dried roots and rhizomes of *Polygonaceae* plants such as *Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf., or *Rheum officinale Baill*	Aloe-emodin (Ae)		Anthraquinone derivative	Suppressed the ASFV-induced inflammation by downregulating the mRNA expression of NF-κB pathway-related proteins, promoting ASFV-induced cell apoptosis, and thereby inhibiting viral replication	Luo et al. 2023
Stephania tetrandra/Stephaniae Tetrandrae Radix	Hunan, Hubei, Jiangxi, Anhui et al.	The dried roots of the *Menispermaceae* plant *Stephania tetrandra* S. Moore	Tetrandrine (TET)		Isoquinoline alkaloid (BBI)	Inhibits this process by blocking the PI3K/Akt pathway, thereby preventing ASFV entry and replication	Qian et al. 2023

Table 3 (continued)

Name/Latin name	Place of origin	Source	Extracts of natural products	Chemical structure	Chemical composition	Pathways against ASFV	References
Myrica/*Myricaceae Rich. ex Kunth*	Nationwide	Myrica(belonging to ordinary plants)	Myricetin		Flavonol	Inhibite ASFV protease and the 3,4,5-trihydroxyphenyl ring are crucial for anti-ASFV drug development	Jo et al. (2020)
Vine tea/*Ampelopsis grossedentata* (Hand.-Mazz.) W. T. Wang	Nationwide	From the branches and leaves of *Ampelopsis megalophylla Diels et Gilg*	Dihydromyricetin (DHM)		Natural flavonoid	Inhibit ASFV-induced NLRP3 inflammasome activation in vitro, reduce cell apoptosis, and target TLR4 to impair ASFV replication	Chen et al. 2023
Mongolian Milkvetch Root/*Astragali* Radix	Neimeng, Shanxi, Hebei et al.	From the dried roots of the *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao and *Astragalus membranaceus* (Fisch.)	Astragaloside IV		Terpenoid	Significantly increase γ-interferon levels in myocarditis model mice, significantly enhancing mucosal immunity, thereby helping strengthen their resistance to ASFV	Zhang et al. 2019
Ginseng Root/*Ginseng* Radix et Rhizoma	Jilin, Liaoning, Heilongjiang et al.	From the dried roots of the *Araliaceae* plant *Panax ginseng* C. A. Mey. (cultivated variety)	Ginsenoside	Unclear	Triterpenoid saponin	Inhibit ASFV-induced cytotoxicity in LAK (lymphokine-activated killer) cells	Zhang et al. 2019

utmost importance. Such research is pivotal for advancing our understanding, as well as for the effective control and management of ASF in practical scenarios.

Traditional formulas

In addition to natural product extracts, traditional formulas have also demonstrated significant potential for the prevention and control of ASF (Table 4). In accordance with the "Infectious Epidemic Disease", the classical Dayuan Yin recipe, comprising seven medicinal herbs, including *Arecae Semen* and *Anemarrhenae Rhizoma*, was modified to treat ASF. Zhao developed Yu Wen Decoction (YWD) by enriching the formula with *Scutellaria Radix*, Radix, *Puerariae Lobatae* Radix, and *Paeoniae* Radix Alba to promote intestinal peristalsis, facilitate the absorption of pneumonia, enhance the excretion of toxins from the body, exhibit anti-inflammatory properties, and benefit bile production while protecting the liver and stomach. It also has reparative effects on the blood system and lung damage. This adaptation has been proven effective against ASFV and remains stable after 15 d. YWD is recommended during the incubation and early symptom stages to quickly eliminate pathogenic toxins, strengthen yin, clear heat, and balance the body's yin and yang (regulating the body's internal responses to counteract the virus's effects, promoting overall health), thus preventing disease progression. If symptoms escalate to severe conditions such as vomiting blood or bloody stools, indicating deep penetration of heat toxins and blood damage, Qing Ying Detoction (QYD) can detoxify the body by removing excess heat while simultaneously supporting vital fluids to promote overall health and balance. This approach aligns with the principles of traditional Chinese medicine in treating both symptoms and underlying imbalances (Zhao et al. 2019).

Similarly, Wu et al. invented Kang Zhi Yuan (KZY), an anti-AFS herbal product primarily containing *Acanthopanacis Senticosi* Radix et Rhizoma Sue Caulis and Ligustri Lucidi Fructus, which enhanced the immune response in infected pigs and reduced the oxidative stress-induced production of prostaglandin E2 and nitric oxide (Wu et al. 2020). The efficacy of KZY was confirmed by Bin et al., who added KZY formula (4 kg/t) and vitamin C (300 g/t) to animal feed and stabilized the health of a suspected infected pig herd within months (Yu et al. 2019). Furthermore, Mao successfully formulated a TCM combination named Xin Wen Kang (XWK) and Jie Mei Hong Jing Tian (JMHJT) for ASF prevention and control. The formulas included detoxifying herbs such as *Bupleuri* Radix and *Scutellaria* Radix, while the latter contained *Rhodiolae Crenulatae* Radix et Rhizoma and *Atractylodis Macrocephalae* Rhizoma, which are known for mold detoxification and mucosal repair. XWK activates nonspecific immune functions, generating a large number of macrophages, natural killer cells, lysosomes, defensins, and immunoglobulins that engulf and deactivate weakened pathogens. JMHJT initially cleanses various toxins from the intestines and repairs damage to the gastrointestinal mucosa, allowing the upper layer cells of the gastrointestinal mucosa to perform immune functions and prevent pathogens from adhering to the intestinal walls. When combined, these two formulations enhance the immunological resilience of swine populations, making them effective for the early prevention and therapeutic management of ASF. This treatment stabilized the suspected afflicted pigs and induced specific antibody production within half a month (Mao et al. 2021).

Xu used a combination of *Artemisia argyi* Levl.et Vant., *Atractylodis Macrocephalae* Rhizoma, *Galla Chinensis*, and *Euryales* Semen for fumigation to effectively prevent ASFV infection by repelling mosquitoes and flies, killing various pathogens, enhancing animal immunity, and treating respiratory diseases (Xu et al. 2020). A compound Chinese herbal formula, Zhu Kang San (ZKS). *Forsythiae* Fructus, and *Isatidis* Radix were developed to enhance humoral immune function, increase ASF antibody levels and immunoglobulin content, and promote B-cell proliferation in pigs (Chen 2021). These findings underscore the significant effect of early TCM interventions on ASF prevention (Yu et al. 2019). Additionally, based on the pathogenesis, the authors suggest that *Astragali* Radix and *Codonopsis* Radix enhance the deficiency of spleen qi in pigs, thereby improving disease resistance (Zheng 2021).

In recent research, various TCM compounds have demonstrated potential for preventing ASFV infection. However, owing to national policies against ASF, which involve culling and the prohibition of treatment, precise cure rate data are lacking, thus hindering the accumulation of comprehensive data to support the efficacy of these herbal formulas. Although TCM has a historical precedent for treating various infectious diseases, its effectiveness and safety in modern contexts require validation through rigorous clinical trials and scientific research. Therefore, the potential of TCM for ASF treatment requires further exploration and application.

Conclusions and future prospects

Since the emergence of ASF in China in 2018, its impact on the pig farming industry has been profound. The task of preventing and controlling ASF is multifaceted and ambitious, with the aim of achieving complete eradication. However, as noted by Zhang et al., this objective presents considerable challenges (Zhang et al. 2023). The ability of ASFV to disrupt cellular signaling pathways and suppress the immune response in pigs, often through coinfection with other swine diseases, such as blue ear disease and circovirus infection, complicates the

Table 4 Chinese herbal compounds for the treatment of ASFV

Name	Composition	Treatment approach	References
Yu Wen Decoction (YWD)	*Arecae Semen, Scutellaria Baicalensis, Puerariae Lobatae* Radix, *Paeoniae* Radix Rubra, *Moutan* Cortex, *Ophiopogonis* Radix et al.	Promote intestinal peristalsis, facilitates the absorption of pneumonia, enhances the excretion of toxins from the body, exhibits anti-inflammatory properties, and benefits bile production while protecting the liver and stomach	Zhao et al. 2019
Qing Ying Decoction (QYD)	*Coptidis Rhizoma, Bubali Cornu, Lonicerae Japonicae* Flos, *Rehmanniae* Radix et al.	Detoxify the body by removing excess heat, while simultaneously supporting its vital fluids to promote overall health and balance	Zhao et al. 2019
Kang Zhi Yuan (KZY)	Manyprinckle Acanthopanax, *Ligustri Lucidi Fructus,* cranberry et al.	Enhance the immune response in infected pigs and reduced the oxidative stress-induced production of prostaglandin E2 and nitric oxide	Wu et al. 2020
Xin Wen Kang (XWK)	*Bupleuri* Radix, *Scutellaria baicalensis, Forsythiae Fructus, Rhei* Radix et Rhizoma et al.	Activate the body's nonspecific immune functions, generating a large number of macrophages, natural killer cells, lysosomes, defensins, and immunoglobulins that engulf and deactivate weakened pathogens	Mao et al. 2021
Jie Mei Hong Jing Tian (JMHJT)	*Rhodiolae Crenulatae* Radix et Rhizoma, *Atractylodis Macrocephalae* Rhizoma, *Puerariae Lobatae* Radix et al.	Clean various toxins from the intestines and repairs damage to the gastrointestinal mucosa, allowing the upper layer cells of the gastrointestinal mucosa to perform immune functions and prevent pathogens from adhering to the intestinal walls	Mao et al. 2021
Herbal incense	Mugwort, *Atractylodis* Rhizoma, *Galla Chinensis, Euryales Semen* et al.	Repel mosquitoes and flies, killing various pathogens, enhancing animal immunity, and treating respiratory diseases	Xu et al. (2020)
Zhu Kang San (ZKS)	Honeysuckle, *Forsythiae Fructus*, Isatis Root, *Gypsum Fibrosum*	Enhance humoral immune function, increase ASF antibody levels and immunoglobulin content, and promote B-cell proliferation in pigs	Chen 2021

development of safe and effective vaccines and control measures. Moreover, it has been difficult for inactivated or subunit vaccines to provide effective protection, and even recombinant vector vaccines have failed (Zhang et al. 2023). A few live-attenuated vaccines can provide effective protection, but there may be concerns regarding their stability and residual virulence (Zhang et al. 2023; Revilla et al. 2018). Therefore, novel antiviral strategies for the prevention and control of ASF are urgently needed.

TCM has long demonstrated efficacy in disease prevention and control, gradually revealing its potential in veterinary medicine for preventing and treating various diseases. TCM has emerged as a viable natural antiviral resource for ASF control. Its potential advantages over chemical or biological antiviral drugs include a reduced likelihood of resistance development, the ability to combat viruses through multiple components and targets, and the ability to regulate host immune system functions such as antioxidation and anti-inflammation. A deeper understanding of the mechanisms of action and targets involved in these processes could be instrumental in the development of anti-ASF drugs. Compared with single natural product extracts, TCM formulas, which have multiple components that act synergistically on various viral targets, can intervene at multiple key stages of ASFV infection.

Given the ongoing global spread of ASF, challenges in its prevention and control have become increasingly apparent. Thus, the TCM concepts of "preventing the disease before its onset" and "medicine and food sharing the same origin" have become particularly relevant for ASF prevention and treatment. Chinese herbal medicine has emerged as a significant research direction for ASF control in the context of antibiotic restrictions and challenges associated with vaccine development. By conducting in-depth research on the antiviral components of Chinese herbal medicines, these natural medicines can be utilized more effectively by integrating them into modern breeding practices, such as incorporation into feed. This approach reduces the stress caused by vaccination or medication and enhances the immunity of pigs, thereby improving epidemic prevention. However, for broader application of Chinese herbal medicine in modern breeding, additional scientific research and validation are necessary. This includes testing the effectiveness of these methods in animal models and real pig farms, assessing drug safety, and studying the bioavailability and stability of the active components in Chinese herbal medicines. Currently, the market features several Chinese herbal compound products, such as soluble Shuanghuanglian powder, which are typically simple combinations of single herbs. This deviation deviates from the complex concept of Chinese herbal formulas and may affect their therapeutic efficacy (Zhang 2019). Future research should thus focus on combining TCM with modern production techniques and exploring innovative production methods, such as ultramicro-crushing technology, Chinese herbal fermentation technology, and reduction soup processes, to develop effective and superior products. Moreover, issues such as the solubility, stability, and bioavailability of the bioactive secondary metabolites of Chinese herbs must be comprehensively addressed (Adhikari et al. 2021). The rapid identification of Chinese herbal components with potential therapeutic effects through high-throughput screening and molecular marker technologies and the enhancement of their bioavailability through nanotechnology could represent promising future research directions.

Research and application of Chinese herbal medicine represent not only a supplement to modern treatment methods but also a deep integration of TCM culture with science. By optimizing extraction processes and thoroughly understanding the mechanisms of action of Chinese herbal compound formulas, Chinese herbal medicine can retain its traditional characteristics and play a more significant role in modern breeding practices. Overall, our review summarizes the progress in the use of Chinese herbal medicine for the prevention and treatment of ASF, focusing on the potential and limitations of natural product-derived extracts and TCM formulas for combating ASFV, aiming to provide a theoretical basis for the incorporation of TCM in the development of ASF-related drugs and comprehensive control of ASF.

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