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The Role of Bioactive Secondary Metabolites in Aquaculture Therapeutics: A Pathway to Safe and Sustainable Fish Diseases Control

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Abstract
Aquaculture has become one of the fastest-growing industries in the production of animal-based foods due to its recent rapid expansion on a global scale. However, with enhanced intensification, disease outbreaks have become a serious obstacle to sustainable production. Even though there has been the use of synthetic drugs to combat such diseases in the previous, Long-lasting biological harm in consumers is one the issues identified as their side effect. Hence, the use of certain synthetic agents to manage aquatic productions has been limited globally. Nonetheless, in order to improve immune status and disease prevention in fish, naturally occurring medicinal herbs and probiotics which are recognized for their diverse array of biologically active substances are being investigated as safer, less expensive, and environmentally friendly substitutes. This review Therefore focus on the use of medicinal plants for the prevention and treatment of aquatic diseases.

***Keywords**: Aquaculture, Disease, Sustainable, Performance, Antiparasitic, Prevention.*

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Introduction

Aquaculture is an established science that has been used for many years. Historical accounts and archeological data from several nations around the world attest to the lengthy history of aquatic animal production by various economic communities (Lijun *et al.*, 2025). Given its potential to provide a sizable amount of the protein required for the expanding global population, modern aquaculture has developed from small-scale backyard farming using crude technologies (Lazado *et al.*, 2021) to become one of the fastest-growing food-producing industries worldwide (FAO, 2020). The billion-dollar sector has benefited tremendously from recent technical improvements and includes a wide range of commodities from many countries (Naylor *et al.*, 2021). Aquaculture products are becoming more diverse, new strains are being cultivated in new places, artificial conditions are being optimized, and high-quality production that satisfies market needs through intensification thanks to these advancements (Lazado *et al*., 2021). The health and welfare of farmed species in these new environments and under different production technologies may not receive the necessary attention, according to aquaculture stakeholders, despite these impressive technological advancements. Other issues include storms, droughts, and high temperatures, which negatively affect the water quality and may jeopardize the immune system of fish and the health of aquatic animals (Ahmadniaye *et al*., 2019). Furthermore, the overuse and misuse of antibiotics to treat bacterial infections has occasionally resulted in the emergence of antibiotic-resistant organisms (Aafreen *et al*., 2021). Adjuvants and immunostimulants included in fish vaccines can serve as a substitute for antimicrobial drugs such as antibiotics used in fish culture in the management of fish diseases. As immunostimulants, medicinal plants can be used to prevent infections, enhance stress tolerance, and stimulate growth in addition to treating illnesses. Therefore, it is crucial to give priority to the biological needs of cultivated strains and make sure they survive in conditions that are competitive (Lal *et al*., 2024). Various synthetic medications have been employed in the past to prioritize the health of aquatic creatures (Joana *et al*., 2021). However, some researches have shown that using synthetic medications to treat aquatic animals has negative impacts, particularly when it comes to environmental pollution, antibiotic drug resistance, and cancer (Ziva *et al*., 2016). Nonetheless, medicinal plants have been utilized for ages to cure a wide range of illnesses. Many cultures around the world have acknowledged and made use of these plants' healing qualities. Because of their potential efficacy and low side effects, these substances have gained popularity as natural substitutes for pharmaceutical medications in recent years (Tejal *et al*., 2023). The purpose of this overview is to give insight into the use of medicinal plants as an effective and safe substitute for aquatic animal medications. The review also highlights the advantages, describing certain well-known instances and stressing their therapeutic qualities. For instance, emphasis on Alkaloids, flavonoids, terpenoids, and phenolic compounds are among the active chemicals found in plant materials that are produced during secondary metabolisms and contribute to their therapeutic qualities (Mayur *et al*., 2023). According to Bhargava *et al*. (2023), they have been essential to Indigenous healing methods, Ayurveda, and Traditional Chinese Medicine (TCM). The potential for a broad range of therapeutic effects is what makes their uses significant (Kendal, 2023). Onyenibe *et al*. (2023), also said that, herbs have anti-inflammatory, anti-cancer, anti-microbial, and antioxidant qualities.

Beneficial Effects of Medicinal Plants in Aquaculture

Plants substances are viewed as a possible alternative to avoid fish infections because of the negative consequences of resistance antimicrobial medications on human health, aquatic environments, and fish health (Freitas *et al*., 2019). Antioxidant chemicals found in abundance in plants efficiently scavenge free radicals, averting cellular harm (Moreno *et al*., 2020). Steroids, proteins, tannins, saponins, terpenoids, and alkaloids are examples of bioactive substances that are resistant to viruses, fungi, and bacteria. These include *Salmonella typhi*, *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Klebsiella pneumoniae*, *Mycobacterium*, and *Escherichia coli*. The fungi include *Aspergillus flavus*, *Aspergillus fumigatus*, *Fusarium solani*, and *Pseudomonas aeruginosa*. Historically, antibiotics like ampicillin, tetracycline, and Terramycin have been created using medicinal herbs (Ullah *et al*., 2016). Furthermore, because of their bioactive components and functional nutrients, medicinal plants can be employed in aquaculture as feed supplements in addition to chemotherapeutics (Gerwick, 2013). According to Tran *et al*., (2017), they provide a variety of biological benefits, such as immune system stimulation, growth promotion, hunger stimulation, stress alleviation, and antibacterial action in aquatic organisms. The dense primary precursors of medicinal plants, such as flavonoids, glycosides, phenolics, saponins, alkaloids, terpenoids, tannins, and steroids, are responsible for their efficacy (Ullah *et al*., 2016). They are readily available, sustainable, and can be employed to increase health and production in intensive aquaculture farming (Cawthorn & Hoffman, 2015). In addition to beneficial bacteria, yeast, and other products originating from animals, medicinal plants can be applied in a variety of ways, including active compounds or crude extracts (Zhong *et al*., 2018). The medical benefits of bioactive plants are best illustrated in Figure 1 below.

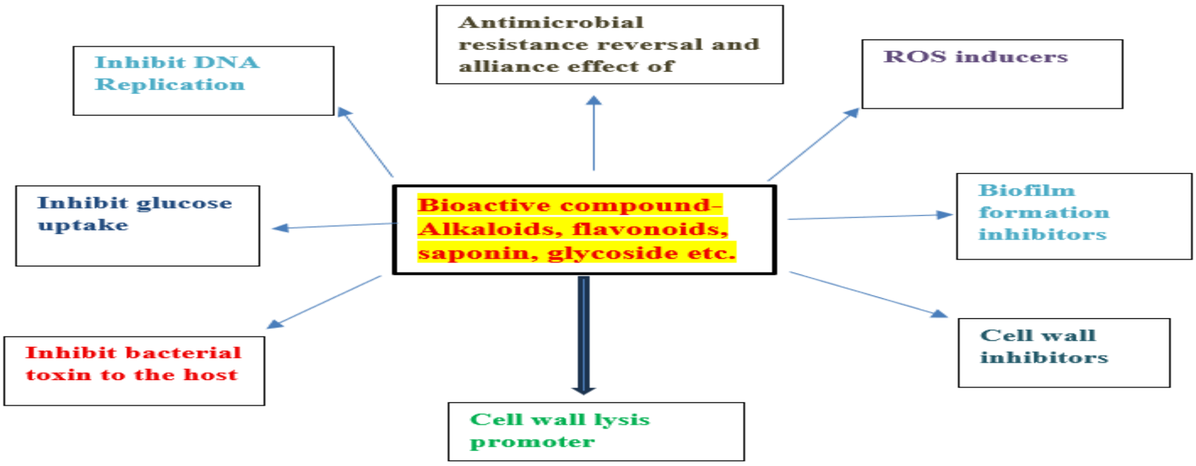

Figure 1: Summary of medicinal beneficial of bioactive compound

Anti-Bacterial impact of plant substances

The primary bottleneck in the fish farming industry is bacterial infections, which have a negative impact on fish health and output and cause significant financial losses. Early detection and care are essential due to the disease's high transmissibility. For instance, ulceration and distension of the abdomen are among the signs of Aeromonas infections, which are mostly caused by *Aeromonas hydrophila* and affect a variety of freshwater fish species, including carp, tilapia, and catfish (Lieke *et al*., 2020). Salmon, shrimp, and groupers are among the marine fish that are seriously infected by *Vibrio*, which results in skin sores, ulcers, and high mortality rates. Both the above diseases have been treated with an active metabolite (*Allin*) extracted from garlic (Putri et al., 2025 and Verma et al., 2021), because of their antibacterial properties. Hence, this plant-derived antibiotic substituents are taken into consideration for bacterial infections despite the rising usage of many antibiotics, including florfenicol, and thus provide sustainable solutions (Zhang *et al*., 2020). Skin infections, *septicemia*, and gastroenteritis in humans and fish are caused by a *hydrophila* (Anurag *et al*., 2023). Certain medicinal herbs, like *Echinacea* (*Echinacea spp*.) and *Astragalus* (*Astragalus membranaceus*), have immunomodulatory qualities that improve the performance of the immune system. These plants can strengthen the body's defenses against illnesses and bacterial infections (Alessandra *et al*., 2021). The antibacterial efficacy of 31 Brazilian plant extracts against fish pathogenic bacteria, specifically *S. agalactiae*, *F. columnare*, and *A. hydrophila*, was discovered. The microbe most vulnerable to numerous tested extracts was *F. columnare*. This bacterium is sensitive to the primary disinfectants used in fish farms, including potassium permanganate, hydrogen peroxide, chloramines, and salt, despite its high pathogenicity to juvenile fish (Victor *et al*., 2018). These substances may be hazardous to fish and aquatic environments despite their widespread use. Plant extracts can be used as a substitute to stop and manage *columnaris* outbreaks, mostly in hatcheries, compared to other products, these compounds have a lesser potential for harm because they are natural. According to the findings, the plants under analysis had a great deal of promise as an alternative treatment for bacterial fish illnesses (Castro *et al*., 2008). Garlic's abundance of bioactive substances, including diallyl sulfides, *ajoene*, and *allicin*, has led to its demonstrated strong antibacterial properties. When garlic is crushed, *allicin* is produced, which can inhibit the growth of bacteria like *Aeromonads hydrophilic* and *Vibrio* species and lower fish mortality rates (Espinoza *et al*., 2020).

Anti-parasitic potentials of plant substance

Slowing of growth rates and high mortality rates are common parasite-related health issues in fish that have a significant effect on aquaculture. Protozoans, helminths, and crustaceans are among the organisms that cause these illnesses (Buchmann, 2022). The illness known as *ichthyophthiriasis* causes white patches on the skin, gills, and fins, as well as increased mucus production and difficulty breathing. However, in order to reduce the severity of this parasite disease and the need for synthetic chemicals, natural medications like as extracts of garlic and neem are currently being evaluated for more environmentally friendly methods (Bula *et al*., 2023). Both freshwater and marine fish are infected by *Trichodina species*, which cause their gills to become inflamed, and their breathing to become fast. Betel leaf extract, Indian almond extract, etc. In the years to come, oral use might begin to emerge as a viable, sustainable alternative treatment for the above disease (Shinn *et al*., 2023). Freshwater fish, like carp goldish and tilapia are frequently found to have *monogenean* parasites, which can result in gill rot, excessive mucus production across the body wall, a red operculum (gills), and unpredictable swimming behavior that may eventually cause death, these can be treated by natural plant remedies like *pomegranate orgarlical*, which have anti-parasitic qualities (Hernández-Orts *et al*., 2023). Fish with a bloated abdomen and visible worms are signs of a nematode infestation. Anthelmintics are one type of treatment; wormwood and garlic are two natural methods being researched (Hadeld and Clayton, 2021). Infestations of copepods are brought on by parasites like *Argulus* and *Lernaea species*, which feed on the skin of fish including carp, trout, and salmon. This creates blisters on the fish's skin and thin shed tissue that comes into contact with ambient materials. To prevent parasite infections, however, natural extracts like turmeric and neem are advocated for sustainable aquaculture management that relies less on artificial pesticides (Ogaba *et al*., 2022). Bioactive substances protect against parasites and mild skin lesions by reducing the need for synthetic chemicals. The environment supports fish health and is biodegradable. In order to combat parasite infestations that continue to plague the aquaculture sector, the application of these natural alternatives for fish health management is still being refined (Piasecki *et al*., 2022).

Pharmaceutical benefit of plants substances against pathogenic aquatic viruses

According to Tian-Xiu et al., (2025), the flavonoid Isoliquiritigenin derived from *Glycyrrhiza glabra*, shows potent antiviral properties by enhancing host defenses through antioxidative and immunomodulatory mechanisms. In another studies, a very high mortality rate, infectious pancreatic necrosis viruses (IPNV) that primarily infect fry and juveniles up to 20 weeks of age (Irtifa *et al*., 2023), also Numerous commercial fish and shellfish species have been affected by IPNV-caused fish infections that have been reported in Asia, America, and Europe (Carlos, 2020). However, out of the three known flavonoids that were isolated from the methanolic extract of the leaves of *V. grandifolia* for the first time i.e. *isoorientin*, orientin and isovitexin, the phyto-components, isovitexin and isoorientin could be a potential candidate for eliminating IPNV from asymptomatic brood stock of fishes. With anomalies in the pancreatic vesicles, islets, and nearly all cells the majority of which are necrotic pancreatic necrosis is the most noticeable pathogenic characteristic are treated with *Astragalus membranaceus*. However, viruses like Herpes simplex virus types 1 and 2, Junin, and Respiratory Syncytial virus could not replicate when species of the *genus Heliotropiu* were present (Liao *et al*., 2020). *Astragalus membranaceus* is a traditional herb that has been used in medicine for a long time with a range of pharmacological characteristics, astragalus polysaccharide (APS) is a significant bioactive constituent of A. *membranaceus* (Wang *et al*., 2018). Li *et al*., (2020) looked into the antiviral effect of APS in zebrafish. The control diet and experimental meals with 0.01% or 0.02% APS were given to the zebrafish for three weeks. After a feeding, SVCV challenging the zebrafish were treated. Garlic is another potent plant material. It has also been demonstrated that garlic possesses antiviral properties (Mikaili *et al*., 2013). Garlic's antiviral properties are known to be attributed to ajoene, an allicin condensation product, which works by preventing integrin-dependent processes in an infected cell system in this case, the human immunodeficiency virus (El-dougdoug *et al*., 2018). Garlic extracts have also been shown to have antiviral properties in both in vitro and in vivo methods. Human-relevant viruses such as *influenza B*, *parainfluenza* virus type 3, herpes simplex virus types 1 and 2, *Coxsackie virus spp*., vaccinia virus, vesicular stomatitis virus, human immunodeficiency virus type 1, and human rhino virus type 2 are all susceptible to antiviral activity, especially from sulfur constituents (Sharma 2019; Singh and Singh 2019). A polyphenolic substance called curcumin is present in natural plants; turmeric plants have previously been used to extract its metabolites (Javad *et al.*, 2020). Curcumin's antiviral effects have been thoroughly investigated, and its mechanism of action primarily entails direct interference with the viral replication machinery in addition to inhibition of cellular signaling pathways that are necessary for viral replication, including nuclear factor kappa B (NF-B) and phosphatidylinositol-3-kinase (PI3K)/Akt (Nicoliche *et al.*, 2024). Additionally, curcumin inhibits VHSV (Srivastava *et al.*, 2022). When VHSV-infected cells were pretreated with 120 mM curcumin, their vitality significantly increased, their viral copy number decreased, and their apoptosis decreased. According to a different study, curcumin prevented VHSV from entering cells by either upregulating F-actin or downregulating fibronectin (FN) 1 (Yang *et al.*, 2021). In order to guard against VHSV infection at the viral entry stage, HSC71 is the main protein that interacts with FN1, actin, and gelsolin (GSN). In fact, curcumin increased the viability of VHSV-infected cells and inhibited VHSV replication while downregulating HSC71 expression. According to current research, curcumin may have antiviral properties via suppressing HSC71 expression (Jeong *et al.*, 2015). Furthermore, curcumin inhibits the action of cyclooxygenase enzymes that convert arachidonic acid to prostaglandins. The inhibition of prostaglandins helps to mediate pains that may represent a stressor for fish species. Additionally, the lipoxygenase enzyme converts arachidonic acid in a different pathway that results in the formation of leukotrienes. Leukotrienes and prostaglandins both act as mediators of pain. Therefore, one possible strategy to lessen inflammation in fish species is to regulate the synthesis of both molecules (Desai *et al.*, 2018). The processes of action are explained in the image below.

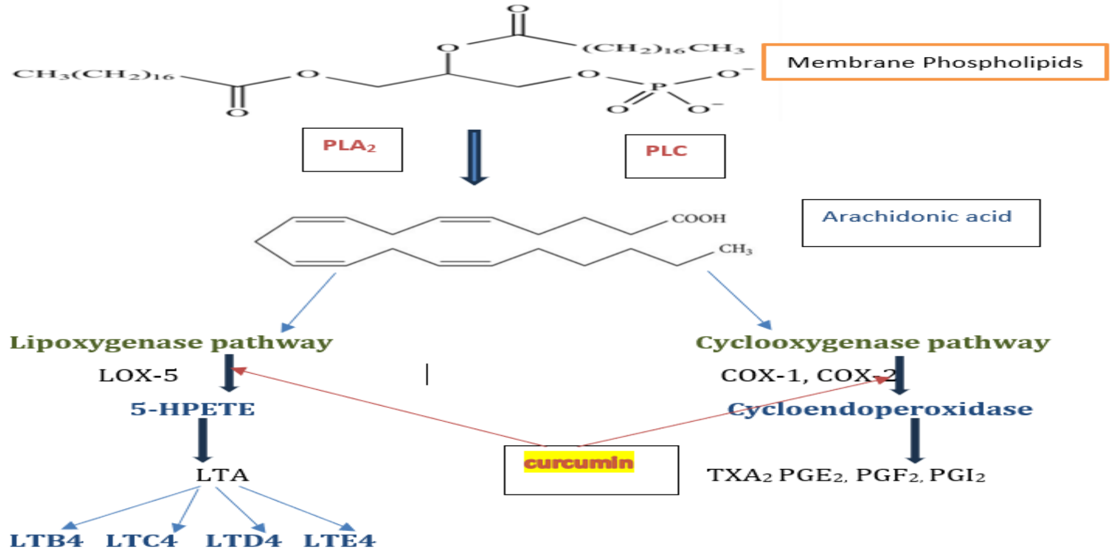

Figure 2: COX: Cyclooxygenase; HPETE: Hydroperoxyeicosatetraenoate; LOX: Lipooxygenase; LT: Leukotrienes PL: Phospholipase; PG: Prostaglandins; TX: Thromboxane.

In the above figure, curcumin act as an inhibitor of LOX-5 and COX-1 or COX-2, theses inhibition stops the cascade of reactions leading to the release of the stress molecules (LTB4 LTC4 LTD4 LTE4) and (TXA_2 PGE_2, PGF_2, PGI_2), giving the compound its anti-inflammatory Properties.

Adverse health effects of herbal plant substances

Plant herbal medicines and related substances in most countries are introduced into the market without any regulation or toxicological evaluation. Effective machinery is some of the limitations to regulate manufacturing practices and quality standards of these substances, especially in developing countries (Ekor, 2014). These herbal products are continuously made available for consumers without prescription in most cases and the potential hazards in an inferior product are hardly recognized (Temitope and Santwana, 2021). For example, long time effects assessment**.** Little is known about the long-time effects of the plant derived medicine applied on the aquatic animals, since its emergence is too long. Moreso, according to Jose *et al*., (2020), the huge utilization of this product has become an environmental concern, because of the widespread occurrence of these compounds in aquatic ecosystems and their potential toxicological effects on nontarget species. Specifically designed to be biologically reactive at very low concentrations, active ingredients have the tendency to inhibit the biochemical and physiological processes in nontarget species, with virtually unknown long-term effects on marine ecosystems. Hence, the urgent need to elucidate such aspects is reflected in international actions, such as the development of guidelines for Eco pharmacovigilance and regulatory approaches in Europe, the United States, Japan, and Australia. Additionally, according to Applequist et al., (2006), The quality of medicinal plants can be altered by several ways, including: carelessness or ignorance of the plant collector, negligence during preparation and foreign object removal, poor storage and preservation practices, accidental contamination with another plant or substance, adulteration and substitution of a different plant.

Future of plants derived medicine in sustainable aquatic disease control

Nearly half of the fish that humans eat originate from aquaculture, which is one of the food production industries with the greatest rate of growth in the world (Naylor *et al*., 2021). The breakout and spread of infectious illnesses among farmed species are one of the major issues brought on by the expansion of aquaculture operations. Historically, the main methods for managing these illnesses have been synthetic drugs and antibiotics (Espinosa *et al*., 2020). But excessive use of them has sparked worries about antibiotic resistance, bioaccumulation, environmental damage, and hazards to human health (Huemer *et al*., 2020). Consequently, there is a growing interest in environmentally safe and sustainable solutions, with the usage of medicinal herbs being one of the most promising (Souto *et al*., 2021). Numerous bioactive substances with antibacterial, antiparasitic, antifungal, immunostimulatory, and anti-inflammatory qualities can be found in medicinal plants, including alkaloids, flavonoids, tannins, saponins, and essential oils. When administered properly, these natural chemicals are less likely to cause resistance than synthetic medications, are biodegradable, and are generally safe. Their application in aquaculture promotes the health of animals, people, and the environment and is consistent with the ideas of one Health and sustainable development (Alvarez-Martínez *et al*., 2021), below table1 summarizes the current work on the effects of the medicinal against pathogens that borders aquatic environment.

Table 1: Summary of some medicinal plants that have been study for aquatic diseases control

Pathogen	**Medicinal Plant**	**Active Compound**	**Microorganism Type**	**Reference**
SVCV	*Glycyrrhiza glabra*	Isoliquiritigenin	Virus	(Tian-Xiu et al., 2025)
IPNV	*Astragalus membranaceus*	Astragalus polysaccharide	Virus	(Sachin et al., 2023)
VHSV	Turmeric	Curcumin	Virus	(Srivastava et al., 2022)
Aeromonas hydrophila	Garlic	*Allium sativum*	Bacteria	(Putri et al., 2025)
Aeromonas hydrophila	Garlic	*Allium sativum*	Bacteria	(Putri et al., 2025)
Vibrosis	Garlic	*Allium sativum*	Bacteria	(Verma et al., 2021)
Vibrio harveyi	Betel Leaf	*Piper betle* L.	Bacteria	(Kurniasari et al., 2021)
Ichthyophthiriasis	Garlic	Extract	Protozoan	(Bula et al., 2023)
Trichodina spp.	Indian Almond	Crude Extract	Protozoan	(Shinn et al., 2023)
Monogenean	Pomegranate	Extract	Protozoan	(Hernández et al., 2023)
Streptococcus spp.	*Moringa oleifera*	Extract	Bacteria	(Dadras et al., 2023)

Current Applications in Aquaculture

Immunostimulant: It is well known that certain herbs, including *Curcuma longa* (turmeric), *Allium sativum* (garlic), and *Azadirachta* indica (neem), can strengthen the innate immune response in shrimp and fish (Chew *et al*., 2022).

Antimicrobial agents: *Aeromonas hydrophila*, *Vibrio spp*., and *Streptococcus spp*. have been demonstrated to be effectively combatted by extracts from plants such as *eucalyptus*, *Phyllanthus niruri*, and *Moringa oleifera* (Dadras *et al*., 2023).

Antiparasitic effects: According to Ranasinghe *et al*. (2023), some plants have shown efficacy against parasites such as *Lernaea* and *Ichthyophthirius multifiliis*.

Future Prospects

- Standardization and Quality Control: Future studies must concentrate on standardizing dosages, extraction techniques, and active ingredient concentration in order for medicinal plants to be utilized in aquaculture with reliability.
- Creating stable formulations that are simple to incorporate into fish feed or water systems, such as powders, pellets, or aqueous extracts.
- Using good agricultural and collection practices (GACP) to guarantee consistency.
- Integration with the Management of Integrated Fish Health will also proffer a significant development in farmers hands on knowledge in the application of medicinal plants in aquatic environment.

Conclusion

A potent and mainly unexplored resource for long-term aquaculture disease prevention is medicinal plants. Aquaculture's future may depend on these environmentally friendly substitutes as worries about antibiotic use and their effects on the environment increase. Medicinal plants can contribute to the development of a robust and health-conscious aquaculture sector that feeds the globe while protecting the environmental, long time adverse effect of antibiotics resistance.

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Appendix 1: List of abbreviations

Abbreviation	Full Form	Abbreviation	Full Form
COX	Cyclooxygenase	TCM	Traditional Chinese Medicine
HPETE	Hydroperoxyeicosatetraenoate	ROS	Reactive Oxygen Species
LOX	Lipooxygenase	PGI2	Prostaglandin I2 (prostacyclin)
LT	Leukotrienes	FAO	Food and Agricultural Organization
PL	Phospholipase	IPNV	Infectious Pancreatic Necrosis Viruses
PG	Prostaglandins	APS	Astragalus Polysaccharide
TX	Thromboxane	GSN	Gelsolin
TXA2	Tranexamic Acid	PI	Phosphatidylinositol
FN	Fibronectin	NF-κB	Nuclear Factor Kappa B
VHSV	Viral Hemorrhagic Septicemia Viruses	HSC	Heat Shocking Cognate
GACP	Good Agricultural and Collection Practices		

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