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Review of the Role of Probiotic and Herbal Supplements as Antibacterial, Antioxidant, and Immunomodulatory Against *Aeromonas hydrophila*)

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Abstract: *Aeromonas hydrophila* (*A. hydrophila*) are classified as zoonotic and opportunistic bacteria. Natural immunostimulants such as herbs are biodegradable and safe for the environment and host health. There has been no systematic review of using these natural ingredients to treat or prevent *A. hydrophila* infection. This review aims to demonstrate the role of herbs and probiotics as antibacterial, antioxidant, and immunostimulatory against *A. hydrophila* infection. This study deployed systematic and comprehensive literature from PubMed, Google Scholar, and Scopus from 2012 to 2022, with keywords: *A. hydrophila*, herbal, probiotics, antioxidant, immunomodulator, antibacterial. Data are obtained from journals, proceeding of research results, excluding article reviews. The review results indicate that the utilization of these two ingredients (herbs and probiotics) is potential to prevent *A. hydrophila* infection in animal models with variation action mechanisms and dose administration. However, an inappropriate combination of herbs and probiotics leads to the development of resistance and toxicity profile, thereby requiring further research to standardize such combination prior to application for humans or animals.

Keywords: *Aeromonas*; Herbs; In vivo; Probiotics; Zoonosis

Introduction

Among various *Aeromonas sp.*, *Aeromonas hydrophila* (*A. hydrophila*) frequently causes infection in humans (Kadhim, 2014). Cases include more than 85% of gastroenteritis due to this bacteria (Khamesipour et al., 2014). The incidence of *A. hydrophila* infection varies from 20-76 cases per 1,000,000 people. Infection occurs in immunocompromised or immunocompetent individuals (Valcarcel et al., 2021), leading to invasive and fatal infections in humans (Rhee et al., 2016). In addition, *A. hydrophila* often attacks animals, especially freshwater fish, causing motile Aeromonas septicaemia (MAS) disease, classified as a secondary infection affecting high economic losses (Hamid et al., 2016), as well as mortality up to 90-100% for 1-2 weeks post infection (Muchtar et al., 2019; Rozi et al., 2018).

Vaccination and antibiotics have the potential to control *A. hydrophila* infection (Abdel-Tawwab et al., 2018). Antibiotics effectively kill bacteria, despite counterindicating harmful effects on biotics in waters and humans Abdelkhalek et al. (2020) due to reducing the host's immune system (Ahmadifar et al., 2019). In addition, consuming fishery products containing residues presents harm Devi et al. (2019), as it is undegradable, triggering pathogenic bacteria in the environment. The application of natural products is urgently required as an alternative to minimize the administration of chemical drugs to prevent bacterial resistance, improve the host immune response and reduce free radicals (Dawood et al., 2020). However, the

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effective administration of vaccines for prevention against certain bacteria must be in the form of a boosted dose (Hardi et al., 2016).

Probiotics and herbs serve to prevent or treat disease. Herbs act as prophylaxis by preventing the early emergence of clinical symptoms to prevent disease proliferation (Adeniyi et al., 2020). However, prior reviews that systematically collect data for the treatment or prevention of *A. hydrophila* infection by herbs and probiotics have been limited. Hence, this review aims to demonstrate the importance of probiotic and herb administration to prevent *A. hydrophila* infection along with providing their properties as health supplements.

Method

Article searches were generated from sources such as PubMed, Science Direct, Springer Link, and Google Scholar in 2012-2022. The keyword searches (in English) included *Aeromonas hydrophila*, herbs, probiotics, antioxidant, immunomodulatory, and antibacterial. The obtained articles were in the form of title and abstract only or full text. Article search criteria were based on PICO (Population, Intervention, Comparison, Outcome), in which Population: studies in animal model (fish and rodent); Intervention: therapy with herbs and probiotics (lactic acid bacteria (LAB) or yeast); Comparison: herbal and/or LAB/yeast vs. controls; Outcome: Antibacterial, antioxidant, and immunomodulatory effects. Inclusion criteria included herbs or probiotics to control in English. Exclusion criteria were as follows: bacteria or yeast strain not acting as probiotics. Antibacterial tests, such as MIC (*minimum inhibition concentration*) and MBC (*minimum bactericidal inhibition*), were excluded.

Result and Discussion

Herbs

Most herbal plants that act as health supplements contain essential oils and metabolic secunder. In this review, the leaves and roots of herbs were examined. The herbs were prepared in whole extract, nanoparticles and nanoencapsulation to accommodate intestinal absorption. In this review, the administration of herbs against *A. hydrophila* was more allocated to fish than to rodents. The application of the herbs was orally administered at a dose of 50 mg – 0.75 g/kg in each feeding while bathing at 5-40 mg/L water for 2-12 weeks (see Table 1). Herbal nanocapsules require lower doses and shorter applications than those in herbal extract preparations. The administration of herbs can be single or in combination. In experimental fish, herbal plants were evident to trigger the growth of fish. The administration of herbs was mainly prophylactic, not therapeutic.

Antimicrobial activity and application

The results of a research review indicated that the antibacterial properties of herbal plants against *A. hydrophila* were based on bactericidal serum tests. The seaweed (*Gracilariopsis persica*) carbohydrate fraction contains antimicrobial activity against *A. hydrophila* due to the presence of sulfate molecules, such as carrageenan, fucans, and laminarin (Khosravi et al., 2018). However, *A. hydrophila* bacteria are resistant to multiple antibiotics (El-Adawy et al., 2018). Less-appropriate administration of antibiotics in cultured fish leads to rejection of overseas shipments due to the effects of antimicrobial residues found on human and aquatic organisms (Babu et al., 2016). *A. hydrophila* is classified as a gram-negative bacterium that is more resistant to essential oils than gram-positive bacteria because the protection of a thicker outer membrane (lipopolysaccharide) is hydrophobic (Bhargava et al., 2015).

Table 1. Review of herbal against *A. hydrophila* infection

Herbal/References	Active compounds and Biology activity	Animal model/ Doses and Route of administration	Main result
Cinnamon nanoparticles (CNP) Abdel-Tawwab et al., (2018)	Cinnamic aldehyde, cinnamyl aldehyde, polyphenol, tannins, saponins, flavonoids, and carbohydrates Antiemetic, anti-diarrhea, antiinflammation, antioxidant, and antimicrobia	Nile tilapia (*Oreochromis niloticus* (L.) Oral, 3-10 gr/kg feed for 8 weeks	Increased MDA, antioxidant activities: superoxide dismutase (SOD) and Catalase (CAT), whereas glutathione peroxidase (GPx) decreased. Increase nitric oxide (NO), nitro blue tetrazolium (NBT), and lysozyme activity
Hesperidin (HES) and ellagic acid (EA)	HES and EA	Male MF1-albino mice	Increased immunoglobulins M (IgM) levels and reduced

Herbal/References	Active compounds and Biology activity	Animal model/ Doses and Route of administration	Main result
Abuelsaad et al., (2013)	HES as antiinflammation, hypotension and analgesia. EA as antioxidant	Oral, HES's dose is 250 mg/kg/week and EA's dose is 150 mg/kg/week	anti-ECP (extracellular proteins) IgA
Cymbopogon citratus) essential oil/LEO and *Pelargonium graveolens* essential oil (GEO) Al-Sagheer et al., (2018)	LEO : citral, delta-3-carene, geranial, trans-caryophyllene and menthone. GEO: citronellol Immunomodulator, antiinflammation, antimicrobia, anti hypoglycaemic and antioxidant	Nile tilapia GEO at 400 mg/kg of diet for 12 weeks	Increased catalase, lysozyme activity and IgM levels; reduced GPx, MDA level, and intestinal total bacteria
Carotenoid Anbazahan et al., (2014)	Carotenoid Immunostimulator, antioxidants	Common carp (*Cyprinus carpio*) 50 and 100 mg/kg diets on weeks 2 and 4	Enhanced phagocytic, lysozyme, and complement activity
Crude extracts (ICE) and purified fractions (ICF) of *Ixora coccinea* Anusha et al.,(2014); Christy et al., (2018)	Alkaloids, saponin, tannins, flavonoid, cardiac glycoside, oxalate, phenol, anthraquinone, and phytate Cytotoxic, antimicrobia, antiinflammation, and antioxidant	Goldfish (*Carassius auratus*) 400 mg/kg feed for 30 days	Improved serum albumin, phagocytic activity, serum bactericidal, and lysozyme activity
Moringa oleifera)/MO (Ayoub et al., 2019; Rašković et al., 2014; Tanvir et al., 2017; Vergara-Jimenez et al., 2017)	MO: vitamins, phenolic acids, flavonoids, isothiocyanates, tannins, and saponins Antidiabetic, antimicrobia, immunostimulator, hepatoprotective and antioxidant	Nile tilapia 1% dietary MO for 2 months	Incresed lysozyme and respiratory burst activity
Tea tree *(Melaleuca alternifolia*) oil/*TTO* Baldissera et al.,(2017)	Terpinen-4-ol Immunomodulator, antimicrobial, antiinflammation, antiparasitic	Silver catfish *(Rhamdia quelen)* TTO for 7 days (50 µl/L water)	Decreased MDA, protein carbonylation and Adenosine deaminase activities
Ethanolic extract of *Myrica esculanta* (MeALE) Bhat et al., (2021)	Aerolysin and β-ketoacyl synthase-1 Antimicrobia and immunomodulator	Rainbow trout (*Oncorhynchus mykiss*) Immersed in 40 mg/L MeALE for 2-6 hour	Increased in hematological NBT and lysozyme activity
Rhodiola rosea polysaccharide (RRP) Cheng (2019)	Galactooligosaccharide, fulvic acid, chitosan, and fructooligosaccharides	Red swamp crayfish (*Procambarus clarkia*) 0.6 g/kg diet	Increased growth, and antibacteria
Nano encapsulated *Origanum majorana* (NOM), *Origanum majorana* essential oil (EOM)	EOM : Myrcene, γ-terpinene, α-terpinene, p-cymene, thymol, carvacrol, β-caryophyllene, limonene,	Silver catfish (*Rhamdia quelen*) Baths with 20 µL/L EOM or 5 µL/L NOM	Increased survival rate, count of leucocyte and lymphocytes

Herbal/References	Active compounds and Biology activity	Animal model/ Doses and Route of administration	Main result
Da Cunha et al., (2018)	linalool, sabinene, β-citronellal NOM : germacrene-D, β-bourbonene, β-caryophyllene, geranyl isobutyrate, cedranoxide, Cubenol, Eudesmol and Agaruspirol Asthma, rheumatism, antimicrobial, insecticide, and antioxidant		
Rutin and florfenicol Deepika et al., (2019)	Rutin : Flavonol, curcumin and esculetin Florfenicol : commersial antibiotic Antibacteria, antibiofilm, antiinflammation, antioxidant	Nile tilapia Rutin (50 mg/kg diet) and florfenicol (30 mg/kg diet) for 30 days	Increased blood cell count and lysozyme. Decreased oxidative stress and pathological changes
Echinacea purpurea (L) *Moench*)/EP El-Sayed et al., (2014)	Polysaccharides, caffic acids and cichoric acid Immunostimulant and antibacteria	Nile tilapia 0.75 g/kg diet for 8 weeks	Weight gain, increased of lysozyme activity, bactericidal, IgM, total globulin, and lymphocyte index
Propionic acid (PA) and oxytetracycline (OTC) El-Adawy et al., (2018	Propionic acid and oxytetracycline Immunostimulant, antibacteria, growth promotor	Nile tilapia PA (200 mg/kg of diet) and OTC (500 mg/kg of diet) for 2 weeks	Increased in total serum protein, globulin, IgM, phagocytic, lysosome activity, hematological, Reduced oxidative damage
Eugenia Caryophllate Extract/ECE El-Araby (2018)	Eugenol, allicin Antimicrobia, antioxidant	Nile Tilapia 0.5 % ECE for 10 days	Increased hemoglobin and leukocyte count; growth performance and antibacteria
Moringa oleifera leaf Abd El-Gawad et al., (2020)	Vitamins, carotenoids, polyphenols, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins, and saponins Antitumour, antiinflammation, antihypertensive, antioxidant, antidiabetic, hepato-protective, antimicrobia, and immunostimulator	Nile tilapia 1.5% *M. oleifera* for 60 days	Increased respiratory burst, phagocytic, lysozyme activities, IgM, antioxidant enzyme but MDA level decreased
Trigonella foenum-graecum (fenugreek) (Gariepinus et al., 2016; Singh et al., 2020)	Trigonelline, isoorientin, orientin, vitexin, and isovitexin	African sharptooth catfish (*C. gariepinus*) 1% of fenugreek for 30 days	Increased Gpx and catalase, Phagocytic

Herbal/References	Active compounds and Biology activity	Animal model/ Doses and Route of administration	Main result
	Appetite stimulation, antistress, immunostimulator		
Petroselinum crispum essential oil Farag et al., (2021)	D-limonene, oleic acid, α-pinene and myristicin Antioxidant, antiinflammation, anti-apoptic and immunostimulant	Nile tilapia 1 mL/kg diet for 60 days	Increased growth, leukocytic, lymphocytic and lysozyme activity
Adiantum capillus-veneris leaves powder (FLP) Hoseinifar et al., (2020)	Phenolics, terpenoids, alkaloids, quaternary, N-oxides, fibre and elements (*e.g.,* Zn and Cu) Antimicrobia, wound healing, antiinflammation, antioxidant, diuretic, and detoxifying	*Cyprinus carpio* 2% FLP in the diet for 56 days	Enhanced in SOD, CAT, bactericidal, and weight gain
Allium Sativum)/AS Kalyankar et al., (2013)	Allicin Antibacteria and immunomodulator	Swordtail (*Xiphophorus Helleri*) AS extract @ 1.5% of total feed ingredient for 6 weeks	Increased growth, Haemoglobin, total erythrocytes, leucocyte count and packed cell volume)

Antioxidant activity and application

A. hydrophila bacteria contain a potential pro-oxidant compound in the liver through increased protein oxidation and inhibition of antioxidant enzymes, generating clinical symptoms (Baldissera et al., 2017). Plant bioactivity contains a therapeutic effect that improves health and physiological status (Alagawany et al., 2021). The review results of prior studies reported that antioxidant activity was navigated based on free radical product tests, MDA (malondialdehyde) and NO (nitric oxide) and antioxidant enzymes such as SOD, CAT and GPx. Curcumin boosts growth and modulates innate immunity as well as anti-inflammatory cytokines such as IL-10 but decreases the expression of pro-inflammatory genes in *Ctenopharyngodon idella* infected with *A. hydrophila*. The optimal dose of curcumin is 438.20 mg/kg diet (Ming et al., 2020).

Antioxidant enzymes inhibit the production of free radicals by removing their precursors (Dawood et al., 2020). Carotenoids serve as a part of antioxidant systems that work to protect against oxidative damage through two mechanisms, including (1) attenuating singlet oxygen and (2) scavenging free radicals Anbazahan et al. (2014), thereby preventing damage to cellular lipids, proteins, DNA, and polysaccharides. Hence, balancing free radicals and antioxidants is deemed pivotal to maintain physiological functions by adding exogen antioxidants (Tanvir et al., 2017).

Immunomodulator and application

The immunomodulator test was based on the review results of articles focusing on phagocytic activity, such as NBT, to determine the production of superoxide ions, lysozyme activity, respiratory burst, complement activity, leucocyte count and lymphocyte count as an innate immune response by preventing adhesion and colonization of bacteria hindering disease (Adel et al., 2016). Macrophages and neutrophils exhibit respiratory burst activity by producing free radicals such as superoxide anions, hydrogen peroxide, and NO in the phagocytosis process (Adel et al., 2016). Nitric oxide is classified as a highly reactive free radical generating pathological reactions such as damage to the immune system and physiological cells (Abdel-Tawwab et al., 2018).

In contrast, the adaptive immune response test was performed based on IgM and IgA measurements. Grass carp and Nile tilapia fed pellets containing 2 g kg^{-1}

Lycium barbarum have the potential to improve total immunoglobulin, bactericidal activity and anti-protease activity when challenged with *A. hydrophila* bacteria (Mo et al., 2016). However, excessive administration leads to adverse effects on health (Ming et al., 2020). However, a dose of 2 g kg^{-1} resulted in significant weight loss of grass carp and Nile tilapia fish (Mo et al., 2016).

Probiotics

Probiotics consist of LAB (producing antimicrobial peptides such as enterocin, polysaccharides, and acids) and yeast containing glucans and mannan-oligosaccharides, peptides, nucleotides, cell solubles and vitamins (Abu-Elala et al., 2013). In this study, LAB were prepared in the form of microencapsulated LAB at a dose of 10^8-10^{11} CFU/g of diet, while yeast was administered at a dose of 10 gr yeast/kg of feed. Additionally, microbial administration was available in a single form or combination with herbs (synbiotics) (see Table 2), with an average feeding time of 7-90 days. Antioxidant testing was performed based on antioxidant enzymes by neutralizing free radicals (hydroxyl radical scavenging and DPPH scavenging activity). The immune response to herbs was observed based on nonspecific and specific immunity. The prepared strains (probiotic agents) included *Lactobacillus, L. plantarum, L. fermentum, L. rhamnosus, L. acidophilus*, and *L. delbrueckii* (Behbahani et al., 2019). Only a few yeasts are used as probiotics in commercial formulations, such as *Saccharomyces cerevisiae*, *S. boulardii, S. bayanus, S. florentius, S. pastorianus, S. sake* and *S. unisporus* (Saber et al., 2019), due to their nonpathogenic nature, lack of plasmid-encoded antibiotic resistance genes, and resistance to bile and acidic pH (Abu-Elala et al., 2013).

Antimicrobial activity and application

The LAB applied in this study were classified as excellent probiotic candidates that were host-specific (Kuebutornye et al., 2020) and nonpathogenic, tolerating various extreme environments, growing, surviving and occupying the gastrointestinal tract of the host (Ramesh et al., 2015), and effortlessly adapted to compete with pathogenic bacteria for nutrients and space (Maeda et al., 2014). A sole administration of *Lactococcus lactis (L. lactis)* L19 or in combination with *Enterococcus faecalis (E. faecalis)* W24 isolated from the gut of *Channa argus (C. argus*) was evident to improve digestive enzyme activity, antioxidant enzyme activity and intestinal microbiota, thereby increasing the generation of probiotics in *C. argus* fish infected by *A. hydrophila* (Kong et al., 2021).

Tabel 2. Main characteristics of studies related to the role of LAB and Yeast against *A. hydrophila*

Probiotic/ References	Active compounds and Biology activity	In vivo study/ Doses and Route of administration	Main result
Lactobacillus fermentum (LF) and/or ferulic acid (FA) Ahmadifar et al., (2019)	FA: ferulic and gallic acids Antioxidant, immunomodulator	*Cyprinus carpio*) LF (10^8 CFU/g) or/and FA (100 mg/kg) of diets for 8-weeks FA or both LF	Increased respiratory burst, lysozyme activity and antioxidant enzymes
Enterococcus casseliflavus (EC-001) Akbari et al., (2021)	Enterocin Growth promotor, immunomodulator, and antibacteria	*Cyprinus carpio* EC-001 at 1 × 10^9 CFU/g feed three times a day for 8 weeks	Increased serum total protein, lysozyme, complement C3,
L. lactis Z-2 Feng et al., (2020)	Microbial exopolysaccharides (EPS) and polysaccharides Immunomodulatorand antioxidant	*Cyprinus carpio* EPS-2 (500, 1000 µg/mL) for 7 days via gavage	Increased phagocytosis, lysozyme, and antiinflammation. Levels of NO, pro-inflammatory cytokines decreased
Symbiotics MOS and DBA® (*Bifidobacterium sp*, *L. acidophilus*, and *Enterococcus faecium*) Cavalcante et al., (2020)	Probiotic: acetic, lactic, butyric acids; Mannan oligosaccharides Antibacteria, immunostimulant	*Oreochromis niloticus* L. Probiotic 3.5 × 10^9 CFU/g of feed (*Bifidobacterium sp*), 3.5 × 10^9 CFU/g of feed (*L. acidophilus*) and 3.5 × 10^9 CFU/g of feed (*E. faecium*) 0,3 g/kg of feed	Reduced mortality, preserved gut microbiota modulation, weight gain

		+ MOS (4 g/kg of feed) for 63 days	
L. plantarum L-137 and β-glucan (BG) Dawood et al., (2020)	β-glucan Immunostimulant, antioxidant, antibacteria, and growth promotor	Nile tilapia (*Oreochromis niloticus*) 50 g of *L. plantarum* [2×10^{11} CFU per g] diets+ 50 mg BG per kg diet for 90 days	Weight gain, increased in SOD, CAT, erythrocyte and albumin but feed conversion ratio and MDA decreased
Lactococcus lactis (L. lactis) 16-7 Dong et al., (2018)	D-lactic acid Immunomodulator, antiinflammation, antibacteria	*Carassius carassius*) *L. lactis* (1.0×10^{9} CFU/ml) For 42 days	Enhanced SOD, phagocytic activity, increased in intestinal permeability, limit inflammation

Antioxidant activity and application

Probiotic strains could lower reactive radicals by stimulating intestinal saccharolytic metabolism and reduce stress-induced oxidation of doxorubicin (Kim et al., 2020). The mechanisms of action of probiotics as antioxidants are through direct neutralization of oxidants in the intestinal tract by antioxidant enzymes and stimulation of the immune system by decreasing oxidative stress-induced cytokines and inhibiting intestinal pathogens. Furthermore, probiotics could increase the absorption of micro- and macronutrients, including antioxidants (Kleniewska et al., 2016). A probiotic strain when heated could kill *Pseudomonas aeruginosa* VSG2 isolated from the intestines of Indian carp Labeo rohita, expressing antioxidant genes (SOD, GPx, and Cat) in *C. carpio* infected with *A. hydrophila* at a dose of 30 mg kg^{-1} for 8 weeks (Giri et al., 2020).

Immunomodulator and application

Live cell mixture and supernatant of *Lactococcus lactis* of Z-2 (5×10^{8} cells mL^{-1}) for 7 days decreased NO levels and pro-inflammatory cytokines but increased levels of anti-inflammatory cytokines (IL-10, TGF-β) in carp (Wang et al., 2021). Yeast hydrolysate refers to yeast cells such as *S. cerevisiae* supplemented with acid enzymes or other hydrolysis methods containing more polysaccharides and amino acids. However, due to the peptide's smaller size, it is easy to digest, acting as an immunostimulant, compared to yeast culture. Administration of 1.5% yeast hydrolysate for 56 days could increase the expression of IL-10, SOD, CAT, and IgM, decreasing MDA levels postchallenge with *A. hydrophila* in largemouth bass fish. Yeast hydrolysate has a positive impact on growth (Gong et al., 2019).

Among the available probiotics, LAB are acknowledged to improve the immune system and antibacterial activity (Dong et al., 2018). Some of the most critical human intestinal probiotics include *Lactobacillus* and *Bifidobacterium* as anti-inflammatory, immunomodulator and antibacterial agents (James & Wang, 2019). *Lactobacillus* produces antibacterial agents such as bacteriocin and galactosidase enzymes (Behera et al., 2020).

Synbiotics consist of an incorporated mixture of probiotic and prebiotic agents that provide a synergistic effect on the host to trigger metabolism and to improve microbial biota in the digestive tract (Devi et al., 2019) and in the immune system through interaction with the host's pattern recognition receptors. However, factors including the dose, time of administration, composition, and type of probiotics are required for supplementation considerations dealing with various body responses (Cavalcante et al., 2020). The combination of prebiotics and probiotics must be synergistic and appropriate based on the mechanism of action, dose, and duration, as an inappropriate combination leads to problems in animal physiology and microbial flora diversity. The combination of *Bacillus subtilis* + inulin (10^{7} CFU/g + 10 g/kg) in the diet for four weeks caused inflammation, decreasing the gut microbiome in the gut of gilthead seabream (*Sparus aurata L.*) infected *A. hydrophila*.

Conclusion

This review serves as a scientific basis regarding the administration of herbs and probiotics to develop new drugs against *A. hydrophila* infection. Significant findings from the review of research results indicate that herbs and probiotics are evidently beneficial as antibacterial, antioxidant and immunomodulatory agents and drugs. Hence, this study suggests the preparation of nanoencapsulation as a drug rather than extracts due to longer availability when absorbed in the body. However, an inappropriate combination and dose leads to the development of resistance and the formation of free radicals, generating tissue damage. Thus, further research is encouraged to standardize the aforementioned compounds and to investigate the toxicity profiles prior to human and animal application.

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Conflict of Interest

No conflicts of interest.

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