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Probiotics: Comprehensive Exploration of the Growth Promotion Mechanisms in Shrimps

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Abstract: As feed accounts for a significant proportion of a farm's expenditure, animal nutrition is one of the key profit determinants. Attributed to the size-dependent market value, enhancing shrimps' growth is essential to maximize profit. Despite not being the best option, antibiotics are often used as growth-promoting agents in farming. Although this trend is less explicit in aquaculture, increasing production yield is paramount, especially when intensive aquafarming compromises animal growth and increases disease prevalence. However, the environmental and clinical pitfalls of indiscriminate antibiotic usage are surfacing. Fortunately, increasing evidence demonstrated probiotics as a safer, more sustainable, and environmental-friendly substitute for antibiotics. Nonetheless, most studies are observational, and the growth-promotion mechanisms of these agents are yet to be elucidated.

In this light, this review aims to decipher the growth promotion mechanisms of probiotics in shrimps based on the primary works conducted. Evidently, probiotic treatment modulates the gut microbiome composition. The growth promotion effect of probiotics is partly mediated through the production of bioactive compounds such as short-chain fatty acids, vitamins, and polyamines. Besides, elevated digestive enzyme activities following the introduction of probiotics may help enhance digestibility and utilization. Histological changes at the hepatopancreas and intestine were evident. Furthermore, probiotics may reinforce the protective mechanisms in the gut and strengthen immune function. Treated shrimps demonstrate better appetite and exhibit superior metabolic and growth-related genes profile. Contrasting these recognized mechanisms with antibiotics helps construct the initial framework for designing high-quality probiotics for growth enhancement in farmed animals.

Keywords: growth; probiotic; feed additives; mechanism; shrimp; antibiotic

1. Introduction

In recent years, progress in the aquaculture industry has been gaining increasing momentum. According to a recent report released by the Fisheries Department of the Food and Agriculture Organization (FAO), global aquaculture production rises by 6.1% annually, with the highest production centred in Asia [1]. Although crustaceans only account for 7.5% of the total global production by weight, it is characterized by a high unit value, which amounts to 24.5% of the total global production value [1, 2]. Shrimp aquaculture, which has emerged as a promising economic endeavour, has been progressively intensified in many developing countries [1]. Over the past two decades, crustacean production has increased by 9.9% annually, achieving 8.4 million tonnes in 2017. Among the shrimp species cultured, the Pacific white shrimp (*Litopenaeus vannamei*) recorded the highest production rate, which is followed by the black tiger shrimp (*Penaeus monodon*) and the giant freshwater prawn (*Macrobrachium rosenbergii*) [1, 2]. Despite the promising development, further intensification of shrimp farming often reaches a bottleneck where the high stocking density significantly increases the risk of disease transmission and severely decimates the production yield [3-6]. Attributed to the high unit price of shrimp and the size-dependent market value, optimizing the growth of shrimp within the shortest production frame became a pivotal factor in maximizing revenue. A higher production yield would compensate for the untoward losses to disease episodes and sustain the culture production [7].

The application of antibiotics at subtherapeutic doses for disease control and growth enhancement has been a time-honored convention in farming practice [8-10]. Data from *The State of the World's Antibiotics 2015* revealed that 65% of the 100,000 tonnes of antibiotics produced globally were capitalized for animal production [11]. However, the negative impacts of antibiotic use are gradually surfacing. The detection of high antibiotic residue levels in the farm wastewater and sediment of shrimp ponds poses a threat to the surrounding marine or coastal ecosystems [12-15]. Antibiotic use exerts a selective pressure on resistant bacteria,

which creates a risk for the transference of antimicrobial resistance genes (ARGs) to other bacteria via horizontal gene transfer mechanisms such as transformation, conjugation, or transduction [14, 16]. This gradually precipitates the emergence of multi-antibiotic-resistance bacteria pathogenic to other animals and humans [17-24]. Besides, the residual antibiotic detected in animal flesh is another alarming concern for public health, particularly when the concentration of antibiotics exceeds the maximum residue limit [25, 26]. The increasing awareness regarding the detrimental consequences of indiscriminate antibiotic use has increased the demand for antibiotic-free products from sceptical consumers. In some countries, drastic antibiotic use restrictions have been reflected in banning certain antibiotics or stringently controlling their application for limited indications [27, 28].

The environmental hazards and health threats accompanying antibiotic application hampered its continuous use in farming. Therefore, the quest for a safer and sustainable alternative to antimicrobial growth promoters (AGPs) is an exigency to safeguard the animal production yield and to forestall the aggravation of antimicrobial resistance (AMR) development. At this juncture, a mounting body of research evaluates the effectiveness of probiotics as a potential candidate to replace antibiotics in farming [29-31]. On average, meta-analysis results revealed that probiotic treatment improved the feed conversion ratio (FCR) of 49 studies and the specific growth rate (SGR) of 60 studies by 19% and 14%, respectively [32]. Several studies reported that probiotics demonstrated comparable growth promotion effects to antibiotics [33-35]. Moreover, besides the growth promotion effects, probiotics also elevate the resistance to disease and environmental stressors, enhance the animal's immune function and ameliorate the quality of rearing water [36-39].

More often than not, the growth enhancement effects of probiotics are typically reported as a mere ‘positive side effect’ to its primal role in disease control. Acknowledging the dire need to enhance aquaculture yield, the growth enhancement effects of probiotics should, instead, be maximally harnessed in the current farming practice to increase farm production. Probiotics use in aquaculture could be a boon to the farming industry. Therefore, further research is warranted to investigate how probiotics can be more efficiently integrated with the feed additives commonly applied in farms. In this light, this review aims to compile the possible probiotic mechanisms contributing to the growth of shrimps. Deciphering the mechanisms of probiotics about the action of AGPs also helps to develop better alternatives to AGPs. Addressing this knowledge gap will shed light on the positive traits of probiotics that facilitate the growth of livestock. Understanding these crucial factors will be critical for developing probiotics tailored for the growth enhancement of shrimps.

2. Antimicrobial Growth Promoters

Antibiotic has been an indispensable confederate in farming practice [40]. It is still the mainstay for disease management among husbandry animals, especially during the early breeding phases [41]. Antimicrobial agents can be administered via different routes, including direct application to water, incorporated into feed, or injected intramuscularly [14, 41]. Sulphonamides, tetracyclines, quinolones, chloramphenicol, and nitrofurans have been extensively exploited for aquaculture use [25, 42]. Usage of oxytetracycline, sulphadiazine, florfenicol, amoxicillin, oxolinic acid, sulphamethoxazole, trimethoprim, and erythromycin have also been recorded [43, 44].

Nevertheless, it is difficult to estimate the total annual global antibiotic use in shrimp farming alone. This is attributed to the discrepancies in farming modes, climates, disease risks, antibiotic limits, and the regular shifts between the diverse farmed species [43, 45]. Moreover, the policies vary significantly between countries, and there is little detail regarding each region's indication and antibiotic usage pattern [46].

Although using antimicrobials at subtherapeutic doses to boost growth performance has been discouraged for animals intended for food supply, some farmers still embrace antibiotics for their growth-promoting effects in aquaculture [17]. On average, antibiotics use could increase feed utilization by 2% to 5%, translating to an estimated growth improvement ranging from 4% to 8% [47]. For example, over eight weeks, the SGR and weight gain rate (WGR) in *L. vannamei* receiving daily supplementation of 0.3% florfenicol to the basal diet increased by 2% and 7%, respectively, when compared to the untreated control [35]. In another experiment, daily inoculation of oxytetracycline directly to the rearing water at a concentration of 4 mg/L resulted in a significantly 8% higher development rate of *L. vannamei* larvae after nine days of treatment [34]. The growth promotion effect may differ according to animal species, antibiotic selection, and treatment regimens.

In recent years, increasing reports unveiled environmental and food safety concerns regarding antibiotics usage [48, 49] [50-53]. Ironically, in contrast to the expected decline in antibiotic use following the heightened consciousness of their negative implications, antibiotic consumption for aquacultural purposes is still threading on an increasing trend [54]. Judging from the continuously increasing demand for food production, the global antimicrobial utilization intended for food production is forecasted to exceed 100,000 tonnes by 2030 if no proper substitute for AGP for farming is sought [41]. Therefore, it is crucial to decipher the mechanisms of antibiotics in enhancing the survival and growth of animals in the quest for a desirable replacement compound.

2.1. Mechanisms of AGPs

For a long time, the growth promotion effect of antibiotics was attributed to the suppression of subclinical infections [55]. The bacteriostatic or bactericidal effect against

opportunistic pathogens helps mitigate disease occurrence in intensive farming [56]. Although the antimicrobial effect at a subtherapeutic dose was speculative [57], this rationale has invariably augmented the unwarranted use of prophylactic antibiotics to overcome the sanitary shortcomings in crowded farming sites [17]. The remarkable growth-promoting effect remains a subject of interest that intrigues many researchers. The underlying mechanism of antimicrobial growth promoters is yet to be fully elucidated. Several hypotheses were proposed to explain the growth-promoting phenomenon of antibiotics. However, there is still ongoing debate regarding the plausibility of these hypotheses [57].

Further research is warranted to fill the knowledge gap. Nonetheless, the mechanisms can be broadly classified into two categories: bacterial-centric and host-associated factors (Figure 1). Rather than treating these factors as exclusive events, it is highly probable that these two mechanisms complement each other and dually contribute to animal growth. These two factors are further compounded by other external factors such as hygiene, stress, and diet [58].

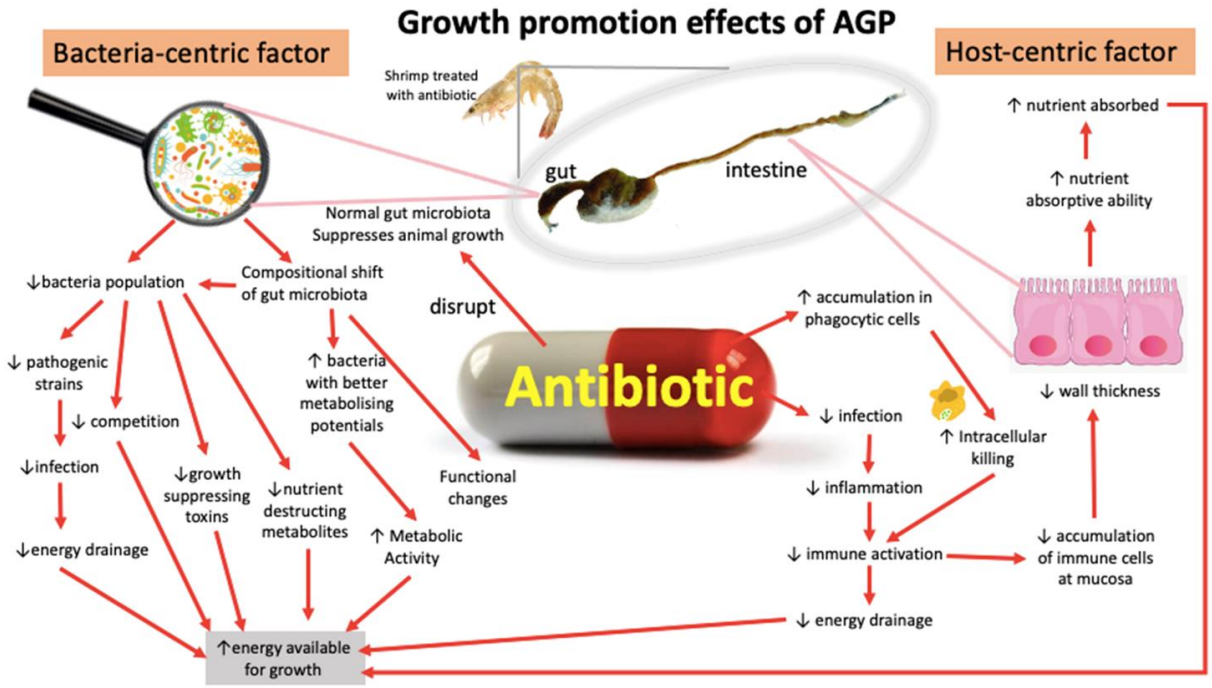

Figure 1. The bacterial-centric and host-centric growth-promoting mechanisms of AGP.

An underlying assumption for the bacterial-centric hypothesis is that normal gut microbiota suppresses animal growth [57]. This notion is well promulgated by the fact that AGPs do not promote the growth of germ-free mice. Meanwhile, depression of growth becomes evident following the inoculation of bacteria to germ-free mice [57]. In this sense, the growth promotion mechanism can be expounded through the concept of 'dysbiosis'. Dysbiosis is a term that describes the compositional shift of bacteria distribution in the gut induced by a disruption to the gut microbial homeostasis leading to metabolic and functional changes. Antibiotic was believed to be an intervening factor that disrupts the homeostatic balance [59]. It causes a significant alteration of gut microbiota composition in the treated

animals. The growth promotion effect becomes evident when microorganisms with better metabolizing potential gain predominance in the gastrointestinal tract [60]. Increasing evidence demonstrated the involvement of gut microbiota in energy conversion and metabolic processes [61]. The gut microbiota composition indirectly influences the host's metabolic activity. This idea has been well supported by several studies involving mice models [62-68]. Another possible explanation within this context is that antibiotics caused a reduction in the bacteria population residing in the gastrointestinal tract. This may reduce in proportion the growth-suppressing toxins or nutrient-destructing metabolites such as biogenic amines and ammonia secreted by the gastrointestinal bacteria. In this sense, AGPs are sometimes regarded as growth-permitting instead of growth-promoting agents [57]. Scaling down the population of competing microorganisms also spares the nutrients and increases the energy sources available for the host cells. Besides, suppressing the pathogenic strains within the gut also indirectly lowers the incidence of intestinal infections [69-72]. Repressing subclinical infections eradicates the unnecessary energy drainage through the immune function and conserves the energy store to favour growth [73].

From the host-centric perspective, the immunomodulation mechanism represents a convincing hypothesis supporting the growth promotion effect of AGPs [57]. Different antibiotics exert different extents of inhibitory effects on the immune system. For instance, the immunomodulatory effect of florfenicol appears to be less pronounced than for oxalinic acid and oxytetracycline [56]. AGP is believed to benefit the animal by limiting the immune activation in response to inflammation which is often obligatorily associated with disease states [74, 75]. This results in the suppression of pro-inflammatory cytokines, thus preventing the initiation of acute-phase response, which is essentially an energy-demanding catabolic process. The acute phase response should be avoided at all costs as its activation is accompanied by metabolic alteration that leads to reduced feeding and nutrient assimilation, which severely compromises animal growth [76, 77].

Some highly penetrative antibiotics can accumulate in the phagocytic cells reaching up to 10- or even 100-fold the ambient concentration [57]. This discrepancy in the immunomodulatory effects between different classes of antibiotics may stem from the differences in the diffusing potential of each antibiotic into the phagocytic cells [74]. To illustrate, clindamycin, macrolides, and quinolones can efficiently diffuse into the phagocytes; whereas aminoglycosides and beta-lactams have limited penetrating potential [78, 79]. Niewold [57] propounded an excellent reference to the intra-phagocytic accumulating potential and the phagocytic inhibitory effect for several antibiotics. Accumulated antibiotics drive the intracellular killing of pathogens and partly attenuate the innate immune response. Notably, the application of antimicrobial agents has been found to impair several downstream immunological cascades such as chemotaxis, phagocytosis, respiratory burst, and cytokine production [58, 80]. For example, rifamycin was reported to dampen the stress-induced inflammation of the intestinal mucosa in the mice model [81]. *In-vitro* studies using immortalized keratinocytes (HaCaT) also demonstrated that low doses of doxycycline at 0.3 µg/mL resulted in the significant 68.7% suppression of interleukin (IL-8) release when

induced by lipopolysaccharide (LPS). A similar trend is noted for other pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and IL-6 in cells treated with low-dose doxycycline [82]. Controlling cytokine production is likely to have a pronounced effect on growth due to its impact on metabolic homeostasis. Compelling evidence shows that proinflammatory cytokines may systematically alter lipid and amino acid intake and metabolism rates [77].

To sum up, downregulating the immune response has a far-reaching effect on growth. Attenuating the immunological cascade would limit the catabolic expenditure in maintaining an immune response. Thereby, more resources can be channelled for anabolic activities directed toward growth [58, 83]. Moreover, dampening the immune system also reduce the accumulation of immune cells in the mucosa. Since the intestinal mucosal is a dynamic layer modulating nutrient absorption, metabolic and immunological functions [84], the thinning of the intestinal wall helps facilitate the absorption of nutrients [85, 86].

3. Probiotics

Probiotics are live microbes introduced deliberately to improve the health of the targeted host [87, 88]. Since their inception to farmed animals as feed supplements in the 1970s, the growth promotion and disease resistance effects have encouraged their continuous implementation in farming [89]. This trend is gradually expanded to the aquaculture industry. Besides the disease control and growth enhancement effect, when administered in adequate amounts, specific probiotic strains can modulate the host's gut microbial composition, improve water quality, elevate the immune function and increase the animals' survival rate [90-97]. These positive reports fueled new interest in research. Increasing evidence suggests that probiotic represents a safer and more sustainable alternative to antimicrobial agents in farming [29, 36, 37, 98].

More than 20 genera of microorganisms have been studied for their growth promotion effect in shrimp models. Among the probiotics, *Bacillus* sp. was the most studied and widely applied genus in shrimp farming. Table 1 presents a list of microorganisms showing promising growth promotion effects in shrimps. The growth promotion effect was evaluated using parameters such as SGR, average daily growth (ADG), weight gain rate (WGR), FCR, and feed efficiency (FE) [99, 100]. The majority of the strains demonstrated multifaceted functions. They represent the up-and-coming candidates to replace AGPs. Further research, particularly deciphering the mechanism underlying the growth promotion effect of probiotics, is warranted before large-scale commercial implementation.

Table 1: Microorganisms demonstrating significant growth promotion effect when introduced as probiotics in shrimps.

	Probiotics with growth promotion effect		Method of Administration	Dosage	Frequency and duration of trial	Shrimp species treated	Ref.
	Genus	**Species**					
Bacteria							
	Aeromonas	*bivalvium*	Feed additive	10^7 cells/g diet	Daily for 28 d	*L. vannamei*	[101]
	Alteromonas	sp.	Water additive	10^6 CFU/mL	Daily for 18 d	*P. monodon*	[102]
	Arthrobacter	sp.	Water additive	10^5-10^7 CFU/mL	Every 5 d for 24 d	*L. vannamei*	[103]
	Bacillus	*amyloliquefaciens*	Water additive (mixture)	10^9 CFU/mL	Once weekly	*L. vannamei*	[104]
		coagulans	Water additive	10^7 CFU/mL	Daily for 35 d	*L. vannamei*	[105]
			Feed additive	10^7-10^9 CFU/g diet	Daily for 56-90 d	*L. vannamei*	[95]
						M. rosenbergii	[106] [107]
		cereus	Water additive	10^6 CFU/mL	Every 14 d for 110 d	*L. vannamei*	[108]
			Feed additive	10^4 CFU/g diet	Daily for 28 d	*M. rosenbergii*	[109]
				0.1-0.4 %/100 g diet	Daily for 90 d	*P. monodon*	[92]
		licheniformis	Water additive	10^4-10^9 CFU/mL	Once weekly/ daily for 8 d	*L. vannamei*	[110] [104]
			Feed additive	10^6-10^9 CFU/g diet	Daily for 60-90 d	*L. vannamei*	[111]
						M. rosenbergii	[112]
						P. monodon	[113]
		megaterium	Water additive (mixture)	2 mL/10 L of water	Once weekly for 9 mo	*L. vannamei*	[114]

		Water additive	10^9 cells/mL, 10 mL to 90 L of water	Every five days for 60 d	*P. monodon*	[115]
		Feed additive	10^9 CFU/g diet	Every five days for 60 d	*P. monodon*	[116]
			10^4-10^8 CFU/g diet	Daily for 28-90 d	*L. vannamei*	[115] [111]
	polymyxa	Feed additive (mixture)	10^8 CFU/g diet	Daily for 90 d	*L. vannamei*	[111]
	pumilus	Water additive	10^6 CFU/mL	Every three days for 18 d	*P. monodon*	[117]
	subtilis	Water additive	10^9 CFU/mL	Once weekly for 120 d	*L. vannamei*	[104]
			10^9 CFU/L	Every three days for 14 d		[118]
			2 mL/10 L of water	Once weekly for 9 mo		[114]
		Feed additive	10^4-10^{12} CFU/kg diet	Daily for 28-98 d	*L. vannamei*	[119] [120] [116] [121] [122] [123] [124] [125] [33]
			3%, 10^7 CFU/g probiotics		*M. rosenbergii*	[126] [127] [90]
			5 g/kg feed		*P. monodon*	[113]
	thuringiensis	Feed additive (mixture)	10^8 CFU/g diet	Once-daily for 90 d	*L. vannamei*	[111]

Bifidobacterium	*bifidum*	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive (mixture)	10^9 cells/L of water			[128]
					L. vannamei	[129]
						[130]
Clostridium	*butyricum*	Feed additive	10^{8-14} CFU/g diet	Daily for 42-60 d	*M. rosenbergii*	[131]
						[132]
					Marsupenaeus japonicus	[133]
Enterobacter	*hominis*	Feed additive	10^7 CFU/g diet	Daily for 28 d	*L. vannamei*	[134]
Enterococcus	*faecium*	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive (mixture)	1g/L of water 10^9 cells/g probiotics		*L. vannamei*	[128]
			10^7 CFU/mL added = Approximately 200 µL/100 postlarvae	Twice daily	*P. monodon*	[135]
		Feed additive	10^7 CFU/g feed	Daily for 28 d	*L. vannamei*	[136]
			10^7 CFU/mL added = Approximately 200 µL/100postlarve		*P. monodon*	[135]
Halomonas	*aquamarine*	Water additive	10^6 CFU/mL, 0.1% v/v	For 12 d	*L. vannamei*	[137]

	sp.	Enrich live feed (*Artemia*)	300 mg/L (24h) 8 naupii/mL/day for 15 days			[138]
		Water additive	10^7 CFU/mL			[139]
		Feed additive	10^7 CFU/g feed	Daily for 42 d	*Fenneropenaeus chinensis*	[140]
Lactobacillus	*acidophilus*	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive	10^7 CFU/mL 1 g/L of water 10^9 cells/g probiotics	Daily for 35 d		[105] [128]
		Feed additive (mixture)	5 g/kg feed	Daily for 60 d	*P. monodon*	[113]
	coagulans	Feed additive	10^8 CFU/g feed	Daily for 56 d	*L. vannamei*	[95]
	fermentum	Water additive (mixture)	2 mL/10 L of water	Once weekly for 9 mo		[114]
	delbrueckii	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive (mixture)	1 g/L of water 10^9 cells/g probiotics			[128]
	pentosus	Feed additive	10^7-10^9 CFU/g feed	Daily for 28-56 d	*L. vannamei*	[136] [125]
	plantarum	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive (mixture)3	1 g/L of water 10^9 cells/g probiotics		*L. vannamei*	[128]

			2 mL/10 L of water	Once weekly for 9 mo	*L. vannamei*	[114]
			10^9 CFU/L	Daily for 90 d	*M. rosenbergii*	[141]
		Feed additive	10^7 -10^{12} CFU/g feed	Daily for 21-90 d	*L. vannamei* *M. rosenbergii*	[142] [143] [144]
	rhamnosus	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
		Water additive (mixture)	1 g/L of water 10^9 cells/g probiotics	Daily for 45 d	*L. vannamei*	[128]
	sporogenes	Enrich live feed (*Artemia*)	10^7 CFU/L (12h)		*M. rosenbergii*	[145]
		Feed additive (mixture)	3-4% in the diet, 10^7 CFU/g probiotics	Daily for 60 -90 d	*M. rosenbergii*	[126] [90]
			5 g/kg feed	Daily for 60 d	*P. monodon*	[113]
Lactococcus	*lactis*	Feed additive	10^8 CFU/g diet	Daily for 56 d	*L. vannamei*	[146] [33]
Nitrobacter	*sp.*	Water additive (mixture)	2 mL/10 L of water 10^6 cells/mL 3 mg/L every 16 d for 12 weeks, then 5 mg/L till the end of the culture	Once weekly for 9 mo	*L. vannamei*	[114] [147]
Nitrosomonas	*sp.*	Water additive (mixture)	2 mL/10 L of water		*L. vannamei*	[114]

			2mL/10 L of water Once weekly for nine months	10^6 cells/mL 3 mg/L every 16 d for 12 weeks, then 5 mg/L till the end of the culture			[147]
	Pediococcus	*acidilactici*	Water additive	10^6 CFU/mL	Every 14 d for 110 d	*L. vannamei*	[108]
			Feed additive (mixture)	10^8 CFU/g diet	Daily for 60 d	*M. rosenbergii*	[148]
		pentosaceus	Feed additive	10^8 CFU/g diet	Daily for 65 d	*L. vannamei*	[149]
	Pseudomonas	*aestumarina*	Feed additive	10^5 CFU/g diet	Once-daily for 28 d	*L. vannamei*	[119]
		sp.	Water additive (mixture)	10^9 CFU/mL	Daily for 15 d	*L. vannamei*	[104]
	Psychrobacter	sp.	Water additive	10^5 CFU/mL	Once weekly	*L. vannamei*	[150]
	Rhodopseudomonas	*palustris*	Water additive	10^7 CFU/mL	Daily for 35 d	*L. vannamei*	[105]
	Roseobacter	*gallaeciensis*	Feed additive	10^5 CFU/g diet	Once-daily for 28 d	*L. vannamei*	[119]
	Shewanella	*algae*	Water additive	10^5 CFU/mL, 0.1% v/v	For 12 d	*L. vannamei*	[137]
		haliotis	Feed additive	10^7 cells/g diet	Daily for 28 d	*L. vannamei*	[101]
		sp.	Feed additive	10^7 cells/g diet	Daily for 56 d	*L. vannamei*	[96]
	Streptococcus	*phocae*	Feed additive	10^7 CFU/mL of probiotics 200 mg/100 post larvae		*P. monodon*	[135]
			Water additive	10^7 CFU/mL added =Approximately 200 µL/100 post larvae	Twice daily		[135]

		salivarius	Enrich live feed (rotifer) (mixture)	0.43 mg/mL (6h) 10^9 cells/g probiotics	Daily for from mysis I to postlarvae 5	*L. vannamei*	[128]
			Water additive (mixture)	1g/L of water 10^9 cells/g probiotics		*L. vannamei*	[128]
	Streptomyces	*fradiae*	Water additive	10^9 cells/mL, 10 mL to 90 L of water	Every 5 d for 60 d	*P. monodon*	[115]
			Feed additive	10^9 cells/g feed	Every five days for 60 d	*P. monodon*	[115]
	Vibrio	*alginolyticus*	Feed additive	10^5 CFU/g diet	Once-daily for 28 d	*L. vannamei*	[119]
Yeast	*Debaryomyces*	*hansenii*	Feed additive (mixture)	10^8 CFU/g diet	Once-daily for 90 d	*L. vannamei*	[111]
	Rhodotorura	*sp.*	Feed additive (mixture)	10^8 CFU/g diet	Once-daily for 90 d	*L. vannamei*	[111]
	Saccharomyces	*cerevisiae*		10^8 CFU/g diet	Daily for 60-90 d	*M. rosenbergii*	[148]
			Feed additive				
			4% in the diet, 10^7 CFU/g probiotics	3-4% diet, 10^7 CFU/g			[126] [127]
			Daily for 60 days				[151]
				10-40 g/kg diet			[90]
				5 g/kg feed	Daily for 60 d	*P. monodon*	[113]

*Mixture means the probiotics contain more than one microorganism.

4. Mechanism of probiotics in promoting animal growth

The growth promotion effect of probiotics is postulated to be driven by several factors. The mechanisms may vary from strain to strain, and the exhibited effect may vary when introduced to different animals [152]. Based on the empirical observational approaches, several events demonstrated strong correlations to growth. This includes the alteration to the gut microbiota composition, elevation of enzymatic activities, modification of the hepatopancreatic and intestinal morphology, enhancement of immune function, and modification of genes expression [90, 134, 153-155]. In startle contrast to AGPs, probiotic administration was found to strengthen the immune function of the animals. Besides, probiotics also help to increase animals' resistance to environmental stressors, including ammonia and oxidative stress, by ameliorating the water quality. This implies that more underlying mechanisms that may contribute to animal growth are yet to be elucidated. This review synthesizes a summary of the underlying mechanisms of probiotics in promoting animal growth based on the available studies involving shrimp models. The growth promotion mechanisms of probiotics are then compared and contrasted with AGPs to generate new insights to propel the pursuance of better growth-promoting agents for shrimp farming (Table 2).

5. Modulating the gut microbiome

Gut microbiota composition is recognised as one of the key determinants for the normal function and maintenance of the digestive tract structure of the host [156, 157]. Due to their pivotal roles and the high collective metabolic activity in the gut, the indigenous microbiota is also regarded as another virtual organ within the gut [158, 159]. These microbes co-evolve with the host along the long evolutionary process. A mutualistic relationship exists between these bacteria and the host [160-162]. To illustrate, the gut microbiota plays vital roles adjunctive to the gut, particularly in homeostasis maintenance, immune regulation, energy distribution, nutrient absorption, and storage [163-166]. In this regard, the involvement of the gut microbiota is likely indispensable to the growth promotion effect of probiotics. Probiotics increase the proportion of beneficial microbes in the gut and help maintain a healthy and functioning gut microbiota.

Table 2: Compare and contrast the mechanisms of AGPs and probiotics in promoting animal growth.

Mechanisms affecting the growth of animals	Antimicrobial Growth Promoters	Probiotics
Gut microbiota	• Reduce the gut microbiota diversity • Reduce the abundance of gut bacteria • Increase the proportion of bacteria that promotes growth	• Increase the gut microbiota diversity • Increase the ratio of beneficial microbes to pathogenic microbes without significant changes to the total abundance of gut bacteria • Establish a healthy and functioning gut microbiota
Enzymatic activity	• No significant alteration	• Enhance the enzymatic activities • Enhance nutrient digestibility
Gastrointestinal tract morphology	• Reduce the muscularis wall thickness	• Increases the number of B cells in the hepatopancreas • Lower the degree of atrophy and necrosis in the hepatopancreas and midgut (during infection) • Increase epithelial integrity • Increase the size of epithelial cell • Increase the villus number and height Increase the surface area of the inner surface of the intestine
Immune system	• Attenuate the immune system • limit the immune activation in response to inflammation • impair immunological events such as chemotaxis, phagocytosis, respiratory burst and cytokine production	• Prime the immune system • Strengthen the protective mechanism • Elevate the inhibitory capacity against pathogens

5.1. Increasing the proportion of beneficial bacteria

It is well established that dietary factors could modulate an organism's gastrointestinal microbial community composition [8, 96, 164, 167-174]. Alteration to the gut microbiota composition of aquatic animals following probiotic supplementation has been well demonstrated [38, 61, 175-177]. Contrary to the action of antibiotics in reducing the bacteria population and diversity in the gut [10, 178, 179], probiotics often only alter the composition of the gut microbiota without significantly affecting the total abundance of the gut microflora [153]. The gut microbiome of probiotic-treated groups generally demonstrates higher species richness and biodiversity [61, 94]. This is reflected in the higher number of operational taxonomy units (OTUs) as well as the higher abundance-based coverage estimators (ACE), Shannon, Chao-1, and McIntosh indexes in the probiotic treatment groups [94, 134, 180]. The diversity of the microbial community could also be analysed based on the variety of carbon sources available in the gastrointestinal tract of shrimps using the Biolog-ECO technique. This parameter can also be employed to index the aerobic metabolism rate [134, 180]. Using this method, Zuo *et al.* [134] demonstrated the elevated intestinal microbiome activity through the significant increase in average colour change rate per hole (AWCD) in cohorts supplemented with probiotics *Lactobacillus* and *Enterobacter hormaechei*. Polymerase Chain Reaction - Denaturing Gradient Gel Electrophoresis (PCR-DGGE) analysis also revealed the incorporation of *Bacillus* spp. probiotics into the feed enriched the individual variation and total diversity of intestinal bacteria in Kuruma shrimps (*Marsupenaeus japonicus*) [181]. This result is consistent with the single-strand conformation polymorphism (SSCP) fingerprint analysis which shows higher intestinal bacteria diversity in *L. vannamei* following the administration of *Bacillus* spp. probiotics [61].

Interestingly, some probiotic strains seem to exert a selective action towards different microbial species. Probiotics introduced were observed to increase the abundance of beneficial bacteria in the gut and suppress the growth of pathogenic strains. Notably, adding a probiotic mixture of *Bacillus subtilis* and *Saccharomyces cerevisiae* together with prebiotics (mannan oligosaccharides and ß-glucan) into the shrimp diet significantly increased the *Lactococcus* count in the gastrointestinal tract by 11% and depressed the pathogenic *Vibrio* population by 32% when compared with the untreated group [182]. Along this line, a shift in the microbiota composition of *L. vannamei* was evident through the increment in beneficial bacteria *Pseudoalteromonas* sp. proportion and depression of *Vibrio* sp. in the group fed 2% dietary yeast (*S. cerevisiae*) culture [183]. This is consistent with the findings of Nimrat *et al.* [153], who noted the addition of *Bacillus* spp. and yeast probiotic mix to *L. vannamei* increases the ratio of beneficial bacteria species such as *Bacillus* spp. and *Debaryomyces hansenii* without altering the total number of culturable heterotrophic bacteria in the gut. This implies that probiotics can enhance the gut ecosystem without adversely affecting the equilibrium of the natural microflora.

Similarly, Wei *et al.* [96] also reported that beneficial *Pseudomonas* sp. increased proportionally. In contrast, pathogenic species such as Bacteroides and *Escherichia shigella* decreased in abundance following the eight-week probiotic *Shewanella* sp. dietary

supplementation trial. This particular activity is harnessed when the probiotics are introduced to enhance the proliferation of beneficial strains, suppress the growth of pathogenic strains and mitigate the risk of animals succumbing to infectious diseases. This protectivemechanism demonstrated by probiotics contrasts with antibiotics, in which the bactericidal activity may create free ecological spaces for other opportunistic pathogens to thrive post-treatment [56, 178]. In this regard, the colonisation of probiotics is a plus point as these beneficial microbes readily occupy the ecological niches and mitigate the colonisation of opportunistic strains, thus prolonging the desirable effects of the treatment [33] (see Section 5.3).

5.2. Establishment of a healthy gut microbiota

From another perspective, it is postulated that probiotics promote the growth of shrimps by establishing a healthy gut microflora [39]. Although positive correlations between several bacteria phyla and the health indices of the host have been identified [184], hitherto, there is no definite microbiota pattern that can conclude the 'desired microbiota' which favours animal growth. Several significant hurdles stumble research in this aspect. Firstly, because only a tiny fraction of bacteria is currently culturable under lab environment, a substantial fraction of the intestinal microbiota remains unknown. Although advances in molecular techniques offer descriptive data, without representative culturable strains to support further studies, the internal processes, mechanisms, and interactions between the microbiota and the host remain speculative [185]. Secondly, the gut microbiota constitutes a dynamic and highly complex ecosystem involving the interplay of a wide array of bacteria species. These bacteria interact with one another differently, some strains antagonize the growth of another, while others support the growth of others [134, 186]. Thirdly, the gut microbiota composition is further compounded by external factors such as individual variations, developmental stages, feeding, stress, and environmental fluctuations [58, 187-190]. Regardless, a healthy microbiome can generally be characterised as a healthy and functioning core comprising a stable yet flourishing blend of microbe species actively involved in physiological regulatory pathways and could ably resist any external or internal perturbations [188, 191-194]. Recent findings suggest the involvement of commensal microbiota in modulating the host's metabolism, digestibility, and immune response [184, 195-197]. This further reinforces the idea that the gut microbiota is closely associated with regulating the host's growth performance [61, 180, 198]. This notion justifies that applying probiotic supplements can modulate gut microbiota composition to enhance the attainment of better health status and boost the growth performance of cultured shrimps [180, 198].

The microbiota modulated by AGPs could not provide a good reference for the 'desired microbiota template'; similar to the case of probiotics, antibiotics also resulted in inconsistent effects on the gut microbiota despite the proven growth promotion effect [56, 58]. However, significant changes in gut microbiota composition following the addition of probiotics is discernable when compared to the untreated controls [38, 175-177]. Luis-Villaseñor *et al.* [61] show that shrimps treated with two different probiotics exhibited a high percentage similarity (73%) in gut microbiota composition. Still, both only show a 24% similarity to the

untreated control group [61]. This indirectly implies that empirical observational studies may offer glimpses of the desired gut microbiota pattern that reinforces growth. Studies consistently showed that Proteobacteria is the most abundant phylum in shrimps' intestines, followed by Firmicutes, Bacteriodetes, and Actinobacteria [94, 96, 176, 180, 198-201]. α-proteobacteria, γ-proteobacteria, and flavobacteria are the dominant classes identified in shrimps regardless of the treatment type [180].

Interestingly, Duan *et al.* [180] discovered that probiotics exert a dose-dependent influence on gut microbial composition. A higher *Clostridium butyricum* dietary supplementation enriched the Proteobacteria phylum and Firmicutes, whereas a lower probiotic dose increased the dominance of Bacteriodetes and Firmicutes. In contrast to the untreated counterparts, the probiotic-treated group demonstrated a broader diversity of microbes [186]. Xie *et al.* [94] also showed that introducing different graded probiotics contributed to the selection of unique bacterial compositions. Clearly, it is rather difficult to reconcile the complex microbiome analysis currently accumulated in the arsenal. The advancement in metagenomics and bioinformatics will eventually foster the pursuit of a unifying principle from the infinite paradigms of microbiota resulting from different probiotic treatment regimes.

At this juncture, the microbiota of healthy shrimps with high growth rates at different growth phases or stocking densities could serve as good references [200, 201]. Otherwise, insights could also be drawn from other animal models or clinical trials. An increasing number of studies relate the weight changes to the proportion of two prominent phyla in the gut, namely Bacteriodetes and Firmicutes. A higher ratio of Firmicutes to Bacteroidetes is hypothesised to contribute to weight gain through the shift in metabolic potential viz the increment in calories and fats absorption [202-205]. This result has also been consistently demonstrated in mice models [67, 206]. Nevertheless, a better understanding of the gut microbiome and its interaction with the host is warranted so that suitable probiotic supplementation could be designed to shape the desired microbiota to optimise animal health and growth [61, 188]. Although it is unlikely to draw a simplistic conclusion on the 'desired microbiota that promote growth' based on the varying results gathered from the available studies, the approach presented may help pave a preliminary path that could guide future research.

5.3 Establishment of a functioning gut microbiota

The protective mechanism of the gut is strengthened via the introduction of probiotics. Probiotics competitively exclude opportunistic pathogens from adhering to the gut lining and reduce the availability of space, nutrients, and energy that supports the proliferation of pathogenic strains [207, 208]. For example, yeast strains, such as *D. hansenii*, demonstrated higher dominance traits in the gut and competitively excluded other strains [153, 209, 210]. Besides, studies consistently show that introducing *Bacillus* probiotics substantially reduced the *Vibrio* count in the digestive tract of shrimps compared to the probiotic-free group. This corroborated with the growth suppression of potential pathogens such as *Desulfobulbus* sp.

and *Desulfovibrio* sp. when beneficial bacteria such as *Lactobacillus* sp., *Lachnospiraceae* sp., and *Lachmoclostridium* sp. were enriched following supplementation of *C. butyricum* [180]. The correlation of this protective effect to growth performance and survival rate post-infection has also been established [211, 212]. Moreover, some probiotic strains are equipped with the potential to antagonise pathogenic microbes through quorum quenching [213, 214]. Probiotics suppress the virulence expression of pathogens through the degradation of signalling molecules such as N-acyl homoserine lactone (AHL) [109, 215-217]. Quantitative polymerase chain reaction (qPCR) results showed that administering *Pseudomonas* sp. probiotics effectively lower the toxin-coding gene *pir*A^{vp} copies in shrimps [218]. In addition, some bacteria also secrete inhibitory compounds such as siderophores, proteases, lysozymes, hydrogen peroxide, organic acids, antibiotics, and bacteriocins that antagonise the growth of pathogens [31, 37, 113, 212, 219, 220].

Also, probiotics promote the re-establishment of normal flora in shrimps, particularly when dysbiosis is prevalent at the subclinical stages [188, 221]. In this sense, probiotics strengthen the barrier effects of gut microbiota against pathogenic microorganisms (see Section 8.2) and act as an additional line of defence to preserve the epithelial integrity of the gut [222, 223]. This protective effect potentially mitigates the risk of infection, reducing energy's unnecessary dissipation in eliciting an immune response to combat diseases [61]. In this sense, the energy obtained is reserved for growth and other basal life processes.

Although a direct comparison between probiotics and antibiotics is lacking, Won *et al.* [33] reported that shrimps fed probiotics demonstrated comparable survival rates to that fed oxytetracycline, which is significantly higher than the cumulative survival rates of the untreated control. Similarly, *L. vannamei* larvae exposed to *Bacillus* probiotic strains and commercial probiotics showed better development rates than the control group. On top of that, mixing both *Bacillus* strains YC3-b and C2-2 at a 1:1 ratio resulted in a significantly better developmental rate when compared to the larvae exposed to antibiotics oxytetracycline [34].

6. Secretion of bioactive compounds

Probiotic application stimulates the secretion of a wide range of bioactive compounds such as short-chain fatty acids (SCFAs), vitamins, polyamines, and exopolysaccharides [224, 225]. These bioactive molecules promote the functional maturation of the intestine, enhance protein and nucleic acids biosynthesis, improve nutrient absorption and facilitate cell differentiation [153, 226]. *Bacillus* sp. [227-231], *Streptomyces* sp. [232-234], lactic acid bacteria [207, 235-237], as well as yeast [238], are some common probiotic examples known for their proliferate secretion of bioactive compounds. These compounds serve as growth factors to stimulate animal growth [8, 239-244]. They may act as critical supplementary sources of beneficial dietary compounds and constitute part of the sustenance for the animal. Probiotics can be introduced as aquafeed additives to improve feed value [207, 245]. Several studies demonstrated the efficiency of probiotic supplementation in lowering the FCR, which correlated with significant weight improvement of shrimps [95, 114, 240, 246, 247].

6.1. Short-chain fatty acids

Like most organisms, shrimps lack the necessary enzymes to digest resistant starches and complex polysaccharides. They, therefore, depend on the gut microbiome to decompose fibrous nutrient or complex carbohydrate molecules into pyruvate and acetyl-CoA via the glycolytic pathway or the phosphoketolase route [199, 248] (Figure 2). These 'intermediate substrates' are later converted into SCFAs through other gut processes mediated by different microbes [195, 199, 248-252]. SCFAs are carboxylic acids with less than six carbons at the aliphatic tails. They are the primary end products of bacterial fermentation of the non-digestible dietary carbohydrates ingested by the host [195, 253, 254]. However, the exact species facilitating each SCFA production pathway in shrimp is yet to be identified to allow targeted control of the metabolic profile of shrimp through the introduction of specific probiotic strains.

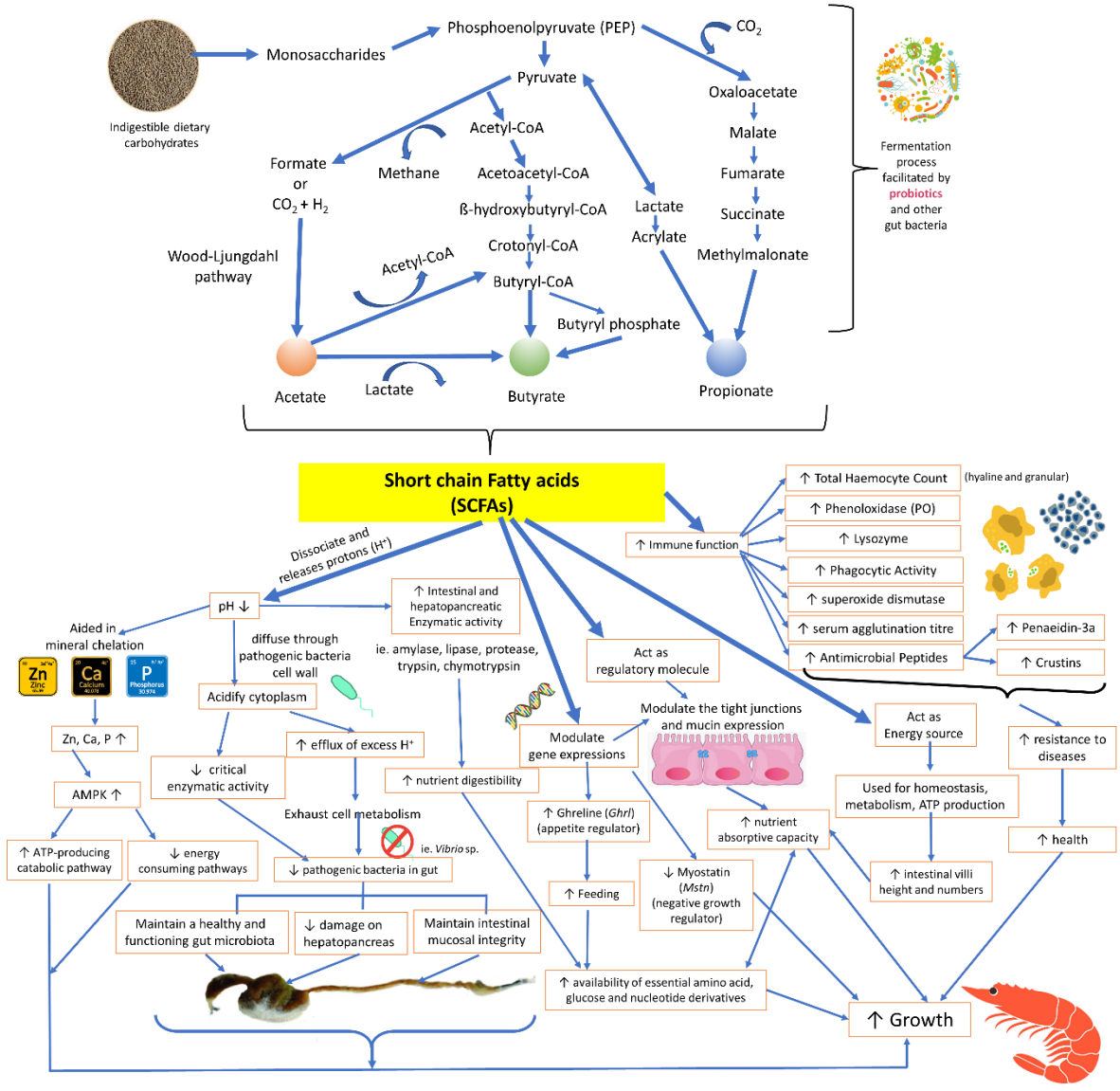

Figure 2. Formation of SCFAs and their effects on shrimps.

SCFAs are important bioactive molecules produced from bacteria fermentation. It is well known that SCFAs play important roles in several physiological processes, including metabolism and immune defences [255]. SCFAs can mediate physiological activities through the modulatory effect on the digestive tract or directly affect the metabolism rate [256, 257]. SCFAs are akin to the link between the gut microflora, diet, and host metabolism [258]. They provide energy sources, help maintain gastrointestinal homeostasis, and act as immune modulators and anti-inflammatory agents [195, 259]. In this sense, SCFAs constitute a pivotal point in explaining the growth promotion effects of probiotics (see Figure 2). As described in Section 5.1, probiotic introduction alters the gut microbiota composition, subsequently altering the host's SCFA content and metabolic profile. SCFAs such as acetate, butyrate, propionate, and their salts have common existence in the shrimps' intestines [199, 260]. Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway integrity and genes enrichment analysis mapped on pyruvate metabolism revealed that acetate was the primary type of SCFA found in the gastrointestinal tract of *L. vannamei* [199]. This corroborated the findings of Duan *et al.* [129].

SCFAs can be perceived as a form of energy recovered by the gut microbiota for host absorption. SCFAs are easily absorbed and constitute an essential energy source to drive cellular processes such as chemotaxis, cell proliferation, and differentiation [225, 254, 255, 261-263]. The proliferation of the epithelial cells lining the intestinal mucosa and the increment in cell size, villus height, and villus number thus, contribute to a larger surface area for better nutrient absorption [86, 133, 239, 264, 265]. Furthermore, SCFAs can act as signal transduction molecules that modulate mucin expression and the tight junctions of the epithelial cells, thereby improving gut permeability and enhancing nutrient absorption [195, 225, 253, 266]. Moreover, the reduction of intestinal pH induced by SCFAs also significantly improves the enzymatic activities of amylase, pepsin, trypsin, and lipase compared to the untreated control, thus implying better nutrient digestive ability [267]. Significant growth augmentation was discernible with increasing SCFA concentration [268, 269]. SCFAs effectively improve the feed efficiency (FE), protein efficiency rate (PER), digestibility, nitrogen retention, weight gain, development, and survival rate of shrimps. The positive results seem to be consistently proven across different shrimp species tested, including *L. vannamei* [268-271], *P. monodon* [272, 273], and *M. rosenbergii* [274]. For example, butyrate increased the bioavailability of several nucleotide derivatives and essential amino acids [239].

The provision of SCFAs as fuel may lower amino acid and glucose oxidation, thereby conserving energy for growth and other physiological processes [239]. Besides that, SCFA is intimately involved in regulating lipid metabolism and maintaining intestinal health [275, 276]. Evidence suggests that SCFA can activate the AMP-activated protein kinase (AMPK) directly or indirectly [277]. AMPK serves as an energy gauge and a chief regulator for cellular metabolic homeostasis [278, 279]. Upon activation, AMPK inactivates the enzymes such as acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which catalyse the fatty acid and cholesterol biosynthesis, thus limiting the energy-consuming biosynthesis pathways and promoting the ATP-producing catabolic processes [277, 280, 281].

Dissociation of SCFAs lowers the pH, alters the transport mechanism, and affects the chelating potential of minerals. Thus, SCFAs elevate dietary minerals like calcium, phosphates, and other trace elements available to the shrimp. Precipitation is reduced when these acids chelate with mineral ions, thereby increasing the absorption of minerals in the intestine [239, 254, 269]. The calcium and zinc levels increase favours the calcium/calmodulin-dependent protein kinase/AMPK (Ca2+/CaMKKß/AMPK) pathway in shrimps and promotes growth [282].

In addition, the proliferation of opportunistic pathogens may also be suppressed by the acidic environment created by SCFAs [239, 283]. SCFAs can diffuse through the bacterial cell wall and dissociate to release protons, thereby triggering the efflux mechanisms to expel the excess intracellular protons in the pathogenic bacteria. This culminates in cell exhaustion, thus resulting in lower growth and even the death of pathogenic bacteria [129, 284, 285]. In other words, a low pH microenvironment in the gut antagonises the proliferation of pathogens such as *Vibrio* sp. and stabilizes the gut microbiota to promote animal health and growth performance [184, 195, 239, 268, 269]. Besides, the oxidative actions triggered by the binding of SCFA to its respective receptor for metabolic activities resulted in a low oxygen environment that restrained the growth of pathogens [243, 286]. The introduction of acetate [269], poly-ß-hydroxybutyrate [274], and sodium propionate [268, 269] significantly reduce the *Vibrio* count in the gastrointestinal tract of shrimps. An intriguing relationship exists between SCFAs and guts microbial composition, where SCFAs could modify the intestinal microbiota composition and vice versa [268, 269].

Last but not least, SCFAs also improve the immunity of shrimps by regulating the immune genes and augmenting the immune components [195, 239] (see Section 9). For example, 60 days of propionic acid supplementation up-regulated the expression of prophenoloxidase (PO), crustin, penaeidin-3a (pen-3a) and lysozyme in the hepatopancreas of *L. vannamei* [287]. Likewise, the dietary inclusion of a 2% organic acid blend significantly increased the shrimp's survival rate post-challenged with *Vibrio harveyi*. Treated shrimps demonstrated a lower degree of hepatopancreatic damage when infected with *V. harveyi*, which corresponds to a higher PO activity [270, 273]. Although the mode of action of SCFAs in modulating the shrimps' immunity is yet to be verified by further mechanistic studies, the results available support SCFAs as effective immune stimulators for aquatic animals [239, 254, 288, 289]. The significantly elevated serum agglutination titre in *L. vannamei* fed propionate and butyrate further attested to the immunomodulatory effect of SCFAs [268].

To sum up, SCFAs are important bioactive molecules for shrimps in mediating energy production, controlling digestive function, modulating gut microbial composition, dictating disease resistance, and regulating the immune response. Interestingly, the introduction of sodium propionate significantly suppressed the expression of the myostatin (*mstn*) gene and elevated the expression of the appetite-related gene, ghrelin (*ghrl*) (see Section 10) and the growth-regulating genes such as growth hormone (GH) and insulin-like growth factor (IGF-1) [254] which favour shrimps' growth. Irrefutably, SCFA is one of the critical substrates affecting shrimps' survival rate and growth performance. The growth promotion effect of

probiotics can be explained through these bioactive molecules as probiotic inclusion has been proven to positively increase the SCFA concentration in the intestine [155, 188, 290, 291]. Therefore, SCFA-producing bacteria could be harnessed to enhance shrimps' growth and survival rate.

6.2. Vitamins

Another essential type of compound produced by probiotics is vitamins. For example, probiotic bacteria *C. butyricum* can directly produce vitamin B in the intestinal tract [129, 292]. Vitamins are groups of heterogenous compounds crucial for the growth and well-being of an organism, including shrimps. Unlike the major nutrient sources such as proteins, lipids, or carbohydrates, vitamins are only required in trace amounts. The vitamin requirement of shrimps is affected by multiple factors, including animal species, culture system, growth rate, physiological condition, nutrient composition, and feeding behaviour [293-295]. Although the vitamin requirements of shrimp seemed to vary between studies, likely due to the various factors described above, the significance of vitamins to penaeid shrimps has long been established [295, 296].

Vitamin availability is closely associated with aquatic animals' growth performance [31, 297]. For example, vitamin B is key player in metabolism and antioxidative mechanisms [293, 298-300]. The B complexes, such as vitamin B_1 (thiamine), vitamin B_5 (pantothenic acid), vitamin B_6 (pyridoxine) and vitamin B_{12} (cobalamin), are also intimately involved in protein, lipid and carbohydrate metabolism [244, 295, 301, 302]. Vitamin B_1 acts as a co-factor that catalyze the cleavage of α-keto acids such as pyruvic acid in producing energy-storing molecules, adenosine triphosphate (ATP) [244, 303]. Vitamin B_6 participates in several metabolic reactions by acting as a prosthetic group of enzymes in the form of pyridoxal phosphate [301]. Elevation of the glutamic pyruvic transferase (GPT) and the glutamic oxaloacetic transferase (GOT) activities following vitamin B_6 supplementation also attested to its role in regulating protein metabolism [302, 304]. Several reports corroborated the dose-dependent effects of vitamin B_6 on the growth performance of shrimps [301, 302]. A similar trend was reported for vitamin B_9 (folic acid), vitamin B_{12} (cobalamin), vitamin C and vitamin E [305-308]. A significantly higher growth rate of *P. monodon* was attained in groups supplemented with vitamin B_9 compared to the non-supplemented group [306]. Vitamin B_9 is a precursor for the active tetrahydrofolate coenzymes, which are essential for nucleotide and amino acid metabolism reactions [306, 309]. Vitamin C is a powerful antioxidant, potent immunomodulator, and haematological booster for shrimps [305, 310-314]. Vitamin E is an effective antioxidant, offering protection against the ascorbic acid-driven lipid peroxidation in cellular membranes, muscles and hepatopancreas [308]. Clearly, vitamins are micronutrients essential for the shrimp's proper growth and survival.

In addition to that, dietary vitamin supplementations can effectively suppress infectious diseases in the treated cohort. Although the information on shrimps is meagre, the results cross-referenced from other species demonstrated the phenomena. For instance, dietary inclusion of vitamin C at 1,000 mg/kg of feed to three-day-old hatchings of the mrigal

carp (*Cirrhinus mrigala*) significantly flattened the mortality curve when challenged with 10^5 *Aeromonas hydrophila* cells per fish at the end of the four-month trial. Moreover, vitamin C supplementation was found to quicken the phagocytic infiltration rate, thus resulting in minimal lesion at the injection site and culminating in complete resolution on day nine following the challenge test [315]. Similarly, supplementing vitamin C was found to effectively reduce the mortality rate of Wuchang bream (*Megalobrama Amblycephala*) [316] and striped catfish (*Pangasianodon hypophthalmus*) [317] when confronted with *A. hydrophila*. Besides, cholecalciferol, the inactive form of vitamin D_3, has been proven as an ideal feed additive for Atlantic Salmon (*Salmo salar*), particularly to harness its effect in resisting *Aeromonas salmonicida* infections [318]. Vitamin E dietary inclusion in the form of α-tocopheryl acetate increases the immune response and resistance of the Parrotfish (*Oplegnathus fasciatus*) against *Vibrio anguillarum* infection [319]. This result corroborates with the findings of Chen *et al.* [320], where adding 300 mg of α-tocopheryl acetate and 6% fish oil enhances the resistance of Chinese mitten crab (*Eriocheir sinensis*) to *A. hydrophila.* Most importantly, vitamin E supplementation was found to improve the specific growth rate of the crab substantially.

Although only required in trace quantity, inadequate vitamin supply can negatively affect animal development and may indirectly impact the production cost [237, 321]. Vitamins, including water-soluble and fat-soluble vitamins, are considered essential for the health maintenance of shrimps. Previous works studied the vitamins required and the suggested dietary intake for different shrimp species [295, 296, 322-324]. The recommended dosage and deficiency signs for each vitamin required by penaeid shrimps are deciphered in Figure 3. Vitamin deficiency may lead to reduced appetite, poor feed conversion efficiency, growth reduction, swollen hepatopancreas, decreased activity, body discolouration, improper molting, poor healing, increased susceptibility to stress and infectious diseases, as well as high mortality rates among the shrimps [261, 293, 298, 308, 323]. It is important to note that crustaceans have limited physiological ability to synthesise vitamins [31, 325]. Besides being supplemented through dietary intake, vitamins are supplied by the mutualistic biota residing in the gut and the rearing water [224, 306, 326]. However, information on the gut microbiota production of vitamins in shrimps is scanty [244, 306].

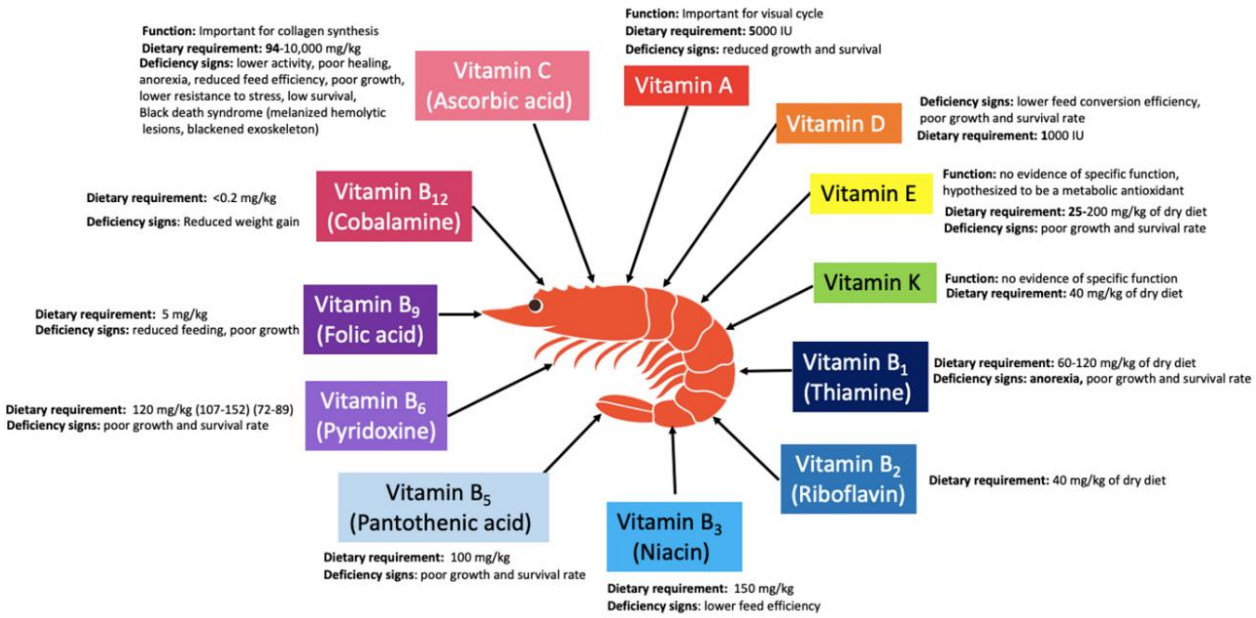

Figure 3. The function, recommended dosage and deficiency signs of vitamins required by penaeid shrimps.

Acknowledging the vitamin synthesizing capacity of the gastrointestinal bacteria as a determining factor for the bioavailability of vitamins [295], probiotics can, thus, be perceived as a supplementary source of vitamins for the optimal growth of the animals. It is proven that introducing probiotic strains such as *Lactobacillus* sp., *Bifidobacterium* sp., and *Propionibacterium* sp. can significantly elevate the production of vitamins [236, 327-329]. These bioactive molecules serve as growth factors for the gut microbial community and render a mutualistic effect to the host when the shrimps also take up the exogenous vitamins released by the microbes. In this sense, it may be reasonable to relate the growth promotion effect of probiotics to the cultivation of a conducive gastrointestinal environment that favours the smooth functioning of all metabolic activities via the production of vitamins and other important bioactive molecules [224].

Since vitamins are among the valuable outputs of probiotics [330], the deliberate inclusion of probiotic strains capable of synthesizing the essential vitamins will foster farmed animals' healthy development [295, 331]. Furthermore, exploiting probiotic use can help ferment the animal feed *in-situ* and fortify the feed with essential vitamins. Tapping on the vitamin-sparing effects of probiotics in culture systems may, in turn, substantially lower the feed expenditure without compromising the survival and growth rate of shrimps [294]. LeBlanc *et al.* [244] detailed a concise list of microbial strains comprising the food-grade probiotics and the commensal strains and their range of vitamin production. An abundance of *in-vitro* studies demonstrated the vitamin biosynthesizing potential of various microbial strains isolated from multiple sources (see Table 3). However, most studies evaluated the vitamin content in the fermented microbial media under well-controlled laboratory conditions.

In contrast, the *in-vivo* production of the specific vitamin by probiotics or gut microbes in shrimps is largely understudied. The high vitamin production *in-vitro* does not necessarily guarantee similar efficacy for vitamin synthesis under treacherous condition in the animal's gastrointestinal tract. This is an evident research gap awaiting urgent attention. Moreover, as intriguing as the idea might suggest, the practicality of identifying an ideal probiotic strain carrying all the desired genes for vitamin biosynthesis is equally challenging. Providentially, the biosynthetic pathways of vitamins have been actively studied. The genes, enzymes, and precursors involved in the production of vitamins have also been progressively unveiled through recent studies [332-334]. This knowledge could be integrated into bioengineering the ideal strain carrying all necessary genes and demonstrating stellar probiotic characteristics to support animal growth. Suitable probiotic strains with prominent vitamin synthesising ability can be screened and introduced to farms to improve the growth and well-being of shrimps.

Table 3: Microbial strains identified with the capacity to biosynthesise vitamins.

Vitamin	Strains identified with the capacity to biosynthesise vitamin	Details/ Insights	References
B_1 (thiamine)	*Lactobacillus acidophilus* CSCC2400	*In-vitro*: - Vitamin B_1 concentration progressively increases by 1.7-fold in the fermented soymilk. - Strain demonstrated high potential to deglycosylate isoflavone glucoside in the media.	[335]
	Bifidobacterium infantis	*In-vitro*: - 48h fermentation in soymilk increases the concentration of vitamin B_1 by 15%.	[336]
	Bifidobacterium longum	*In-vitro*: - 48h fermentation in soymilk increases the concentration of vitamin B_1 by 12%.	[336]
B_2 (riboflavin)	*Enterococcus faecium* C43 *Lactococcus lactis* subsp. *lactis* C173 *Lactococcus lactis* subsp. *lactis* C195	*In-vitro*: - The strains produce 230 ng/mL, 223 ng/mL and 175 ng/mL of vitamin B_2, respectively - Strains simultaneously produce vitamin B_9 - Strains demonstrated good probiotic characteristics.	[237]
	Lactococcus lactis	Info: - Under normal conditions, *L. lactis* does not accumulate vitamin B_2 extracellularly.	[337]

		- The JC017 mutant strain screened using the Microfluidic Droplet technology can produce vitamin B_2 extracellularly. *In-vitro*: - strain produces 0.82 mg/L of vitamin B_2 when cultured in a medium containing 0.5% of glucose.	
	Lactobacillus brevis ATCC367 *Lactobacillus crispatus* ST1 *Lactobacillus delbrueckii* subsp. *Bulgaricus* 2038 *Lactobacillus fermentum* IFP 3956 *Lactobacillus plantarum* JDMI *Lactobacillus plantarum* subsp. *Plantarum* ST-III *Lactobacillus reuteri* DSM 20016 *Lactobacillus reuteri* JCM 1112 *Lactococcus lactis* subsp. *lactis* CV 56 *Lactococcus lactis* subsp. *lactis* I11403 *Lactococcus lactis* subsp. *lactis* KF 147 *Lactococcus lactis* subsp. *cremoris* NZ9000 *Lactococcus lactis* subsp. *cremoris* NZ9000 *Lactococcus lactis* subsp. *cremoris* A176 *Lactococcus lactis* subsp. *cremoris* MG 1363 *Leuconostoc citereum* KM20 *Leuconostoc mesenteroides mesenteroides* ATCC 8239 *Leuconostoc mesenteroides mesenteroides* J18 *Pediococcus pentosaceus* ATCC 25745	Info: -The strains listed were predicted using the Prokaryotic Operon DataBase to carry all four genes required for the biosynthesis of vitamin B_2 (*rib*A, *rib*B, *rib*G and *rib*H).	[338]

	Lactococcus lactis	Info: - (Biosynthetic) The overexpression of all four biosynthetic genes: *rib*A, *rib*B, *rib*G and *rib*H, are required to achieve a substantial production of vitamin B_2.	[339]
	Bifidobacterium infantis	*In-vitro*: - 48h fermentation in soymilk increases the concentration of vitamin B_2 by 13%.	[336]
	Bifidobacterium longum	*In-vitro*: - 48h fermentation in soymilk increases the concentration of vitamin B_2 by 21%.	[336]
	Bacillus subtilis *Candida famata* *Ashbya gossypii*	Info: - supplying glycine enhances the production of vitamin B_2 by *C. famata* and *A. gossypii* - supplying hypoxanthine enhances the production of vitamin B_2 by *A. gossypii*.	[340]
B_9 (folate)	*Lactococcus lactis* subsp. *lactis* C173 *Lactococcus lactis* subsp. *lactis* C195	*In-vitro*: -The strains produce 595 ng/mL and 58 ng/mL of vitamin B_9, respectively. - strains simultaneously produce vitamin B_2 - both strains demonstrated good probiotic characteristics.	[237]
	Lactobacillus plantarum *Lactobacillus sakei*	*In-vitro*: - out of the 180 *Lactobacillus* strains isolated from Japanese prickles, only one *L. plantarum* and two *L. sakei* strains produce a high level of vitamin B_9 extracellularly (>100 µg/L) after 24h of fermentation.	[235]
	Streptococcus thermophilus *Bifidobacterium animalis* *Enterococcus faecium*	*In-vitro*: - *S. thermophilus* was the most dominant producer of vitamin B_9; it increases the folate level by 3.5-4.3-fold. - The combination of *S. thermophilus* and *Bifidobacterium animalis* increases the vitamin B_9 level by 6-fold.	[341]

	Streptococcus thermophilus *Lactococcus lactis* *Leuconostoc lactis* *Leuconostoc paramesenteroide*	*In-vitro*: - *S. thermophilus* fermentation is sensitive to the pH level of the fermentation medium. - *S. thermophilus* produced the highest folate/biomass (214 µg/L/OD_{600}). - *L. lactis* produces the highest level of vitamin B_9 in anaerobic conditions (291 µg/L).	[342]
	Streptococcus thermophilus *Bifidobacterium longum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* ssp. *bulgaricus*	*In-vitro*: - Lactic acid bacteria produce higher vitamin B_9 in reconstituted milk compared to complex media. - All strains produce the maximum vitamin B_9 levels after 6h of fermentation. - Vitamin B_9 productions by *S. thermophilus* and *L. acidophilus* are most stable; they decline by approximately 8% in week 2 and about 12% in week 3.	[343]
B_{12} (cobalamin)	*Lactobacillus reuteri*	Species with proven probiotic properties *In-vitro*: - Supply the required precursor compounds [δ-aminolevulinic acid (ALA) and 5,6-dimethylbenzimidazole (DMB)] production to enhance the production of vitamin B_{12}. - Produces the active forms of vitamin B_{12}: (i) α-(5,6-dimethylbenzimidazolyl)-cobinamide cyanide (ii) cyanocobalamin	[327]
	Propionibacterium spp. (eg. *P. freudenreichii*)	Info: -Two-step production; - Genus necessitates both the anaerobic (step 1) and aerobic (step 2) conditions to produce Vitamin B_{12} enzymes necessary. - Genes associated (coding the): *cbi* (step 1), *cob* (step2).	[328]
	Propionibacterium freudenreichii *Rhodopseudomonas protamicus* *Propionibacterium shermanii*	Info: - When glucose is the main component of the	[344]

		culture medium, the strains produced 206, 135 and 60 mg/L of vitamin $B_{12,}$ respectively.	
	Propionibacterium freudenreichii	Info: - A classical dairy microorganism that can be used for fermentation to produce vitamin B_{12} for feed application.	[345]
		Euglena bioassay method to determine vitamin B content in samples (*in-vitro* and *in-vivo*).	[346]
	Klebsiella sp.	*In-vitro*: - *Klebsiella* sp. utilize methanol as a sole carbon source for the production of vitamin B_{I2} - Supplying organic nutrients like peptone, yeast extract, and vitamin enhances the production of vitamin B_{I2}.	[347]
	Selenamonas ruminantium *Peptostreptococcus elsdenii* *Butyrivibrio jibrisolvens*	*In-vitro*: *E.coli* Cup-plate assay: - *A*mong the 21 microbial species isolated from the cow's rumen, *S. ruminantium* is the most prolific producer of vitamin $B_{12,}$ followed by *P. elsdenii*. *O. malhamensis* assay: - Assay reflects the actual activity of vitamins in animal. - Results suggest that the relative proportion of vitamin B_{12} to the analogues under the pure culture conditions was not as high as that in the rumen.	[348]
C (ascorbic acid)	*Gluconobacter*	Info: - Strain developed for the biosynthesis of vitamin C intermediate (2-keto-L-gulonic acid).	[334]
A	*Escherichia coli* mutant (contains genes coding for the four key enzymes involved in the ß-carotene biosynthesis:	*In-vivo* (mice): - Detection of ß-carotene-producing bacteria and ß-carotene in the faeces demonstrate the persistence of the probiotic strains in the intestine.	[349]

	geranylgeranyl pyrophosphate, lycopene cyclase, phytoene desaturase and phytoene synthase from *Erwinia herbicola*)		
E (tocopherol)	*Lactobacillus rhamnosus* WQ2	*In-vitro*: - Strain produced a high level of α-tocopherol (376.6 µg/g). - Strain is able to increase the antioxidant capacity of the media within a short incubation time. - The antioxidant capacity highly correlates to the bacterial proteolytic activity.	[335]
K (menaquinones)	*Bacillus subtilis*	*In-vitro*: - The production of Vitamin K parallel increases in proportion with the number of cells in the first 8h. - The Vitamin K extracellular secretion increases rapidly after 10h (1.7%) and reaches a plateau after 32h (31%).	[350]
	Bacteroides ovatus *Enterobacter agglomerans* *Enterococcus faecalis* *Escherichia coli* *Prevotella buccae* *Staphylococcus capitis* *Staphylococcus epidermidis* *Staphylococcus haemolyticus* *Staphylococcus warneri*	*In-vitro*: - Strains produce Vitamin K.	[351]
	*Bacteroide*s sp. *Citrobacter freundii* *Enterococcus faecium* *Serratia marcescens* *Staphylococcus capitis* *Staphylococcus warneri*	*In-vitro*: - Strains produce Vitamin K.	[351]

6.3. Polyamine

Polyamines are small polycationic molecules composed of multiple amine groups on an aliphatic hydrocarbon backbone [352, 353]. These compounds are essential metabolites ubiquitously found in almost all living organisms. Some standard polyamines include spermine, spermidine, and putrescin [352-354]. These polyamines have distinct valences and different molecular structures and assume different functional roles. Moreover, the respective concentration of each polyamine varies in other organisms. For instance, spermine is absent in the fungal Saccharomycotina subphylum. In contrast, the concentrations of spermine and spermidine are high in eukaryotes, whereas putrescine is the dominant polyamine identified in *Escherichia coli* bacteria [352]. For the case of shrimp, gas chromatography-mass spectrometry (GC-MS) revealed that polyamines such as spermidine, N, N'-bis(3-aminopropyl)-l,3-propanediamine (BAP) and 3,3'-diaminodipropylamine (DAD) were present in the white shrimp (*Penaeus setiferus*). However, the non-detection of common polyamines such as putrescine and 1,3-diaminopropane can be attributed to the rapid carbon flux through these intermediates, or possibly the BAP and DAD are selectively derived from dietary sources [355]. Unfortunately, information related to polyamine in shrimps is relatively limited, although the presence and significance of polyamines in shrimps have been established.

Polyamines are vital components to ensure normal cellular processes such as stress response, genetic expression, cell division, differentiation, growth, and survival [352, 354, 356, 357]. In this regard, polyamine levels within cells are tightly regulated through a complex mechanism which includes the mediation of catabolism and the *de novo* biosynthetic pathways of polyamines to meet the cellular demand [352, 358]. Sugiyama *et al.* [359] comprehensively analyzed polyamines' biosynthesis and transport mechanism in dominant bacteria identified in the human gastrointestinal tract. Natural polyamines are formed through a series of precisely regulated energy-dependent reactions driven by several key enzymes such as ornithine decarboxylase, S-adenosylmethionine decarboxylase, spermidine synthase and spermine synthase [352, 354, 357, 360, 361]. In some bacteria and plant species, an alternative pathway, namely the arginine decarboxylase pathway that involves another two enzymes, polyamine oxidase, and spermidine-spermine acetyltransferase, directs the conversion of spermine to putrescine [352, 354].

Besides that, regulating the transportation of the extracellular polyamine across the plasma membrane through passive diffusion or distinct polyamine transporters is essential to ensure proper cellular function because polyamines are also supplied through extracellular sources such as a gut microbial pool or via dietary inclusion [358, 362]. Therefore, this implies that probiotic strains could be another novel source to supply polyamine *in-situ* to support growth and cellular function. Yeast is an important dietary source for polyamine supply [360, 363]. Polyamine production varies between different yeast species. *D. hansenii* is one of the strains known for its distinct potential in secreting polyamines. The concentration of spermidine, spermine and putrescine measured in *D. hansenii* are significantly higher than that in *S. cerevisiae* and *Saccharomyces boulardii* [226, 364]. Reyes-Becerril *et al.* [365] studied

the polyamine-producing capacity of 13 different *D. hansenii* strains isolated from diverse sources. High-pressure liquid chromatography (HPLC) analysis revealed two strains, *D. hansenii* CBS004 and *D. hansenii* L2, isolated from marine water and citrus fruit, respectively, as the most prolific producers of polyamines among the 13 strains studied. Furthermore, Tovar *et al.* [226] noted the strong adhesion potential of *D. hansenii* to the intestinal mucus, thus demonstrating the probiotic efficiency of the strain. The inclusion of 1.1% of *D. hansenii* in the diet, which corresponds to an approximately 10^6 CFU/g of diet, was shown to improve the survival rate of sea bass *(Dicentrarchus labrax)* larvae by 10% as well as lower the malformation rate by 14%. Most importantly, the final average weight of the treated cohort is two times higher than the untreated group [364]. This finding corroborates the effect of D. hansenii on gilthead seabream (Sparus aurata) [366] and *longfin yellowtail (Seriola* rivoliana*)* [367]. These effects of *D. hansenii* are likely attributed to the polyamine metabolites produced by the live yeast in the intestinal tract [364]. This postulation could likely be proven by comparing the growth parameters in animals fed with probiotic supplements (live yeast strains with polyamines production capacity) and those provided with inactive yeast supplements [368].

Although the growth-related effects of polyamine are yet to be fully deciphered, its primal role in regulating the broad range of cellular processes, ranging from cell growth to differentiation, mRNA transcription to protein translation, has been established [352, 354, 356]. Increasing evidence points to the involvement of polyamines in Ca^{2+} signalling, which is vital for regulating the stimuli of growth factors and hormones on the cell surface receptor. Besides, polyamine was also known to play a role in the formation of the cytoskeleton by facilitating the conversion of tubulin to microtubules and actin polymerization. Spermine and spermidine are known to induce cytokinesis [361]. Some studies also identified the involvement of polyamine in the nervous system, particularly in the mediation of synaptic function [354]. The rat model demonstrated that polyamine putrescine is rapidly absorbed and converted into succinate, which serves as a form of instant energy supplied to the intestinal cells [369].

At the molecular level, polyamines help to stabilise the cell membrane, proteins, and nucleic acid structures, including DNA and RNA [352-354, 370, 371]. Under physiological pH, polyamines are positively charged. As polycations, polyamines bind electrostatically with the negatively charged macromolecules, thus stabilizing the structural conformation and protecting them from enzymatic degradation or thermal denaturation [358, 361]. Besides, polyamines also participate as substrates and stimulate DNA, RNA, and protein synthesis, to facilitate cell division [226, 358]. The polyamine levels strongly correlate with the proliferative activity of cells, where the uptake and utilization of exogenous polyamine are significantly higher in rapidly proliferating cells compared to the quiescent cells. It was also noted that maintaining the polyamine concentration is indispensable for cells to proliferate [354].

On the contrary, genetic studies revealed that the deletion of genes involved in the polyamine metabolic negatively affects cell proliferation and survival rate [352]. Sustained depletion of polyamines limits the formation of hypusine (an amino acid component of the

initiation factor eIF-5A, whose precursor is spermidine), thus blocking the subsequent mRNA translation pathways such as initiation and elongation of the new peptide chain on the ribosome [361]. Depleting polyamine through mutating its biosynthetic pathways resulted in retarded growth of the organisms [372]. Besides, polyamine deficiency was reported to culminate in severe hypoplasia in the intestinal mucosa [362]. Under extreme cases, dysregulation of polyamine levels can negatively impact energy homeostasis and disrupt the regulation of lipids and glucose [358].

The implication of polyamines is not solely limited to the growth and survival of cells but is also expressed in catalysing the maturation of the gastrointestinal tract. To illustrate the mRNA expression of enzymes like alkaline phosphatase, aminopeptidase, lipase, maltase, and trypsin showed that the pancreas and intestine of sea bass fed with yeast probiotics developed at a significantly higher rate as compared to the group devoid of this supplement [364]. Similarly, the dietary inclusion of purified spermine significantly enhances the intestinal maturation of sea bass [373]. This phenomenon is further evidenced by direct polyamine supplementation to neonatal mice that appreciably improved intestinal health and increased the proportion of beneficial microbes in the gut [374]. Additionally, polyamines have been regarded as essential players in regulating paracellular permeability. Polyamines enhance the epithelial integrity through their stimulative effectiveness in producing intercellular junction proteins like E-cadherin, occludens-1, occluding, and zonula [358, 375]. Therefore, it can be inferred that polyamines play vital roles in promoting the development of the intestinal mucosa and stimulating the maturation of the larvae's digestive organs, which enhances the animal's growth and survival [360].

Last but not least, polyamines appear to exert an influence on the immune system [360, 368]. For example, the polyamine secreted by the *D. hansenii* L2 strain is postulated to be the cause of elevating the immune function of gilthead seabream (*S. aurata*) [366]. Evidence demonstrates that extracellular polyamine concentrations are significantly elevated during inflammation due to the secretion from the damaged cells or excretion during tissue regeneration [354]. These extracellular polyamines suppressed the production of inflammatory cytokines and elevated the release of cytokines that promotes healing [376, 377]. Moreover, polyamines exert an antioxidant effect by acting as scavengers for reactive oxygen species [378, 379]. In this regard, polyamine levels can be used as surrogate markers to determine the growth condition of the organism. In one of the few works studying polyamines in crustaceans, Stuck *et al.* [380] concluded that expressing the polyamine level as a ratio to DNA constitutes an effective method to more accurately reflect the nutritional status of *L. vannamei* postlarval. This is because DNA is never catabolised even under prolonged starvation and can therefore compensate for the effect of differential catabolism during starvation. In another experiment, Watts *et al.* [381] noted that the polyamine level at the head of *L. vannamei* is significantly higher than the tail and more appropriately reflects the development and growth status of the animal. Results showed that the polyamine to DNA ratio is highly dependent on feeding. The parameter is significantly lowered in the starved group compared to the fed group and is immediately upregulated upon resuming feeding [380]. The extent of

probiotics' contribution to polyamine levels in shrimp is yet to be further assessed. These studies can be applied to optimized future studies to verify the effect of polyamines conferred by probiotics in shrimps.

Besides *D. hansenii*, the introduction of probiotics *Bifidobacterium* spp. also elevated the polyamine content in the intestinal lumen [382]. Intriguingly, *Bifidobacterium* spp. lack the homologs of enzymes for polyamine biosynthesis. It is postulated that *Bifidobacterium* spp. acidifies the intestinal microenvironment by producing lactate or acetate and thus stimulates the autochthonous microbiota to synthesise polyamines. [383]. The involvement of the intestinal microbial in polyamine production is further strengthened when the gastrointestinal organ maturation effect is only evident and when polyamines are administered orally and not via other routes [384]. Furthermore, this notion is further vindicated that this putrescine-enhancing effect is completely eliminated when the animal is co-treated with arginine and antibiotics [385]. Recent findings further deciphered the mechanism of this novel pathway of polyamine production. Polyamine putrescine is produced from arginine by transforming the reactive intermediate, agmatine, in an acidic environment. Kitada *et al.* [383] tested 91 different combinations of strains and concluded that *E. coli*, *Enterococcus faecalis*, and *Bifidobacterium* spp. formed an excellent combination to induce putrescine production. The three strains act as the acid tolerant-arginine supplier, energy cum agmatine deiminase system provider and acidic environment creator, respectively. This may imply that the direct polyamine biosynthesis ability of strains is not a mandatory prerequisite for probiotic selection. Right combinations of strains that facilitate the polyamine production *in-vivo* can too generate polyamines. To illustrate, *Clostridium* sp., *Enterococcus* sp., *Lactobacillus* sp., *Lactococcus* sp. and *Streptococcus* sp. are a few prevalent examples of commensal genera identified for their arginine deiminase pathway to degrade arginine anaerobically but lack the essential polyamines biosynthetic enzymes [358, 386]. Combining these strains with those that supply the required enzymes complement the activities between strains and can orchestrate the production of polyamines *in-vivo*. In other words, probiotics could be an effective means to optimize the polyamine composition in the gastrointestinal tract by modulating the biochemical reactions between the gut microbial community.

7. Increasing the digestive enzyme activity

Enhancing the digestive enzyme activities represents another convincing pro-growth rationale for probiotics. A recent quantitative analysis by Fernandes *et al.* [104] demonstrated the significance of probiotics in elevating the total enzymatic activity in the gastrointestinal tract of *L. vannamei*. At the end of the 120-day culture, lipase activity significantly increased by 58%, protease activity increased by 49%, and amylase activity increased by 34% in the shrimps treated with the salt pan bacteria compared to the untreated shrimps. Pearson's correlation analysis further revealed a strong positive correlation between the enzymatic activities and the final yield of shrimps. This result is congruent with the findings of Ziaei-Nejad *et al.* [387], in which the administration of *Bacillus* spp. Probiotics significantly increased the total protease, lipase, and amylase activity and recorded 8 to 22% higher wet

weight compared to the control group. Similarly, Gamboa-delgado *et al.* [388] reported that the weight gain of *L. vannamei* increases with lipase and chymotrypsin activities.

Intriguingly, the range of enzymatic activity greatly varies between probiotics, even among strains from the same genus. For instance, among the three promising Actinomycete strains investigated, the ability to degrade many molecules, such as lipids, proteins, and carbohydrates, varies between strains [389]. *In-vivo* investigation revealed that the salt pan bacteria probiotics increased the cellulase activity in *L. vannamei*, but the 10% increment compared to the control group is not statistically significant. In contrast, commercial probiotics increased cellulase activity significantly by 30% [104]. The outcome may vary depending on the probiotic strain selected. In this regard, *in-vitro* screening for the enzymatic activity of probiotic strains will provide a helpful prediction of the *in-vivo* effect of probiotics in enhancing digestive function [104, 222, 390-392]. Additionally, it is important to note that the dose and duration of probiotic supplementation may also affect the results [393]. Notably, although the significance of each enzymatic elevation differs at different stages of growth, Zhou *et al.* [394] reported that adding *Bacillus coagulans* increases the lipase, protease, and amylase activity in *L. vannamei*. It could be inferred that probiotic strains exhibiting different enzymatic properties can be tailored in the treatment regime to complement the digestive function of the animal at specific life phases.

Bacillus sp. [212, 240, 387, 394-396], *Enterobacter* sp. [134], *Lactobacillus* sp. [134], *Pediococcus* sp. [149] are some examples of probiotics that have been reported to increase the enzymatic activity in shrimps. Some earlier works have covered a concise list of probiotics and their respective enzymatic augmentation effects in aquatic species. Probiotic strains, particularly *Bacillus* sp. and yeast, are renowned for their ability to synthesize a wide array of extracellular enzymes such as amylase, cellulase, chitinase, lipase, phytase, and protease [153, 397-399]. Certain unique strains thrive in extreme niches, such as the hypersaline bacteria and *Streptomyces* spp. isolated from mangrove soils are excellent sources of exogenous enzymes that work efficiently under extreme conditions [104, 400-404]. These extracellular enzymes supplemented by probiotics may function optimally at broader pH and salinity range, thereby extending the period of enzymatic digestion to facilitate more efficient hydrolysis of substrates [405, 406].

To date, a lack of study distinguishes whether the activity arising from the exogenous enzymes is directly contributed by probiotics or indirectly through inducing the endogenous enzymes produced by the host [222, 395]. Usually, enzymatic activity improvement is assayed using the pooled gastrointestinal samples or whole-body extract of shrimps [33, 104, 182, 211, 387, 393, 395, 407]. Ziaei-Nejad *et al.* [387] reported that *Bacillus* sp. probiotic additives significantly elevated the total enzymatic activities in the Indian white shrimps(*Fenneropenaeus indicus*) reared in earthen ponds. However, the colonisation rate of the probiotic bacteria detected in the digestive tract is very low. This may suggest that although these exogenous enzymes secreted by probiotics may only constitute a minor contribution to the overall digestive activity in shrimps, the presence of probiotics may likely enhance the microbial activity in the gut and stimulate the secretion of endogenous enzymes [90, 134, 387, 395, 408]. This speculation

is well supported by the recent work of Zuo *et al.* [134], in which the epithelium cells in the midgut of *L. vannamei* treated with probiotics revealed an actively secreting state under the observation of an electron microscope. This phenomenon is congruous to the increment of digestive enzyme activities in the shrimps throughout probiotic treatment.

The digestive enzymes identified in shrimps include proteases (aminopeptidase, carboxypeptidase, chymotrypsin, metalloprotease, trypsin), lipase, esterase, and carbohydrase (amylase, cellulase and chitinase) [222, 238, 407, 409, 410]. Despite being an omnivorous animal, shrimp has a limited capacity to digest some forms of complex carbohydrates like starch due to the lack of specific enzymes such as the α-1,6-glucosidase. Supplying this enzyme that is not naturally present in the host via the introduction of probiotics may aid in the digestion of the α-1,6-glycosidic bond of amylopectin and thus facilitate the digestion of those inherently indigestible nutrients [406]. Arellano-Carbajal and Olmos-Soto [411] isolated a *Bacillus* sp. strain from the marine environment, endowed with the capacity to synthesise high levels of thermostable α-1,4-glucosidase and α-1,6-glucosidase in a relatively short time. Although *in-vivo* data is lacking, it is a promising candidate for shrimp probiotics. This is because the enzymes function at an optimal temperature and pH similar to the shrimps' enzymes [411, 412]. Similarly, Ochoa-Solano and Olmos-Soto [406] also demonstrated the capacity of several *Bacillus* strains in producing α-1,4-glucosidase, α-1,6-glucosidase and α-galactosidase through the quantitative assay using substrates such as amylose, amylopectin, melibiose, and raffinose. Another promising probiotic strain for shrimp culture is *Lactobacillus casei* which produces the extracellular enzyme inulinase. Inulinase works by hydrolysing the ß-2,1-glycosidic linkages of prebiotic inulin in the gastrointestinal tract to release small fructooligosaccharides or fructose, which can become an energy source for the host [413]. The idea is further supported by the findings of Shiau and Peng [414], in which complex carbohydrates such as starch is proven to be better feed options for *P. monodon.* They resulted in higher feed efficiency and protein efficiency, which resulted in higher weight gain and better survival rates compared to the group fed simple sugars like glucose. In this regard, introducing carefully selected probiotic strains that are prolific producers of carbohydrase will further improve the nutritional value of the animal feed by augmenting the assimilation of carbohydrates in shrimps.

From another perspective, these enzymes derived from probiotics can degrade the feed's antinutritive factors, thereby enhancing shrimp's receptivity to plant-substituted fish meal [208, 406]. This is an important property to be harnessed when corn, soybean, and wheat are becoming increasingly popular aquafeed ingredients due to their lower prices and easier accessibility [415-417]. Supplementing these feed substitutes with probiotic strains that actively secrete enzymes such as cellulase, galactosidase, glucosidase, glycosidase, and pectinases will significantly improve the energy intake from the diet substituted with plant-based ingredients [415, 418-420]. Moreover, the improved digestibility mediated by higher enzymatic activity also maximizes feed utilisation. For instance, *Lactobacillus* and *Enterobacter hominis* supplementation resulted in higher carbon utilization ability in *L. vannamei* [134]. Increased AWCD measurement reflected the relative increment of carbon sources, including

amines, amino acids, carbohydrates, and polymers available to *L. vannamei* juveniles following the probiotic intervention [155]. An oxygen bomb calorimeter can be employed to measure the energy content of shrimps [421]. Several studies consistently demonstrated the substantial improvement of energy utilization parameters (feeding rate, absorption rate, conversion index, excretory and metabolic rate) in shrimps fed the diet incorporated with probiotics [421, 422]. In this regard, probiotics can significantly improve feed efficiency and increase feed expenditure savings in shrimp farming [73, 406, 420].

In addition, the elevated digestive enzyme activities in the intestinal canals of shrimps induced by probiotics led to improved nutrient digestibility. The enzyme catalyses the breakdown of complex food molecules into smaller, more digestible forms that could be readily taken in. Take the example of protein; higher protease activity hydrolyses peptide bonds and liberates free amino acids that can readily be assimilated [152]. Higher levels of alanine, arginine, isoleucine, and proline were detected in *M. rosenbergii* fed with the probiotic-supplemented diet compared to the control group fed with a basal diet. Both essential (arginine, histidine, isoleucine, leucine, lysine, threonine, and tyrosine) and non-essential amino acids (alanine, glutamine, glycine, proline, and serine) are essential for animal development as each amino acid perform specific functions. These amino acids are building blocks for synthesizing new proteins [90]. Notably, a higher crude protein level is detected in *M. japonicus* fed with *C. butyricum* probiotic [155]. This finding agrees with Seenivasan *et al.* [421], who also reported that the protein composition, amino acid, lipid, carbohydrate and ash content are significantly higher in *M. rosenbergii* treated with 2% *Lactobacillus sporogenes* and *S. cerevisiae* probiotics. In an experiment in which chromic acid (Cr_2O_3) was employed as an indicator for digestibility, *B. subtilis* probiotic has been found to significantly increase the apparent digestibility coefficient (ADC) of amino acids in *L. vannamei* [124]. Besides, several studies demonstrated that probiotic application could effectively increase the protein efficiency ratio (PER) and lower the FCR [422, 423]. Indirectly, by increasing the enzymatic activity, probiotics inflect shrimps' metabolic function, which translates to a better growth profile. The exogenous enzyme activities of probiotics could therefore serve as valuable indicators for nutrient digestibility, feed utilization, and growth index of shrimps [424, 425].

Interestingly, antibiotics seemingly do not demonstrate this boosting effect on enzymatic activity. In a recent publication, probiotic-supplemented diets significantly improved lipase activity in *L. vannamei* compared to the control group and the group fed with antibiotic oxytetracycline [33]. However, information on shrimps is somewhat limited. An early study using rainbow trout (*Oncorhynchus mykiss*) shows no apparent increase in lipid digestibility following the administration of oxalic acid, oxytetracycline, and chloramphenicol [426]. On the contrary, the treatment of antibiotics (ampicillin trihydrate, streptomycin sulphate, and antifungal nystatin) significantly diminished the cellulase, chitinase, lipase, and protease activity in northern krill (*Meganyctiphaunes norvegica*). The lower enzymatic activity corresponded with the decline in bacteria counts in the hepatopancreas and stomach of animals reflected in the lower Acridine Orange Direct Count

(AODC). This finding surmises a commensal relationship between gut bacteria and the digestive enzymatic activities in the host organism [179].

8. Modifying the gastrointestinal morphology

When examining the growth promotion effects of probiotics, gut physiology could not be neglected. The digestive tract of decapod crustaceans can be arbitrarily divided into three parts, namely the foregut, midgut, and hindgut [427, 428]. Histological studies revealed that significant morphological changes typically occur in the midgut region of shrimps following probiotic administration [162]. Probiotics improve the architecture of the hepatopancreas (see Section 8.1) and intestine (see Section 8.2), thereby facilitating digestion and assimilation of nutrients in the animal. Strengthening the gut function protects the animal from opportunistic disease, safeguards animal health, and improves growth performance.

8.1. Hepatopancreas

Hepatopancreas, also known as the midgut gland, is a vital organ that sits in the cephalothorax region of the crustacean, connected right behind the stomach in the gastrointestinal tract. It is relatively large and typically constitutes 2 to 6% of the total body weight of a decapod [428]. The hepatopancreas is a versatile organ that plays essential roles in the digestive system through the regulation of numerous processes such as steroid hormone synthesis, digestive enzymes secretion, carbohydrate and lipid metabolism, nutrient absorption, storage, and distribution [427-432]. Besides, the hepatopancreas also acts as the main detoxification organ for shrimps, particularly during the rapid growth phase [432]. These biological processes are closely associated with growth performance. The role of the hepatopancreas in shrimp is akin to the combined functions of both pancreas and liver in mammals [38, 432]. Hence, the health of the hepatopancreas is the main index in the growth profile of the animal.

The hepatopancreas is primarily composed of five different types of epithelial cells, namely Embryonalzellen/ embryonic cells (E cells), Fibrenzellen/ fibrillar cells (F cells), Blasenzellen/ blister/ vesicular/ extrusion cells (B cells), Restzellen/ resorptive/ reabsorption cells (R cells) and midget/ basal cells (M cells) [270, 427, 433-436]. Meanwhile, M cells may not be present in some shrimp species [437] (see Figure 4). Each cell type has unique features and functions (see Table 4). The small cuboidal E cells widely distributed at the distal tubules are undifferentiated cells responsible for epithelial renewal through mitotic divisions [427, 437, 438]. E cells serve as precursors for other cell types in the hepatopancreas. The F cells further differentiate into B cells. The cells become more differentiated, moving from the distal to the proximal tubules [432, 435, 439]. F cells have a distinctive fibrillar appearance, a characteristic large oval nucleus at the centre, and well-developed reticulum and ribosomes [182, 438]. Silva *et al.* [437] further discovered that F cells not only secrete digestive enzymes but are also involved in the production of protective mucus. Besides, the F cells are involved in detoxification, protein synthesis, nutrient absorption, metabolism, and storage [427, 432, 440]. B cells are the largest epithelial cell type distributed primarily in the middle and proximal

regions of hepatopancreatic tubules. B cells are characterised by a distinctively large vacuole accompanied by several pinocytic apical vacuoles and a round basal nucleus in the cytoplasm. They are the primary producers of endogenous digestive enzymes in shrimps. Also, B cells assume the roles of intracellular digestion, nutrient accumulation, and distribution [182, 427, 432, 435, 437]. R cells can be recognised through their prismatic appearance with multiple small vacuoles in the granular cytoplasm. They are ubiquitously distributed throughout the hepatopancreatic tubules but mainly concentrated in the proximal region. R cells are the main storehouses for lipids, glycogen, and trace elements. They are also involved in absorbing and metabolizing nutrients and detoxifying heavy metals [432, 435, 437, 440]. Since R cells serve as the primary energy storehouse in the hepatopancreas, it is often used as an indicator to assess the nutrition status of shrimp. A higher expression of R cells may imply higher energy utilization and nutrition value [441, 442]. M cells are triangular basal cells with a rounded nucleus containing several nucleoli [437]. Detection of M cells at the embryonic zone suggests that M cells have their origin independent of E cells [440]. They are few but sparsely distributed across the hepatopancreatic tubules, usually located close to R and B cells. Unlike the B cells, F cells and R cells, M cells do not have microvilli, and their apex does not extend to the lumen [427, 437]. M cells are believed to function as a storage reserve for organic substances [435].

Following a 5-week supplementation with *Bacillus* AQAHBS001, a healthy hepatopancreas structure demonstrating a complete set of epithelial cells such as F, B, and R cells was evident in *L. vannamei* [123]. Moreover, the probiotic treatment resulted in a comparatively higher number of B cells in the hepatopancreatic tubules than in the control set [443]. A similar observation was reported in juvenile *L. vannamei* following a 10-day feeding of probiotics (mixture of *S. cerevisiae* and *Lactobacillus* acidophilus) at a 1:1 ratio with two different doses of 10^8 and 10^9 CFU per kilogram of diet. Both probiotic mixtures not only resulted in a significant increase in B cell count in the hepatopancreatic tubules but also substantially reduced the hepatopancreas pathology in shrimps infected with acute hepatopancreatic necrosis disease (AHPND) [444].

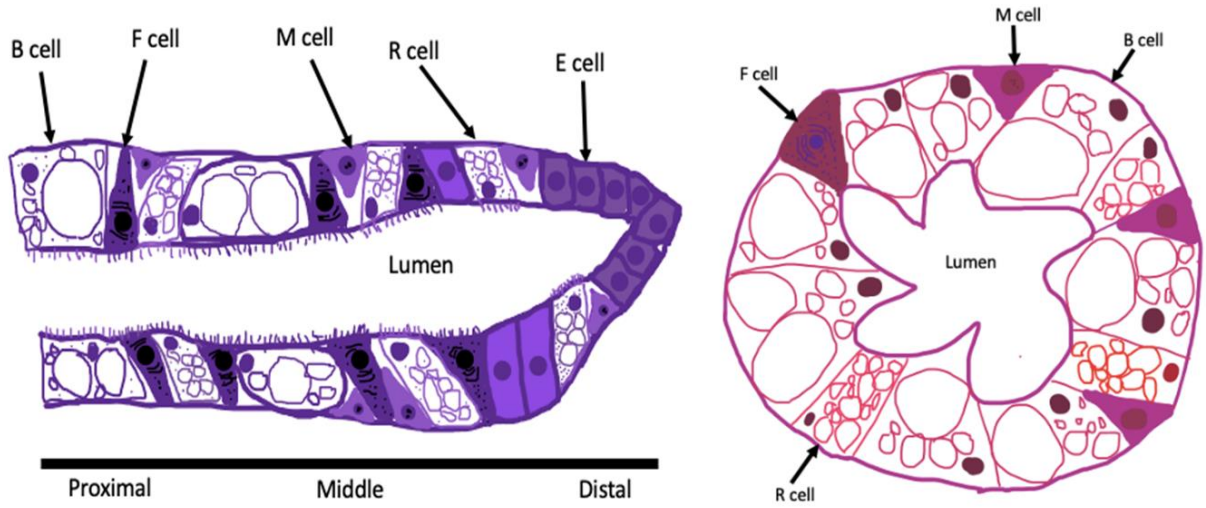

Figure 4. Longitudinal and lateral cross-section illustration of hepatopancreatic tubules.

Table 4: Five different types of epithelial cells in the hepatopancreas.

Hepatopancreatic epithelial cells	Other names	Features	Distribution across tubule	Functions
E cell	-Embryonalzellen - embryonic cell	- cuboidal shape - small - undifferentiated cells - cytoplasm presents intense basophilia	- mainly in the distal region	- mitotic division - renewal of epithelial tissue - precursor cell for other cell types in the hepatopancreas
F cell	- Fibrenzellen - fibrillar cell	- fibrillar appearance -prismatic/triangular/cylindrical shape - contain a large amount of well-developed endoplasmic reticulum and ribosomes - large oval nucleus at the centre - cytoplasm presents intense basophilia - with microvilli - apex extends to the lumen	- mainly in the middle and distal region	- secrete a digestive enzyme - secrete protective mucus - absorb nutrient - synthesise protein - store nutrients - differentiate into B cells - detoxify organic xenobiotics and heavy metals
B cell	- Blasenzellen - blister cell - vesicular cell - extrusion cell	- largest epithelial cell - globular shape - large vacuole - small pinocytic apical vacuoles - round basal nucleus - acidophilic cytoplasm - with microvilli at the apical region of the cytoplasm - apex extends to the lumen	- mainly in the proximal and middle region - also, in the distal region	- secrete digestive enzymes - intracellular digestion - nutrient accumulation - transport digested materials
R cell	- Restzellen - resorptive cell - reabsorption cell	- elongated/ prismatic shape - contain multiple small vacuoles - round nucleus - granular cytoplasm - with microvilli - apex extends to the lumen	- across tubule	- absorb nutrient - metabolize nutrient - synthesise lipoprotein - storage of lipids and glycogen - sequester trace elements (copper, magnesium, phosphorus, sulphur and zinc) - detoxification (i.e. heavy metals)
M cell	- Midget - Basal cell	- triangular/rounded shape - round nucleus containing several nucleoli -cytoplasm presents intense basophilia - without microvilli -remain in contact with the basal lamina -restricted at the basal lamina -apex does not extend to the lumen	- across tubule - located close to R and B cells - few in number	- storage of organic reserve

Besides, the histopathology studies showed that exposing *P. monodon* to probiotic *Bacillus thuringiensis* did not negatively impact the internal organs. The hepatopancreatic epithelial cells retain normal nuclei and vacuoles [445]. This may imply that the probiotics are safe and non-toxic to the shrimps. In addition, lesser necrotic tubules and a remarkably lower degree of atrophy were observed in the hepatopancreatic tissues of shrimps treated with probiotic *Streptomyces* spp. (N7 and RL8) when compared to the untreated counterpart. Shrimps treated with *L. acidophilus* presented less intense hemocytic inflammation and multifocal necrosis at the hepatopancreatic tubules after being challenged with *Vibrio* spp. [446]. This also corroborated with Wee *et al.* [109], who noted higher epithelial integrity in the hepatopancreas of *M. rosenbergii* treated with *Bacillus cereus*. Although there was slight sloughing of the hepatopancreatic tubules in the treatment group, most of the epithelial cells remained intact. The shrimps exposed to probiotics demonstrated higher hepatopancreatic integrity post-infection with *A. hydrophila* than the control set, which demonstrated significant haemocyte infiltrations accompanied by major sloughing and highly necrotic tissues [109]. Similar trends have also been noted in shrimps treated with synbiotics (co-administration of probiotics with prebiotics) [182, 447]. In this light, the health of the hepatopancreas constitutes one of the major elements dictating the growth performance of shrimp. Selecting the right probiotic strain could positively reinforce the hepatopancreas' functionality and help secure a better growth rate and farm harvest [432].

8.2. Intestine

The effect of probiotics is also manifested through the changes to the intestinal morphology of shrimps. Most importantly, the cell surface protein's function in mediating probiotics' effects has been established as the shrimps fed the probiotics deprived of surface protein did not demonstrate significant improvement in the intestinal environment [162]. The surface proteins likely execute the modulatory effect on the intestine upon binding to the intestinal epithelial cells and the gastrointestinal mucins [162, 448, 449].

The most evident morphological alteration in the shrimps' intestine induced by probiotics is reflected in the architecture of the intestinal villi. The introduction of *Bacillus coagulans* [95], *B. subtilis* [123], mixed probiotics (*Bacillus* spp. + *Lactobacillus* sp.) [94] and *S. cerevisiae* [183] consecutively demonstrated a consistently increasing trend in the villus height of the enterocytes. Probiotic supplementation improved the size of the intestinal epithelial cells, which is reflected in the increased thickness of the intestinal wall and the width of the mucosa [123]. Higher villus number, submucosa, and lamina propria were reported following an eight-week feeding of *Bacillus lichenformis*. The disparity against the control group became evident in the fourth week of the trial [450]. Shrimps fed probiotics *Lactococcus lactis*, and *Pediococcus pentosaceus* exhibited a significantly thicker muscular layer at the mid-intestine compared to the control group and the antibiotic oxytetracycline-treated group. The same experiment also affirms the importance of strain selection as *Bacillus* spp. probiotics did not induce any statistically significant alteration to the intestinal muscular layer in *L. vannamei* [33]. Higher intestinal height correlates with animal weight gain [451].

In addition, the electron microscopic view discloses the epithelial cells in the probiotic group presented an active secretory state. High-density granules were noted in the cytoplasm of the probiotic-treated cohort [134]. These results correlated with the higher digestive enzyme activities observed following probiotic interventions (see Section 7). Furthermore, small clusters of bulges can be observed on the inner surface of the intestine. A higher fold depth and fold density were apparent in the probiotic treatment groups when contrasted with the non-treated group [134]. A more significant number of smaller crypts implied by probiotic treatment fabricate a larger surface structure of the intestine for nutrient assimilation and significantly improve the absorptive capacity of the intestine [452]. Since the intestine functions through a luminal absorption mechanism, these modifications induced by probiotics bolster the digestive and absorptive efficiency of the organ.

It is often neglected that the intestine also plays an essential role in regulating immune homeostasis and growth [154, 167, 176, 222, 453]. Patrolled by immune proteins and further barricaded by a stable microbiome, the structural integrity across the large surface area of the intestine forms a protective barrier against inflammation and pathogen invasion [453]. From another perspective, intestinal mucosal is the first line of defence against pathogens. Pathogenic bacteria may invade the digestive system by triggering the onset of mechanisms that foster the permeability of the gut mucosal layer to acquire passage [140, 454-456]. In this context, probiotics represent a promising strategy to mitigate infectious diseases [264, 457, 458]. Probiotics are postulated to effectuate their protective effect against infectious diseases by strengthening the protective mechanisms in the gut, thus enhancing the immune function (see Section 9) and maintaining the intestinal mucosal integrity.

A histopathology study revealed a significantly healthier intestinal tissue in the probiotic cohort is discernible post-infected by *Vibrio parahaemolyticus* [162]. The qualitative morphological disparity between treatment groups becomes evident when examined under electron microscopy. Transmission electron microscopy (TEM) images showed a higher mucosal layer density and better epithelial cell integrity in the probiotic-treated group [134]. Besides, dietary supplementation of *Halomonas* sp. to Chinese white shrimp (*Fenneropenaeus chinensis*) resulted in a regular and compact arrangement of epithelial cells in the intestine, which is in startle contrast to the sparse and irregular epithelial cells arrangement observed in the untreated counterpart [140]. This is consistent with the effect of *Lactobacillus pentosus* treatment in *L. vannamei*, in which the mucosal layer of the treated group is denser and has more blooms.

In contrast, the untreated group demonstrated looser and thinner mucosae [162]. The results strongly supported the application of probiotics for improving the mucosal structure, thereby fortifying the epithelial barrier integrity to guard against the invasion of opportunistic pathogens. Securing the health of the animal allows more resources to be invested for growth rather than being depleted to sustain the defence activities. Clearly, a better growth profile could be attributed to probiotics via the improvement in the intestinal microstructure.

9. Priming the immune function

Strengthening the immune function has a far-reaching effect on the animals' health and growth. Intriguingly, probiotics exhibited a unique spectrum of immunomodulatory properties not seen in antibiotic treatments. In recent years, probiotics have been exploited for their immunostimulatory effects and stress-relieving properties in aquatic animals [31, 264, 459-461]. Probiotics represent a promising alternative to chemotherapeutics for prophylaxis against infectious diseases affecting shrimps [461]. Similar to the concept of vaccination, probiotics can act as immunostimulants to boost the animals' immune systems and augment their resistance to infectious diseases and environmental stressors [462-466].

Although one may argue that stimulating the immune function may be an energy-draining exercise, in the desired scenario, immunostimulants should not trigger a massive immune reaction in the host. On the contrary, immunostimulants expedite the innate immune response by enhancing the recognition and elimination mechanisms of a wide array of foreign substances and infectious agents [461]. This is achieved by stimulating the immune function via the introduction of pathogen-associated molecular patterns (PAMPs). The cell surface components of probiotic bacteria, such as peptidoglycans, lipopolysaccharides (LPS), lipoteichoic acid, and glucans, act as immunostimulants and form complexes with the pattern recognition protein (PRPs) in the host. 11 PRRs have been identified in shrimps [467]. Each PRR exhibits different binding specificity and effector functions [467, 468]. Nonetheless, the formation of the PAMP-PRR complex constitutes a key event to activate the immune response, leading to the upregulation of immune gene expression and thereby improving immune function [123, 469-471]. This mechanism aids the animal to appear in the best state of defence. Therefore, upon pathogen invasion, the animal can elicit an immediate defence to clear the pathogen [472-474].

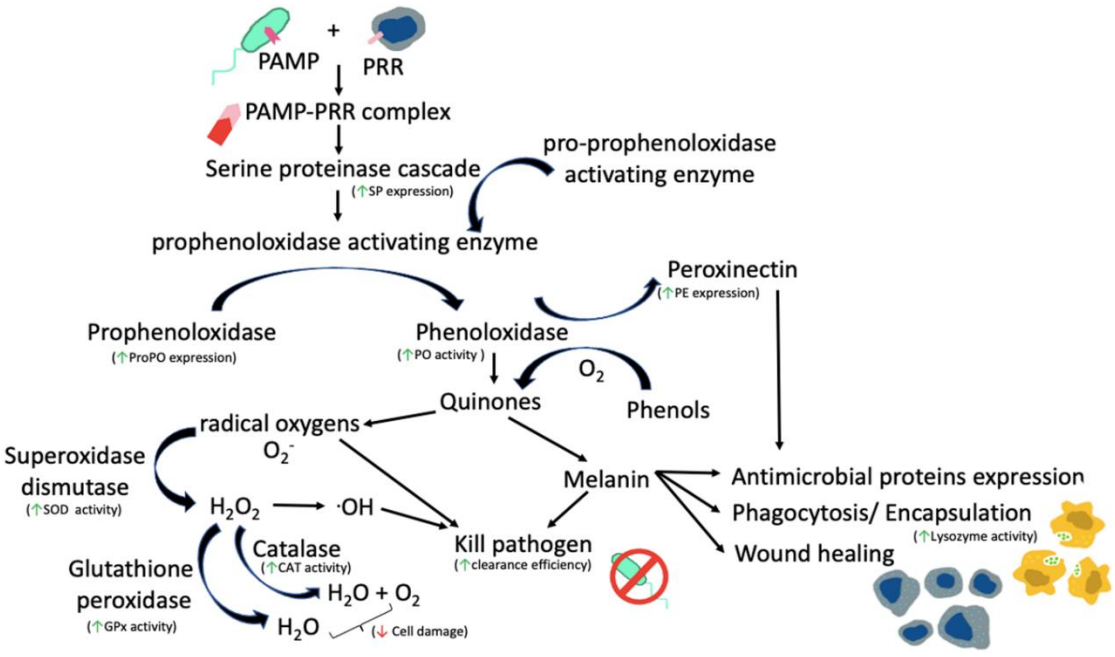

Figure 5. The innate immune system of shrimps. The modulatory effects of probiotics have been bracketed.

Shrimps lack an adaptive immune system, in which their immunity is heavily dependent on the innate immune response that plays a pivotal role in driving the defence mechanisms [475]. Although the existence of immune memory in shrimps remains controversial due to the lack of memory cells and immunoglobulin (antibody) production, recent findings proved that some forms of immune memory do exist in shrimps [476-478]. Ideas such as 'immune priming', 'quasi-immune response', and 'trained immunity' further supported the rationale of this argument [477, 478]. The prophenoloxidase (proPO) system is one of arthropods' most well-defined defence mechanisms (see Figure 5). Briefly, the PAMP-PRP complex triggers the serine protease cascade and catalyses the proteolytic cleavage of proPO, which eventually culminates in the release of the terminal enzyme PO. The released PO actively mediates several critical reaction pathways, including melanin synthesis, cytotoxic reactant liberation, phagocytosis, encapsulation, and nodule formation [479-484].

Notably, the serine protease, peroxynectin, and proPO expressions in shrimps-fed probiotics are substantially higher than those in the control group and antibiotic oxytetracycline-treated group [33]. The activity of immune enzymes, such as PO and lysozyme, was also significantly elevated following probiotic feeding [33, 129, 134, 485]. Lysozyme is an effective antibacterial agent that kills the invading pathogens by disrupting the peptidoglycan, which leads to the building up of osmotic pressure within the pathogen and eventually ruptures the cell [486]. Besides, the introduction of probiotics such as *Bacillus* sp. has been shown to elevate the phagocytic activities in different shrimp species, such as *P. monodon* [487] and *L. vannamei* [123]. The immunostimulatory effect of probiotics effectively reduces the mortality rates of shrimps when confronted by common pathogens such as *A. hydrophila* [488], *V. parahaemolyticus* [95, 123, 182, 218, 443, 489], *V. harveyi* [35, 212, 490], *Vibrio alginolyticus* [125, 491, 492], *Pseudomonas aeruginosa* [493] and white spot syndrome virus (WSSV) [134].

In proportion to the increment of phagocytic activity, the liberation of reactive oxygen species (ROS) such as reactive oxygen intermediate (ROI), singlet oxygen ($O_2\cdot$), hydroxyl ions (OH^-), hydroxyl radical ($\cdot OH$), hydrogen peroxide (H_2O_2) and superoxide anion radical ($O_2^{-}\cdot$) may be the culprits for oxidative damage in the body [38, 494]. Fortunately, probiotic addition also induced the secretion of antioxidative enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) to enhance the clearance efficiency of pathogens and safeguard the general wellbeing of the animal [35, 123, 495]. To illustrate, Duan *et al.* [129] demonstrated that dietary inclusion of *C. butyricum* probiotic effectively improved the total antioxidant capacity (T-AOC) of *L. vannamei.* The antioxidative mechanisms of probiotics have been clearly detailed in the recent work of Wang *et al.* [496]. Additionally, the introduction of *C. butyricum* probiotic significantly increased the inducible nitric oxide synthase (iNOS) and heat shock protein (HSP) gene expression of *L. vannamei* under ammonia stress. HSP70 is a vital regulator for signalling pathways and protein homeostasis, thus rendering a protective effect to shrimps against environmental stressors [497]. On top of that, priming the immune system also diminishes the shrimps' susceptibility to environmental stressors, including ammonia and oxidative stress [96, 99, 129,

[290, 450, 498]. The synergistic improvement in both the antioxidant and innate immune defence systems irrefutably promotes shrimps' health and growth performance.

In general, the immunomodulatory effect of probiotics is clearly established. However, discrepancies in results may be discernible between studies which are likely attributed to the differences in study designs, probiotic strains, dose, duration of treatment, shrimp species, growth phase, and environmental factors [95]. Augmenting disease resistance is critical to secure optimal growth as the shrimps affected by diseases typically display symptoms such as highly necrotic tissues, inactivity, anorexia, and poor growth [495]. Careful consideration needs to be taken when designing probiotics as immunostimulants. Proper mitigation is necessary to establish a more robust immune function of shrimp while avoiding the overactivation of the immune response, which may lead to the direct opposite effect [75, 461]. Overstimulation of the immune system will cause detrimental consequences such as unregulated generation of immune effectors leading to the depletion of immune components and eventually culminating in immune exhaustion. Besides, prolonging the immune response unnecessarily may incur a massive energy cost to regenerate the immune components, which may draw resources away from sustaining other physiological processes and thus negatively impact animal growth [461]. Clearly, a rigorous testing protocol is important to assess the large assortment of immune indices pertinent to the specific shrimp species targeted. Long-term data covering the entire production phase is also critical to evaluate the suitability of probiotics as immunostimulants [461]. Despite the complexity of the immune system, probiotics can be exploited as an effective means to enhance growth if properly utilized.

10. Altering the growth-related genes expression

In the context of decapod crustaceans, the shrimps' development is an intermittent process interrupted by the recurring moult cycle [499]. The muscle tissues in shrimps undergo frequent dramatic remodelling across each moult cycle. The shrimp experiences a characteristic deliberated atrophy during the pre-moult phase, followed by significant muscle growth in the early post-moult phase to fill up the available space before the hardening of the exoskeleton [499-501]. Regulation of the moulting process is greatly dependent upon the coordination of growth-related hormones, such as 20-hydroxyecdysone (20E) and crustacean hyperglycaemic hormone (CHH) [502, 503]. Endogenous factors such as the inherent hereditary genetic and hormonal factors also contribute to the variation in growth [504]. Irrefutably, the investigation of the influence of probiotics on the metabolism and growth profile of shrimp remains incomplete without looking into their effect on these pathways.

Dietary supplementation of probiotics represents a novel approach to intervening with the metabolic function of aquatic animals to promote growth [504-507]. Growth-related gene expressions can therefore serve as surrogate markers for growth status. Their expression levels in tissue samples can be quantitated using real-time polymerase chain reaction (RT-PCR) [504, 508]. Duan *et al.* [180] investigated the effect of probiotic supplementation on the expression levels of immune and digestive-related genes in *L. vannamei*. Results show that the expression levels are higher in the group fed with *C. butyricum* than in the control group

[180]. Besides, the introduction of *C. butyricum* remarkably up-regulated the genes in the mechanistic target of the rapamycin (mTOR) pathway, which includes the target of rapamycin (TOR), eukaryotic translation initiation factor 4E-binding protein (4E-BP), eukaryotic translation initiation factor 4E (eIF4E1α) and (eIF4E2) in *L. vannamei*. The mTOR pathway is a key regulatory centre for growth through the mediation of the moulting process, protein synthesis, nutrient transport, immune response, cell proliferation, autophagy and cell apoptosis [130, 509-516]. Notably, these changes correlated with the significant improvement of growth parameters like weight gain, SGR and FCR in the probiotic treatment group. By contrast, the control and cell-free fermentation supernatant group treatment group with low expression of eIF4E1α and eIF4E2 portrayed a poorer growth profile. The results imply the significance of the mTOR pathway associated with growth performance [130].

KEGG enrichment analysis revealed that administering probiotic strain with a high adhesive ability to the intestinal mucosa significantly increased the differential expression of proteins involved in metabolic regulation, immune processes, and cell signalling pathways. Immune pathways were activated, such as endoplasmic protein processing, oxidative phosphorylation, mitogen-activated protein kinase (MAPK), and mTOR signalling pathway [162]. Moreover, feeding *L. vannamei* with *C. butyricum*-enriched diet also significantly increases immune deficiency (Imd) and Toll genes expression [129]. Imd and toll pathways are two primary components of the shrimps' immunity which mediate the antagonising action against the Gram-negative and Gram-positive bacteria via the production of various antimicrobial peptides (AMPs) [517]. Besides, cell signalling machinery for calcium, oxytocin, wingless-related integration site (*Wnt*), and forkhead box protein O (FoxO) signalling pathway in *L. vannamei* was enhanced [162]. Du *et al.* [162] substantiated the involvement of cell surface proteins in mediating the modulatory effects of probiotics in shrimps by demonstrating the comparatively insignificant alteration to the proteomic and histological parameters when lithium-chloride (LiCl)-treated probiotics were introduced to the shrimps instead. LiCl was applied to detach the cell surface proteins non-covalently bound to the probiotic cell surface. However, documentation on the molecular mechanisms of probiotics in shrimps is somewhat limited.

From another perspective, growth hormone (GH) is one of the rate-limiting enzymes that play a pivotal role in glycolysis, lipolysis, protein synthesis, cell proliferation and immune response regulation [461, 504, 518-521]. The effect of GH is mediated through the expression of insulin-like growth factor-1 (IGF-1) [505, 508]. IGF-1 positively regulates animal growth through the direct stimulation of cell proliferation and differentiation [504]. Functional studies associated IGFs with metabolic control in crustaceans [522]. IGF-1 is a primary indicator gene for somatic growth [523]. The positive correlation between IGF-1 and animal growth rate has consistently been proven [523-525]. Through a series of periodic dietary restrictions and reintroduction of diet, Montserrat *et al.* [526] demonstrated the association between IGF and the nutritional status of the animal. Although molecular data on the effect of probiotics in the shrimp model is lacking, information gathered from other aquatic species suggests that gene expression modulation can be regarded as a highly probable growth

promotion effect of probiotics in shrimps. For instance, adding *L. rhamnosus* to the rearing water yielded a remarkable elevation of IGFs expression and increased the average body weight of treated *A. ocellaris* by 3-fold [525]. Long-term dietary supplementation of L. rhamnosus likely accelerates growth by modulating growth-promoting factors such as IGFs, retinoic acid receptor γ (rarγ) or peroxisome proliferator receptors [527].

Although reports gathered from other aquatic species can be used for cross-references in the speculation of the molecular mechanisms of probiotics in shrimp, it should be noted that the growth promotion effect in relation to myostatin (*mstn*) expression in the vertebrates may not be directly modelled to shrimps. *Mstn*, also known as growth differentiation factor-8 (GDF8), a member of the transforming growth factor-ß (TGF-ß), is typically noted as a negative growth regulator in the vertebrates due to its recognised function in inhibiting myoblast proliferation [528, 529]. The administration of *Lactobacillus* sp. and *Bacillus* spp. probiotics have been reported to lower the level of *mstn* while increasing the growth of *D. labrax* [524] and sea bream (*S. aurata*) [525], respectively. Unlike mammals, *mstn* can be found not only in muscular tissues but also widely expressed in non-muscular tissues, including eyestalk, thoracic muscle, heart, gill, abdominal ganglion, abdominal muscle, intestine, hepatopancreas and swimming leg of shrimps. The highest expression of *mstn* concentrates in the heart and abdominal muscle [499-501, 530, 531]. The ubiquitous expression of *mstn* in different tissues may suggest that the *mstn* ortholog in shrimp may have other functions as that in the vertebrates. The *mstn* ortholog in shrimp was found to perform the opposite role to those in the vertebrates [499-501]. A decline in *mstn* transcripts in the abdominal, pereiopod, and pleopod muscles of shrimps was detected with the introduction of 20-hydroxyecdysone (20E), thus propounding the involvement of *mstn* in the moult cycle [501]. Results also imply that *mstn* expression may be regulated by hormones [499, 501]. Significant elevation of *mstn* is common in the early post-moult phase and gradually down-regulated following the moulting phase [499]. Increased expression of *mstn* was found to positively regulate the growth of *L. vannamei* [530], *P. monodon* [500], freshwater shrimp *Macrobracium nipponense* [499], and *F. chinensis* [532]. On the contrary, reduced expression of *mstn* featured a significant stagnated growth pattern [500]. Thereby, it is essential to note the different functions of orthologs when mapping findings across species.

Recent studies through the genome-wide association approach successfully identified several novel genes and single nucleotide polymorphisms (SNPs) associated with the growth trait of shrimps, namely the *L. vannamei* class C scavenger receptor (*LvSRC*) [533], *L. vannamei* insulin growth factor binding gene-1 (*LvIGFB1*) [534], *L. vannamei* myostatin/growth differentiation factor (*Lvmstn/GDF11*) [530], ras-related protein (*Rap-2α*) and the delta type protein kinase C (*PKCδ*) [535]. Future research can investigate the effect of probiotics on these growth-related genes to validate the correlation between gene expression and the growth promotion effects of probiotics (see Section 13).

11. Increasing feed intake

Growth is an index for a multitude of parameters. Besides the immune status, nutrition is an indispensable factor. Another growth promotion factor of probiotics may stem from their effect in encouraging feed intake by shrimps. Probiotics have been reported to stimulate the appetite of animals, thereby allowing more resources to be allocated for growth [208, 211]. However, the reason behind the improved appetite is yet uncertain. The increased appetite may probably be associated with the effect of probiotics in improving nutrient digestibility (see Section 7) [156, 208]. Otherwise, increased feeding may arise from the improved attractiveness and taste of feed supplemented with probiotics [208]. Huynh *et al.* [536] surmised that some attractive compounds produced by synbiotics trigger increased feed intake. Recently, proton magnetic nuclear resonance (^{1}H-NMR) based metabolomic analysis identified that three metabolites out of the total 22 compounds detected were significantly higher in concentration in the hepatopancreas of shrimps treated with synbiotics compared to that of the untreated cohort. These three compounds are betaine (an organic osmolyte), inosine monophosphate (IMP) (a nucleotide), and valine (an essential amino acid) [537]. Interestingly, betaine is a common chemoattractant applied to prompt feeding in aquaculture. Thus, synbiotics/probiotics can act as betaine enhancers and initiate shrimps' feeding response. Furthermore, betaine plays a central role in DNA methylation, modulating gene expression, and regulating cell proliferation and differentiation [537, 538].

From another perspective, it is also hypothesised that the secretion of antinutritive compounds, SCFAs (see Section 6.1), and vitamins (see Section 6.2) by the probiotics may contribute to a better appetite [208]. Although *in-vivo* studies in shrimps are limited, da Silva *et al.* [269] demonstrated that SCFA introduction resulted in a substantial increase in feed intake, phosphorous availability, and higher apparent gross energy in shrimps. In another experiment, SCFA, specifically sodium propionate, was observed to demonstrate a remarkable dose-dependent effect in elevating the expression of ghrelin (*ghrl*) in zebrafish [254]. *Ghrl* is a gene encoding the orexigenic *ghrl* hormone that stimulates feed intake and regulates weight gain [539]. However, the up-regulation of *ghrl* may not always correspond to higher feed intake [523]. To illustrate, the report from Santos *et al.* [523], which portrayed the upregulation of the ghrl gene in zebrafish following the 30-day administration of transgenic phytase-expressing probiotics, recorded significant growth enhancement in zebrafish without significantly increasing feed intake. This may be attributed to the multifunctional facets of *ghrl*. *Ghrl* is not only an orexigenic hormone (appetite stimulant); it is also actively involved in homeostasis regulation and other physiological processes [523, 540].

Most importantly, it should be noted that not all probiotics can lead to elevation of *ghrl* gene expression, better appetite, or increased feed intake. For example, Falcinelli *et al.* [541] recorded the appetite suppression effect of probiotic *Lactobacillus rhamnosus*, which could be harnessed for managing glucose intolerance. Therefore, the selection of good probiotic strains for the intended result should be treated with circumspection. Future research can also look into the effects of probiotics in regulating the expression of other

appetite-related factors in shrimps, including neuropeptides (*npy*) such as moult-inhibiting hormone-like neuropeptide (*rMIH-B*) and cholecystokinin (*cck*) [542-544].

12. Environmental bioremediation

As far as aquaculture is concerned, the quality of the rearing environment is a key index for growth. Water quality parameters such as temperature, salinity, pH, dissolved oxygen, and chemical composition of water are essential factors in the health status of shrimps [93, 189]. Fluctuations of these variables might inflict stress upon the animals, alter their normal physiological functioning and ultimately affect the growth performance of the animals [164, 168, 545-547]. Environmental changes can impose selection pressure on microbial populations in culture water, which indirectly mould the gut microbiota of aquatic animals [548-550]. Notably, Zhao *et al.* [168] documented that water quality accounts for nearly one-fifth of the variations of gut microflora in shrimps. This suggests that besides the direct modulation of the water quality measures to favour the growth of shrimp, probiotics also indirectly aid in disease control by dictating the bacteria composition in water [37, 551].

The growth promotion effect of probiotics with regard to water quality could be comprehended through the involvement of the microbial population in manipulating the nitrite and ammonia levels in the rearing water, which are common end products of nitrogen catabolism. Certain species of bacteria are endowed with the nitrifying potential to convert nitrite and ammonia into nitrate, which is a less toxic form [147, 241, 552, 553]. In this regard, Gram-positive bacteria often demonstrated better efficiency in the decomposing organic matter when compared to their Gram-negative counterparts [241, 554]. This nitrification process also indirectly improved the pH level of water through the secretion of hydrogens as by-products [147, 210, 555]. Besides, this process also facilitates the turnover of carbon and nitrogenous compounds and increases nutrient availability to support growth [556]. Stemming from the aspects narrated, ameliorating water quality may account for the growth promotion phenomenon evinced by probiotics.

13. Future perspectives

As one of the fastest-growing industries worldwide, aquaculture is a key insurer for global food security [557]. Besides addressing the food security crisis, a steady supply of aquaculture produce would eventually culminate in a promising economic prospect for the global aquaculture industry. Creative strategies have been applied to intensify aquaculture production to meet the global demand. However, the progressive development of the AMR catastrophe resulted in the exigency for an alternative to the antimicrobial growth-promoting agent. Nevertheless, the state-of-the-art probiotic application as growth promoters in aquaculture witnesses several critical knowledge gaps. To illustrate, a vast array of the available studies involving probiotics were products of the empirical observational approach, whereas reports on the mechanistic molecular studies in shrimps are meagre [239]. Only a handful of studies concerned genomic studies in aquaculture animals. In recent years, genome-association studies are gradually replacing marker-assisted selection (MAS) in

selecting quality crops and animals for breeding. Gene-assisted selection (GAS) offered an added edge to MAS due to its higher accuracy and efficiency in selecting beneficial growth traits in animals [535, 558-563]. Several genes associated with body weight, metabolism, immunity regulation, moulting cycle, apoptosis, cell migration, and cytoskeletal arrangements have been listed in Section 10. Since the heritability factor can account for 24 to 52% of growth traits, therefore, introducing probiotics inducible to the growth-related genes to the livestock bred from selective broodstock would synergistically boost farm production yield [535, 562, 564, 565].

From another outlook, the progressive unveiling of the knowledge regarding the gut microbiome and its interaction with host physiology will increase the appreciation for probiotic application in aquaculture. Over the past few decades, the slow implementation rate of probiotics in aquaculture may partly be ascribed to the paucity of technological advances and research expertise [566]. Only a tiny fraction of bacteria in the biosphere can be cultivated using conventional culturing techniques [567-569]. Since there is a tremendous underestimation of the gut microbiome diversity, many key players in the gut still exist in the dark, and their actual roles and relations to the growth performance of the host are yet to be disclosed. Nonetheless, the popularization of molecular-based methods and their increasing affordability reignited great research interest in this arena. Next-generation sequencing (NGS), 16S rRNA sequencing, denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), fatty acid methyl ester (FAME) analysis and terminal restriction fragment length polymorphism (T-RFLP) are some prominent examples of the culture-independent techniques [570-573]. Revealing the microbiome diversity extends the frontiers of human understanding in the microscopic province. When viewed concurrently through the lenses of other omics such as metabolomics, proteomics, transcriptomics, and metagenetics, new insights will surface [573]. Mastering the mechanics of the microbiome will undoubtedly pave the way for more sophisticated research endeavours.

When the technical hurdles are triumphed over by technological advancement and assiduous research effort, probiotics can be effectively tailored as growth promoters in aquatic livestock. Unravelling the mechanisms of probiotics' growth promotion effect helps clarify the selection criteria when shortlisting putative strains as growth promoters. In other words, the growth-promoting factors elaborated on in this review could form the basis for the growth-promoting probiotic strain selection. For instance, the ability to secrete metabolites and digestive enzymes of probiotic strains could be screened through *in-vitro* assays. Strains exhibiting antimicrobial resistance could be excluded for further testing. Small-scale *in-vivo* pilot runs can focus on studying the effects of probiotics on gut microbiota, immunity, midgut histology, digestive enzyme activities and growth-related genes expression to provide a preliminary abstraction of the growth-promoting effect of promising probiotic strain [222, 566, 574, 575]. This approach could effectively increase the efficiency of designing growth promoters for shrimps. Thereby, less promising candidates could be eliminated, whereas more potential strains could proceed for larger-scale validation [576]. Besides the widely applied probiotics such as Firmicutes, Bacteroidetes and Proteobacteria, the Actinobacteria,

marine purple non-sulphur photosynthetic bacterium, salt pan bacteria, and other bacteria from varying sources are also potential candidates for aquaculture application lie in wait for further bioprospection [96, 104, 577-586].

14. Conclusion

Introducing probiotics opens a new vista for promoting animal growth and curbing infectious diseases in the aquaculture industry. Although large-scale implementation data is still lacking, studies have attested to probiotics' positive effects in improving shrimps' growth performance and survival rate. Different probiotics may trigger animal growth through distinct mechanisms (see Figure 6). This paper condenses the outcomes of empirical observational studies on probiotics revolving around shrimp models. The most notable changes induced by probiotics are reflected in the gut microbiota. Probiotics introduction helps increase the microbiota population's diversity and suppress the pathogenic strains. Probiotics also contribute to the growth promotion effect by aiding the establishment of healthy and functioning gut microbiota. The results of probiotics are closely associated with the secretion of bioactive compounds such as SCFAs, vitamins, and polyamines. These bioactive compounds act as growth factors for the animal. Besides supplying exogenous enzymes, the administration of probiotics has been noted to stimulate the secretion of endogenous digestive enzymes. This is consistent with the histological changes in the hepatopancreatic tubules. Morphological changes reflected in the midgut region, particularly the increase in intestinal villi height and numbers, increased the total surface area for nutrient absorption.

In contrast to AGPs, probiotics could act as immunostimulants that prime the immune system in the animal and confer a better resistance to infectious disease. Mitigating the risk of illness helps to conserve energy directed for growth. Additionally, probiotic additives tend to increase feed intake in animals. A higher nutrient input also contributed to animal growth. Body metabolism, in particular, the catabolic activities, are postulated to increase, which is coherent with the increase in the expression of growth-related genes and proteins. Last but not least, several probiotic strains are equipped with environmental ameliorative effects. Probiotics modulate the microbial composition in the water. This indirectly mediates critical parameters such as ammonia and nitrate, thus relieving the chemical stresses inflicted on the shrimps to create a conducive environment to support animal growth. To summarise, the factors contributing to growth discussed in this review should not be viewed as fragmented events. Condensing the constellation of results generated from the multitude of observational studies regarding the effects of probiotics in shrimps helps to offer a better picture of the growth promotion effect of probiotics. The information provides a more coherent overview of the potentialities of probiotic application in aquaculture and dictates the knowledge gap in state-of-the-art research. Understanding the growth promotion effect of probiotics about the critical features of AGPs helps to quicken the quest for alternative growth-promoting agents that will be a boon to the aquaculture industry.

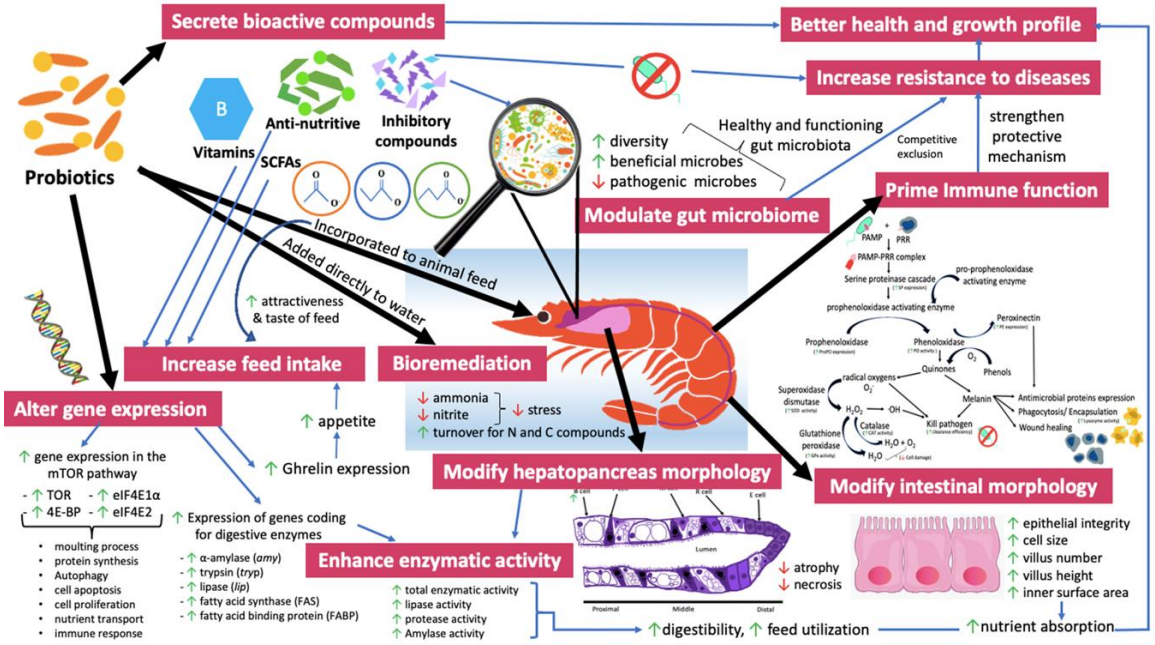

Figure 6. Mechanisms of probiotics in promoting animal growth.

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