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The metabolic regulation of dietary L-carnitine in aquaculture nutrition: present status and future research strategies

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Abstract

L-carnitine is a multi-functional nutrient which plays a leading role in fatty acid metabolism in mammals and other eukaryotes. Its main physiological function is to promote fatty acid β-oxidation to produce energy, which reduces body fat content and improves body weight without affecting moisture content in whole body and muscle. In recent years, its dietary supplementation in aquaculture nutrition has been studied in different cultured species. It has been proved that L-carnitine can improve growth and increase lipid utilization rate in some aquatic animals. However, such beneficial effects of dietary L-carnitine are limited or absent in other species. The reasons for the conflicting results obtained on L-carnitine functions in aquatic animals need to be elucidated. This review explores comprehensively the different physiological functions of L-carnitine in various aquatic animals. In the end, research strategies are provided to elucidate the existing conflicts on dietary L-carnitine application in aquaculture nutrition in order to promote its utilization in aquatic feed industry.

Key words: aquaculture nutrition, energy metabolism, L-carnitine, β-oxidation.

Introduction

The current trend of increasing cost and limited supply of fish meal worldwide has necessitated the use of high-fat diets (HFDs) in aquaculture to provide a protein-sparing effect, which means the protein-sourced energy is replaced by lipid-sourced energy (Hillestad & Johnsen 1994; Morais *et al.* 2001; Boujard *et al.* 2004). However, HFDs often lead to severe lipid accumulation in the liver and abdominal adipose tissue in cultured fish, causing metabolic disturbances (Lu *et al.* 2014; Jing *et al.* 2015), such as fatty liver and excess mesenteric fat deposition (Morais *et al.* 2001; Wang *et al.* 2005a). Therefore, potential metabolic regulatory mechanisms to decrease fat deposition in fish have received considerable attention in aquatic nutrition research and in the field of functional foods development. Consequently, research on the regulation of nutritional metabolism by using efficient lipid-lowering feed additives such as L-carnitine has obtained high attention in current fish nutrition research (Harpaz 2005). Accordingly, over the past few decades, L-carnitine has been used as a feed additive in aquaculture nutrition for different cultured fish species, such as red sea bream (*Pagrus major*), Nile tilapia (*Oreochromis niloticus*), crucian carp (*Carassius auratus gibelio*), Asian catfish (*Clarias batrachus*), rainbow trout (*Oncorhynchus mykiss*), caspian roach (*Rutilus rutilus caspicus*), silver perch (*Bidyanus bidyanus*) and yellow catfish (*Pelteobagrus fulvidraco*) (Dias *et al.* 2001; Du *et al.* 2002; Huan *et al.* 2009; Desai *et al.* 2010; Selcuk *et al.* 2010; Kordi *et al.* 2012; Yang *et al.* 2012; Zheng *et al.* 2014).

The potential nutritional functions of L-carnitine have been studied in many cultured fish species, including channel catfish (*Ictalurus punctatus*), tilapia, Asian catfish, caspian roach, silver perch and yellow catfish (Dias *et al.* 2001; Azab *et al.* 2002; Du *et al.* 2002; Desai *et al.* 2010; Selcuk *et al.* 2010; Kordi *et al.* 2012; Yang *et al.* 2012; Zhang *et al.* 2014; Zheng *et al.* 2014). However, studies conducted in fish exhibit conflicting results: in a number of cases, L-carnitine supplementation led to better growth (Santulli & D'Amelio 1986; Chatzifotis *et al.* 1995; Twibell & Brown 2000) and changes in lipid utilization (Jayaprakas *et al.* 1996; Keshavanath & Renuka 1998; Ozório *et al.* 2003)

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while in others no effects have been detected (Torreele *et al.* 1993; Burtle & Liu 1994; Chatzifotis & Takeuchi 1997; Yang *et al.* 2009). The contradictory results of L-carnitine supplementation in fish have caused controversial acceptance on further utilization of L-carnitine in fish feed industry by practitioners. Consequently, this phenomenon has largely restricted our understanding on the functions of L-carnitine supplementation in cultured fish.

Moreover, the majority of the studies on L-carnitine in fish have only focused on the effects of L-carnitine on the growth and body composition, whereas studies on the systemic regulation of nutritional metabolism and the underlying mechanisms are lacking. Despite the existence of latest studies on the metabolic regulatory mechanisms of L-carnitine in fish nutrition (Li *et al.* 2017a, 2018), most previous reviews have mainly concentrated on application and dosage of L-carnitine in aquatic animal diets (Liu & Zhu 2001; Harpaz 2005; Ozório 2009; Li 2014). Previous reviews in vertebrates have indicated indispensable functions of L-carnitine in intermediary energy metabolism in sows (Eder 2009), pigs (Li & Li 2014), dogs (Dove 2001), humans (Venkataraman 2008; Pekala *et al.* 2011; Vidal-Casariego *et al.* 2013; Esfahani *et al.* 2018) and poultry (Arslan 2006; Adabi *et al.* 2011; Rehman *et al.* 2017). However, these essential functions are still unfocused and scattered in aquatic animal nutrition.

This review summarizes comprehensively the metabolic regulation of dietary L-carnitine in aquaculture nutrition from past and recent studies and attempts to put forward future research strategies in cultured fish. We anticipate that the information provided expands the knowledge on L-carnitine supplementation for its better utilization in the nutritional metabolic regulation in cultured fish.

The physicochemical properties of L-carnitine and its general physiological functions

The general historical discovery and function of L-carnitine

L-carnitine (L-β-hydroxy-γ-N, N, N-trimethylaminobutyric acid) is a multi-functional organic nutrient, used as a carrier to transport long-chain fatty acids (LCFAs) from the cytosol to the mitochondria for β-oxidation to produce energy (Fritz & McEwen 1959; Longo *et al.* 2016). L-carnitine research began in the early 20th century. In 1905, Gulewitsch and Krimberg (1905) first extracted L-carnitine from meat and later in 1952, Carter *et al.* (1952) determined its biological function. It was found that L-carnitine is an essential nutrient in mealworm (*Tenebrio molitor*) larvae thereof, it was named vitamin BT. In 1958, Fritz and McEwen (1959) explored the role of L-carnitine in fat metabolism. They revealed that L-carnitine is an essential carrier for the transport of LCFAs across the inner mitochondrial membrane into the mitochondrial matrix, the site for fatty acid β-oxidation. Presently, some researchers consider L-carnitine, sometimes referred to as a quasi amino acid, as a new kind of functional nutrition additive (Harpaz 2005).

The synthesis of L-carnitine in animals

L-carnitine can be synthesized naturally from the essential amino acids lysine and methionine in the presence of vitamin C and other secondary chemical compounds produced in microorganisms, plants and animals (Harpaz 2005; Geng *et al.* 2007). The synthesis of L-carnitine is catalysed by four different enzymatic steps and the process requires two essential amino acids (lysine and methionine), iron (Fe^{2+}), vitamin C, vitamin B6 and niacin in the form of nicotinamide adenine dinucleotide (NAD) (Harpaz 2005). During L-carnitine biosynthesis, the methyl groups of L-carnitine come from the S-methyl group of methionine while the carbon and nitrogen atoms of L-carnitine come from lysine (Bremer 1983). It has been shown that 6-N-trimethyllysine (TML) and γ-butyrobetaine (γ-BB) are essential precursors of L-carnitine biosynthesis in fungi, mammals and plants (Rippa *et al.* 2012). In vertebrates, the endogenous biosynthesis of carnitine occurs mainly in the liver, kidneys and brain (Fraenkel 1951; Rippa *et al.* 2012). Despite the ability of organisms to biosynthesize L-carnitine, dietary supplementation is usually needed whenever the body lipids concentration exceeds the organism's capacity to synthesize. Thus, L-carnitine is deemed as a conditionally essential nutrient for animals.

The general functions of L-carnitine in living organisms

Although L-carnitine is involved in several metabolic reactions, its most widely known function is probably its participation in the overall context of normal fatty acid metabolism (Zeyner & Harmeyer 1999). The role of L-carnitine in transport of LFCAs and the mechanism have been described earlier (Fritz & Yue 1963). L-carnitine serves as the carrier that transports activated long chain fatty acyl groups (LCFAGs) across the inner mitochondrial membrane. During the transfer process, the LCFAs entering the mitochondria are converted into CoA derivatives in the matrix and the majority is 'activated' to acyl-CoA derivatives on the inner surface of the outer membranes of the mitochondria (Longo *et al.* 2016). L-carnitine acyl transferases are able to transfer reversibly an activated fatty acyl group from CoA to the hydroxyl group of carnitine to form an acylcarnitine ester (Fig. 1). Since the reaction is reversible, the fatty acyl CoA derivatives can be regenerated from the carnitine ester. Carnitine acyltransferase I (CPT I), the enzyme that transfers LCFAGs from CoA to carnitine is

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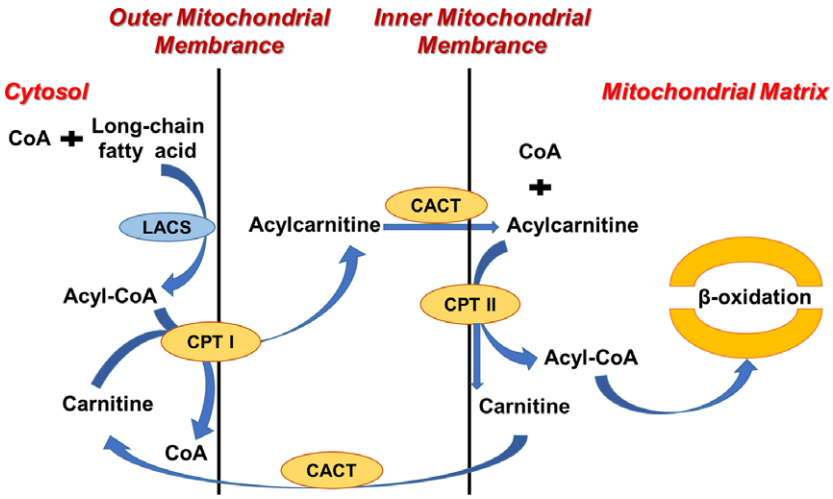


Figure 1 The mitochondrial L-carnitine transport system. Long-chain fatty acid is transformed into acyl-CoA after the catalysis of LACS. The carnitine palmitoyltransferase system then transport acyl-CoA from cytoplasm into mitochondrial matrix for oxidation: CPTI converts acyl-CoAs into acylcarnitines. CACT exchanges acylcarnitine and carnitine between outer and inner membranes of mitochondrial and finally acylcarnitine is converted back into acyl-CoAs for oxidation by CPTII. LACS, long-chain acyl-CoA synthetase; CPT I, carnitine-palmitoyl transferase I; CACT, carnitine acylcarnitine translocase; CPT II, carnitine-palmitoyl transferase II; CoA, coenzyme A.

located on the outer mitochondrial membrane. Acylcarnitine crosses the inner mitochondrial membrane with the aid of a translocase. The fatty acyl group is transferred back to CoA by a second enzyme, carnitine acyltransferase II (CPTII). The carnitine released in this reaction returns to the cytosolic side of the mitochondrial membrane by the same translocase that brings fatty acylcarnitine to the matrix side. Long-chain fatty acyl CoA, now located within the mitochondrial matrix, is a substrate for β-oxidation (Garland *et al.* 1965). Ultimately, a major factor controlling the β-oxidation of fatty acids is the rate of entry into the mitochondria.

Metabolic function is another important role played by L-carnitine in living organisms. In this case L-carnitine acts as a buffer for excess acyl residues. It modulates the mitochondrial acetyl-CoA/CoA (coenzyme A) ratios by transesterification from CoA and subsequent removal of acylcarnitine esters (Sleboda *et al.* 1995; Altamimi *et al.* 2018). It has been reported that accumulation of toxic acetyl-CoA metabolites in mitochondria due to L-carnitine deficiency impairs the citrate cycle, gluconeogenesis and fatty acid β-oxidation (Harpaz 2005; Seline & Harmeyer 2007). Also, carnitine facilitates removal of short-chain organic acids from mitochondria, thereby freeing intramitochondrial CoA and acetyl-CoA to participate in the fatty acid β-oxidation, Krebs cycle and other energy metabolism pathways (Gross & Henderson 1984; Marcovina *et al.* 2013; Jang *et al.* 2014; Zhang *et al.* 2014; Novakova *et al.* 2016). Moreover, L-carnitine is a substrate for CPT I, CPTII and carnitine acylcarnitine translocase (CACT) enzymes that participate in fatty acid utilization and regulation (Borum 1987). Therefore, carnitine modulates lipid content in living organisms' tissues and regulates several cellular pathways by modifying the mitochondrial acyl-CoA/CoA ratio, affecting enzymes activities and mRNA expression of genes related to energy metabolism.

The concentration of L-carnitine in tissues of vertebrates

Sufficient concentrations of L-carnitine in tissues are required for efficient utilization of fatty acids for the production of energy (Harpaz 2005). L-carnitine content in vertebrates varies among different groups and is mostly concentrated in tissues that use fatty acids as their primary dietary fuel, such as skeletal and cardiac muscles (Table 1). Of course, other tissues such as liver, heart and brain with strong energy metabolism also have high carnitine contents. For example, the total carnitine contents in skeletal muscles in dogs (Sanderson *et al.* 2001) and pigs (Owen *et al.* 2001b) are higher than that in fish (Ozório *et al.* 2012; Zheng *et al.* 2014; Li *et al.* 2017a, 2018) (Table 1).

L-carnitine content also varies within different tissues of the same species (Ji *et al.* 1996; Nogueira *et al.* 2010; Ozório *et al.* 2012; Zheng *et al.* 2014; Li *et al.* 2017a). The concentration of L-carnitine was 30 times higher in skeletal muscles than in the blood in rats (Zeng & Sheng 2013). In African catfish, the concentration in the muscle was around 400 times higher than that found in the plasma (Ozório *et al.* 2010), while in yellow catfish, the levels of L-carnitine in muscle ranged from 250 to 300 nmol g^{-1} and in liver was about 150–180 nmol g^{-1} (Zheng *et al.* 2014). In most studies conducted in cultured fish, the carnitine inclusion

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Table 1 L-carnitine concentrations in different tissues of some animals

Animal	Tissues sampled						References
	Plasma (nmol mL^{-1}, means ± SD)	Liver (nmol g^{-1}, means ± SD)	Muscle (nmol g^{-1}, means ± SD)	Heart (nmol g^{-1}, means ± SD)	Brain (nmol g^{-1}, means ± SD)	Other tissues (nmol g^{-1}, means ± SD)	
Pig	13.7 ± 1.1	101 ± 1.7	1019 ± 49.1	758 ± 19.5			Owen *et al.* (2001b)
	FC: 5.9 ± 0.9 AC: 0.74 ± 0.14	FC: 61.2 ± 12 AC: 1.04 ± 0.85	FC: 429–456 AC: 255–296				Kaup *et al.* (2018)
	FC: 3.75–4.45; SC: 2.45–2.29 LC: 0.87–1.00 TC: 7.73–7.78 AC: 3.32–3.97					(whole body) 394 ± 25	Heo *et al.* (2000)
Sow	20–25						Waylan *et al.* (2005)
	FC: 6.1–6.9; TC: 7.5–9.0						Ramanau *et al.* (2005)
	12.8–15.6					94–139	Eder (2009)
Boar	1.578–1.609						Čeřovský *et al.* (2009)
Steer	0.058		21.9375 μmmol $gprot^{-1}$				Greenwood *et al.* (2001)
Rabbit	(FC) serum: 38.2 ± 2.3, vitreous humour: 6.4 ± 1.0, aqueous humour: 10.8 ± 0.4					(FC) cornea: 33.6 ± 1.8, ciliary body: 39.7 ± 3.6, iris: 46.8 ± 4.7, lens: 148.5 ± 11.8, choroid-retina: 64.9 ± 5.1	Pessotto *et al.* (1994)
Dog	FC: 9.0–36.0 SCAC: <7.0 LCAC: 0.6–2.0 TC: 12.0–40.4		(cardiac muscle) FC: 3500–11 500SCAC: <5000LCAC: <660TC: 4500–14 000				Sanderson *et al.* (2001)
Rat	45.8 ± 2.32	136.119 ± 2.44	74.3 ± 3.15		60.44 ± 5.21		Sakvarelidze (2006)
	15.625		(skeletal muscle) 487.5 ± 13. 2	853.1 ± 8. 9			Zeng and Sheng (2013)
	30						Winter *et al.* (1995)
					(cerebellar tissues) 150–180		Svalbe *et al.* (2011)
	61 ± 8.4 μmol L^{-1}		(skeletal muscle) 1000				Tomohiro *et al.* 2008
	60.7 ± 7.2		(cardiac) 1029 ± 86	820 ± 0.15			Degrace *et al.* (2004)
	15.9 ± 2.3	78.3 ± 12.9					Davis *et al.* (2007)
	52.9–64.0	376–597		935–1123			Liepinsh *et al.* (2009a)

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Table 1 (continued)

Animal	Tissues sampled						References
	Plasma (nmol mL^{-1}, means ± SD)	Liver (nmol g^{-1}, means ± SD)	Muscle (nmol g^{-1}, means ± SD)	Heart (nmol g^{-1}, means ± SD)	Brain (nmol g^{-1}, means ± SD)	Other tissues (nmol g^{-1}, means ± SD)	
Growing rat	250	2813					Hosomi *et al.* (2009)
Valproate-treated rats	FC: 32.5 ± 2.2 AC: 12.0 ± 1.3 TC: 44.5 ± 3.2	FC: 1030 AC: 290 TC: 1320	FC: 2950 AC: 880 TC: 3820				Nishida *et al.* (1987)
Goto-Kakizaki rats	46.8 ± 5.1						Liepinsh *et al.* (2009b)
Wistar rat	30.5 ± 1.7						
Hypertensive Dahl rats	55 ± 6						Vilskersts *et al.* (2011)
Red porgy (*Pagrus pagrus*)			125–219				Nogueira *et al.* (2010)
Silver perch (*Bidyanus bidyanus*) juveniles			FC: 186.56–223.69 AC: 334.81–401.81 LCAC: 11.69–12.19				Yang *et al.* (2012)
African catfish (*Clarias gariepinus*) juveniles						(whole body) FC: 25.2 ± 3.7; AC: 8.6 ± 1.5; TC: 33.8 ± 1.5	Ozório *et al.* (2001)
	6.2–7.7						Ozório *et al.* (2003)
	FC: 1.73–1.88; AC: 1.83–2.38		FC: 631.25–862.5; AC: 750–1287.5				Ozório *et al.* (2010)
Rainbow trout (*Oncorhynchus mykiss*)		FC: 18.75–26.25; AC: 80.625–100; TC: 100–125.625	FC: 89.375–114.375; AC: 385.625–397.5; TC: 475.625–511.875				Ozório *et al.* (2012)
Hybrid striped bass (*Morone saxatilis*♂ × M. *chrysops* ♀)	TC: 4.4 FC: 1.7 AC: 2.7						Twibell and Brown (2000)
			FC: 187.5–268.75				Gaylord and Gatlin (2000)
Red sea bream (*Pagrus major*)			(dorsal muscle) FC: 212.5; AC: 231.25; LCAC: 87.5				Chatzifotis and Takeuchi (1997)
Yellow catfish (*Pelteobagrus fulvidraco*) juveniles		150–180	250–300				Zheng *et al.* (2014)

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Table 1 (continued)

Animal	Tissues sampled						References
	Plasma (nmol mL^{-1}, means ± SD)	Liver (nmol g^{-1}, means ± SD)	Muscle (nmol g^{-1}, means ± SD)	Heart (nmol g^{-1}, means ± SD)	Brain (nmol g^{-1}, means ± SD)	Other tissues (nmol g^{-1}, means ± SD)	
Atlantic salmon (*Salmo salar*)	85.6 ± 13.5	78.9 ± 22.3	134.1 ± 45.5		67.9 ± 21.6		Ji *et al.* (1996)
Turbot (*Scophthalmus maximus*) juveniles			562.5			(whole body) 470.6–660.0	Gonçalves *et al.* (2010)
Nile tilapia (*Oreochromis niloticus*) juveniles		281.25					Pan *et al.* (2017)
Zebrafish (*Danio rerio*)		FC: 62.50 TC: 93.75 FC: 93.75 TC: 250	FC: 50 TC: 156.25 FC: 312.5 TC: 562.5				Li *et al.* (2017a) Li *et al.* (2018)

FC, free carnitine; AC, acyl-carnitine; SCAC, short chain acyl-carnitine; LCAC, long chain acyl-carnitine; TC, total carnitine.
It is worth noting that the unlabelled carnitine types are total carnitine.

level in the diets range from a few hundred to above 4000 mg kg^{-1} diet (Chatzifotis & Takeuchi 1997; Harpaz 2005; Magliano *et al.* 2010; Yang *et al.* 2012). The supplementation of L-carnitine in cultured fish increases greatly its concentration in blood and other tissues (Twibell & Brown 2000; Ozório *et al.* 2003; Gonçalves *et al.* 2010; Li *et al.* 2017a). Furthermore, the L-carnitine concentration in tissues of cultured fish is also affected by nutrients composition of diets, such as the content of lysine (Burtle & Liu 1994; Chatzifotis *et al.* 1996), vitamin C (Sharifzadeh *et al.* 2017), lipid levels (Azab *et al.* 2002; Ozório *et al.* 2010) and the crude protein contents (Gang *et al.* 2010; Li *et al.* 2010). Therefore, the concentration of L-carnitine in animals varies widely across species, tissue type and dietary nutrients content of the animals.

Similar to cultured species, variations in L-carnitine exist among different aquatic animals in the wild environment (Table 2). Özogul *et al.* (2013) reported relatively similar concentration of L-carnitine in muscles of fishes which ranged from 111.54 nmol g^{-1} for big-scale sand smelt to 455.71 nmol g^{-1} for Atlantic chub mackerel (*Scomber colias*) and crustaceans such as for Mediterranean prawn (*Penaeus kerathurus*) and cephalopods such as squid (*Loligo vulgaris*) which contained 139.58 nmol g^{-1} and 489.45 nmol g^{-1}, respectively. On the contrary, Tada *et al.* (1984) reported higher concentrations of L-carnitine content in shellfish ligament (2965.26 nmol g^{-1}), ark shell (1346.15–8337.47 nmol g^{-1}), octopus (1054.59–1674.94 nmol g^{-1}), giant Pacific oyster (657.57 nmol g^{-1}) than fish such as Bluefin tuna (117.87–217.12 nmol g^{-1}) and red sea bream (502.48–669.98 nmol g^{-1}). Clear differences also existed between crabs and prawn species. For instance, the blue swimming crab (*Portunus pelagicus*) had approximately twofold higher L-carnitine content than Atlantic blue crab (*Callinectes sapidus*) whereas the Mediterranean prawn contained more than threefold L-carnitine compared with green tiger prawn (Özogul *et al.* 2013). In general, the concentration of L-carnitine in cultured and wild animals varies widely across species.

Effects of L-carnitine on nutrients metabolism in vertebrates

The roles of L-carnitine in vertebrates have been studied extensively. L-carnitine has been used as a supplement in vertebrates including broilers, sows, pigs, steers and others due to its multifunctional purposes including: (1) promoting growth (Khadem *et al.* 2006; Corduk *et al.* 2007; Eder 2009; Ying *et al.* 2013); (2) improving energy metabolism (Greenwood *et al.* 2001; Hosseintabar *et al.* 2015; Murali *et al.* 2015); and (3) enhancing reproduction (Eder *et al.* 2001; Miah *et al.* 2004). The role of L-carnitine dietary supplementation on growth promotion has been verified in different species such as broilers (Rodehutscord *et al.* 2002; Zhan *et al.* 2002; Khadem *et al.* 2006; Oladele *et al.* 2011), weanling pigs (Rincker *et al.* 2003) and gestating sows where it altered the IGF system (Woodworth *et al.* 2007) and foetal growth and development (Waylan *et al.* 2005).

The most studied role of L-carnitine supplementation in mammals and poultry is that related to its ability to

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facilitate the importation of activated LCFAs from the cytosol to mitochondria for fatty acid β-oxidation to alter energy metabolism. L-carnitine supplementation has been used in metabolic syndrome (obesity and dyslipidaemia, cardiovascular and others) to enhance fatty acid β-oxidation so as to ameliorate diet-induced disturbances in energy metabolism (Mondola *et al.* 1992; Broderick *et al.* 1995b; Zaugg *et al.* 2003; Iwami *et al.* 2006; Tomohiro *et al.* 2008; Panchal *et al.* 2015). In many past studies, L-carnitine supplementation has been shown to promote fatty acid β-oxidation resulting into reduced fat content and elevate energy metabolism, such as in regenerating rats (Tanaka *et al.* 1990), foetuses of sows (Woodworth *et al.* 2007; Xi *et al.* 2008) and boilers chicken (Miah *et al.* 2004; Khadem *et al.* 2006; Hosseintabar *et al.* 2015; Murali *et al.* 2015).

The effects of carnitine on energy metabolism in mammals are not only related to fatty acids β-oxidation but also glucose and protein metabolism. L-carnitine supplementation increased glucose oxidation in animals by increasing glycolysis, lactate dehydrogenase (LDH) activity and hexose transport (Broderick *et al.* 1995b; Palmero *et al.* 2000; Woodworth *et al.* 2007; Xi *et al.* 2008), while it stimulated CO_2 production from pyruvate in mitochondria from human skeletal muscle accompanied by increased pyruvate dehydrogenase complex (PDHC) activity (Uziel *et al.* 1988). Carnitine stimulates glycolysis based on its ability to shuttle acetyl groups out of the mitochondrion as acetylcarnitine (formed by the action of CAT), resulting into reduction of acetyl-CoA/CoA ratio, which in turn activates pyruvate dehydrogenase (PDH). For protein content and metabolism, L-carnitine supplementation depressed muscle protein catabolism in sows (Woodworth *et al.* 2007) and mitochondrial oxidation of branched-chain amino acids (BCAAs) in tissues of swine (Owen *et al.* 2001a). The reduction of protein catabolism after L-carnitine supplementation is related to the increased energy supply from fatty acid β-oxidation and glucose utilization.

L-carnitine supplementation also has been shown to increase reproductive performance of sows (Ramanau *et al.* 2002, 2005), ponies (Woodworth *et al.* 2004), dairy cows' when applied in concomitant with choline (Pirestani *et al.* 2011; Altamimi *et al.* 2018), broiler breeder hens (Beer & Coon 2009) and improved male sexual performance in male rats when administered in combination with ginger (Abo-Ghanema *et al.* 2012). In these animals, L-carnitine improve reproductive performance by mobilizing more energy from different tissues such as adipose tissues (Eder 2009).

It is clear that L-carnitine supplementation in mammals and birds inhibit fat accumulation in tissues, enhance growth performance and reproduction by improving energy production from lipids, glycolysis and protein. These functions have led to its increased used in vertebrates' production.

Regulation of L-carnitine on nutrients metabolism in aquatic animals

The growth performance and physiological status of aquatic animals under high stocking densities in aquaculture are different from those in the wild environment. These changes probably reduce the ability of aquatic animals to synthesis endogenous L-carnitine, such that the existing low levels in the body cannot meet the needs for metabolism, which in turn influences the various physiological functions of animals. Infants and fingerlings are particularly susceptible to L-carnitine depletion, which affects their normal growth (Harpaz 2005). When carnitine deficiency occurs, fatty acids oxidation is reduced, resulting in mitochondrial failure. The addition of sufficient quantities of L-carnitine to the diets prevents these problems (Bremer 1983; Harpaz 2005; Mcdowell 2008).

Currently, aquaculture practices focus on satisfying the energy requirements of aquatic animals' nutritional metabolism by supplementing L-carnitine in formulated compound diets. The supplementation of L-carnitine in aquatic animals' diets has been advocated for multifunctional purposes based on its established roles in nutrients metabolism in mammals. For the past years, a large number of studies have shown that the dietary L-carnitine supplementation in aquatic animals basically regulates growth to increase feed efficiency, reduces body fat to improve muscle quality and modulates energy metabolism to provide a protein-sparing effect (Table 3). These results have been reported mainly on various cultured fish, some on shrimp and crabs (crustacean) (Ozório *et al.* 2003; Harpaz 2005; Wang *et al.* 2005a; Yang *et al.* 2009; Selcuk *et al.* 2010; Zheng *et al.* 2014). However, these effects remain controversial in different aquatic species as reviewed in the following section.

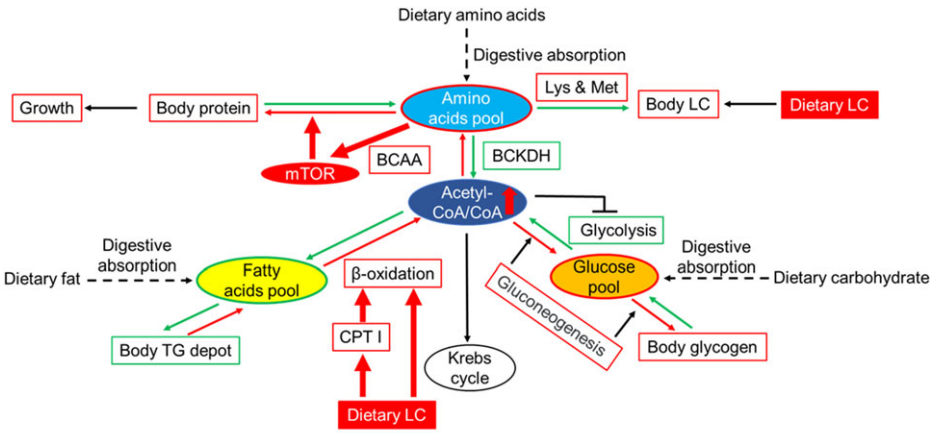
The role of L-carnitine in fish nutrients metabolism

The supplementation of L-carnitine in fish accelerates growth of fish by affecting energy-source nutrients such as lipid, carbohydrate and protein. The comprehensive metabolic effects of the L-carnitine on growth, lipid, carbohydrate and protein metabolism in fish are provided in Figure 2 and the detailed discussions of each nutrient are given in the next sections.

The effects on fish growth - regulating growth to increase feed efficiency

Growth (measured as weight gain) is of great importance to fish farmers and therefore deserves a special attention

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Abbreviations: LC, L-carnitine; CPT I, carnitine-palmitoyl transferase I; TG, triglyceride; CoA, coenzyme A; Lys, lysine; Met, methionine; BCKDH, branched-chain α-keto acid dehydrogenase complex; BCAA, branched-chain amino acids; mTOR, mammalian target of rapamycin. Green color indicates decreased and red color is increased.

Figure 2 Schematic representation of proposed systemic effects of L-carnitine supplementation on nutritional metabolism in fish. L-carnitine supplementation of fish increases the concentrations of tissues carnitine and the activation of fatty acids β-oxidation-related enzymes (CPTI), which accelerates the fat catabolism to reduce the fatty acids pool. This will lead to an increased the ratio of acetyl-CoA/CoA and carbon forms and enhances the efficiency of energy production in cells, which would correspondingly decrease the acetyl-CoA sourced from glycolysis pathway (inhibited the activities of pyruvate dehydrogenase, PDH) and amino acids catabolism (downregulated the mRNA expression of BCKDH). In addition, acetyl-CoA can be used as the raw material to reinforce gluconeogenesis, eventually increase the glucose level and the glycogen content. The supplementation of LC, moreover, increases the carnitine level to reduce the synthesis of endogenous carnitine, which saves *in vivo* of the Met and Lys. This effect will avoid the loss of other amino acids due to imbalance ratio, thereby, improving their utilization rates to protein synthesis. With the decreased amino acids breakdown, the amino acids pool in cell will increase, especially the three BCAA, including leucine, isoleucine, and valine. The increasing of BCAA will activate the protein of mTOR, which is one of the most important regulators of protein synthesis. Therefore, LC supplementation on fish will affect the energy homeostasis is based on the ability of carnitine to promote fatty acids β-oxidation, resulting in an increased in the acetyl-CoA/CoA ratio, which alters glucose metabolism and improves protein deposition. These effects of LC on fish nutrient metabolism ultimately is reflected in the enhancement of growth performance.

with respect to dietary L-carnitine supplementation. As indicated earlier, the ability to synthesize L-carnitine in intensively cultured fish is limited and it varies depending on growth stage. Limited L-carnitine synthetic ability is more pronounced in larval stage, whereby its biosynthesis rate is greatly slow (Dias *et al.* 2001; Azab *et al.* 2002; Yu *et al.* 2008; Li 2014). Thus, it is more likely that juvenile fish are L-carnitine deficient. This is not surprising because the mechanism of L-carnitine synthesis in larval fish is under developed. The limited synthesis ability due to development stage causes L-carnitine deficiency in juvenile fish. However, when fish grow, their L-carnitine synthesis ability is fully developed to meet the needs of metabolism in adult fish. Nevertheless, under certain conditions, limited L-carnitine synthesis in fish may occur due to prone L-carnitine deficiency. In this case, fish may have abnormal metabolism of fat and other nutrients, causing slow growth and low feed efficiency (Harpaz 2005; Zhang 2009; Li 2014; Wang *et al.* 2015). Fish with this condition can be supplemented with dietary L-carnitine to improve their growth and increase feed efficiency.

The effects of L-carnitine on growth performance in fish are still contradicting, with results showing improved and no effects (Table 3). Increased growth performance and feed utilization after dietary L-carnitine supplementation have been reported in hatchery-reared European sea bass (*Dicentrarchus labrax* L.) fingerlings (Santulli & D'Amelio 1986), red sea bream fingerlings (Chatzifotis & Takeuchi 1997), yellow catfish larvae (Zheng *et al.* 2014), hybrid striped bass juveniles (*Morone chrysops* ♀ × *M. saxatilis* ♂) (Gaylord & Gatlin 2000; Twibell & Brown 2000), silver perch juveniles (Yang *et al.* 2012), hybrid tilapia broodstock (*Oreochromis niloticus* × *O. aureus*) (Becker *et al.* 1999), rainbow trout juveniles (Sharifzadeh *et al.* 2017), rohu (*Labeo rohita*) fingerlings (Keshavanath & Renuka 1998), beluga sturgeon (*Huso huso*) juveniles (Mohseni *et al.* 2008), common carp (*Cyprinus carpio* L.) juveniles (Zhao *et al.* 2004), common carp fry (Focken *et al.* 1997), rainbow trout juveniles (Sayedmohammadali *et al.* 2010), hybrid tilapia juveniles (*Oreochromis niloticus* × *O. aureus*) (Huang *et al.* 2010), Nile tilapia fingerlings (Azab *et al.* 2002; Dikel 2003; Gang *et al.* 2010; Soltan *et al.* 2010) and crucian carp broodstock (Zhang 2009).

Although dietary L-carnitine supplementation exerts beneficial effects on growth performance in fish, the mechanisms thereof are still little understood. It has been reported that dietary L-carnitine supplementation in fish

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Table 2 L-carnitine content in muscle (edible portion) in some wild aquatic animal species

Wild species	Muscle (nmol g^{-1} means ± SD)	Reference
Atlantic bonito (*Sarda sarda*)	345.10 ± 2.45	Özogul *et al.* (2013)
Atlantic chub mackerel (*Scomber colia*)	455.71 ± 1.99	
Atlantic horse mackerel (*Trachurus trachurus*)	406.82 ± 4.93	
Big-scale sand smelt (*Atherina boyeri*)	111.54 ± 1.06	
Bogue (*Boops boops*)	342.74 ± 3.77	
Brown meagne (*Sciaena umbra*)	219.85 ± 0.57	
Common Pandora (*Pagellus erythrinus*)	169.67 ± 1.68	
Common sole (*Solea solea*)	341.44 ± 2.40	
Common two-banded Seabream (*Diplodus vulgaris*)	322.70 ± 4.39	
Corb (*Umbrina cirosa*)	182.82 ± 2.77	
European anchovy (*Engraulis encrasicolus*)	334.43 ± 2.81	
European conger (*Conger conger*)	453.29 ± 3.47	
Filefish (*Stephanolepis diaspros*)	172.95 ± 2.05	
Goatfish (*Upeneus pori*)	204.96 ± 2.23	
Goldband goatfish (*Upeneus mollucensis*)	150.62 ± 2.52	
John dory (*Zeus faber*)	213.59 ± 1.33	
Kluzinger's ponyfish (*Leiognathus kluzingeri*)	197.08 ± 0.97	
Lizardfish (*Saurida undosguamis*)	205.33 ± 1.79	
Mackerel (*Scomber scombrus*)	174.88 ± 1.64	
Red mullet (*Mullus barbatus*)	325.93 ± 3.43	
Sardine (*Sardinella aurita*)	405.21 ± 2.36	
Sea bass (*Dicentrarchus labrax*)	163.40 ± 1.25	
Sea bream (*Sparus aurita*)	137.16 ± 1.99	
Silver whiting (*Shillago sihama*)	312.59 ± 4.29	
Spotted flounder (*Citharus linguatula*)	127.17 ± 1.21	
Striped bream (*Lithognathus mormyrus*)	426.36 ± 2.45	
Thinlip grey mullet (*Liza ramada*)	419.04 ± 6.16	
Thornback ray (*Raja clavata*)	152.67 ± 1.41	
Tub gurnard (*Trigla lucerna*)	315.76 ± 2.41	
White grouper (*Epinephelus aeneus*)	189.83 ± 1.93	
Yellowstripe barracuda (*Sphyraena chrysotaenia*)	134.49 ± 0.44	
Atlantic blue crab (*Callinectes sapidus*)	187.34 ± 2.77	
Blue swimmer crab (*Portunus pelagicus*)	415.57 ± 3.91	
Common cuttlefish (*Sepia officinalis*)	205.09 ± 1.23	
Green tiger prawn (*Penaeus semisulcatus*)	453.23 ± 5.47	
Mantis shrimp (*Eurogosquilla massavensis*)	213.40 ± 2.66	
Mediterranean prawn (*Penaeus kerathurus*)	140.01 ± 2.22	
Octopus (*Octopus vulgaris*)	164.21 ± 1.36	
Spiny hands (*Charybdis helleri*)	307.38 ± 4.27	
Squid (*Loligo vulgaris*)	489.45 ± 2.14	
Japanese little-neck manila clam (*Venerupis philippinarum*)	533.50	Tada *et al.* (1984)
Freshwater clam (*Corbicula fluminea*)	80.65	
Shrimp	179.90–214.94	
Japanese tiger prawn (*Penaeus monodon*)	527.30	
Red sea bream (*Pagrus major*)	502.48–669.98	
Shellfish ligament	2965.26	
Ark shell (*Anadara broughtonii*)	1346.15–8337.47	
Octopus (*Octopodidae*)	1054.59–1674.94	
Giant Pacific oyster (*Crassostrea gigas*)	657.57	
Southern bluefin tuna (*Bluefin tuna*)	117.87–217.12	
Japanese yellow horse mackerel (*Trachurus japonicus*)	372.21	
Pacific saury (*Cololabis saira*)	750.62	
Bigfin reef squid (*Sepioteuthis lessoniana*)	2983.87	

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diets regulates growth attributed to two aspects (Fig. 2). First, dietary L-carnitine modifies energy metabolism by promoting fatty acid β-oxidation in the mitochondria. This leads to an increased utilization of diets to produce enough energy to speed up metabolic reactions as a result of increased feed efficiency and reduced use of protein for energy utilization (Ji *et al.* 1996; Harpaz 2005; Stålej *et al.* 2010; Castro *et al.* 2013). Evidently, dietary L-carnitine induced pyruvate carboxylase (PC) (or a reduction in turnover of carbon) and enhanced protein synthesis in Atlantic salmon (Ji *et al.* 1996). Furthermore, L-carnitine supplementation converted several waste by-products into amino acids and protein in animals by promoting the role of PC (Wang *et al.* 2005b). Secondly, as aforementioned, biosynthesis of L-carnitine uses lysine and methionine as substrates. These are the most important essential amino acids which are usually insufficient in cultured fish diets. Therefore, they are in most cases, the limiting factors for growth in cultured fish. Hence, diets supplemented with L-carnitine ensures continued supply of these growth-limiting amino acids which allocates more protein for fish growth leading into improved growth rate of cultured fish (Wang *et al.* 2005c).

Notwithstanding the above results, some studies have indicated contradicting results. Insignificant growth effects of dietary L-carnitine were observed in Atlantic salmon (*Salmo salar*) juveniles (Ji *et al.* 1996), European sea bream broodstock (Dias *et al.* 2001), rainbow trout grow-out (Rodehutscord 1995; Ozório *et al.* 2012), channel catfish fingerlings (Burtle & Liu 1994), African catfish (*Clarias gariepinus*) juveniles (Ozório *et al.* 2003), cobia (*Rachycentron canadum*) grow-out (Wang *et al.* 2005a), hybrid tilapia adults (Yang *et al.* 2009), Nile tilapia fry (Gang *et al.* 2010; Erdogan *et al.* 2015), hybrid tilapia broodstock (*Oreochromis niloticus* × *O. aureus*) (Du *et al.* 2002), common carp larvae (Chen *et al.* 2011) and caspian roach juveniles (Kordi *et al.* 2012). In these studies, although dietary L-carnitine supplementation altered lipid metabolism in tissues, growth rate was not improved significantly. The lack of L-carnitine influences on growth may be attributed to dietary L-carnitine content in diets (Selcuk *et al.* 2010; Zheng *et al.* 2014) (Kuka *et al.* 2012; Ye *et al.* 2014) and environmental factors. L-carnitine increased the growth of hybrid tilapia at temperature range from 22 to 28.8°C (Becker *et al.* 1999), European sea bass at temperature ranging from 12 to 21.8°C (Santulli & D'Amelio 1986) and rohu fingerlings at temperature ranging from 23.5 to 34°C (Keshavanath & Renuka 1998).

Clearly, these results indicate that, although supplementing dietary L-carnitine at different doses facilitates lipid metabolism modification, such changes do not necessarily result into better growth of fish. Actually, the related mechanisms remain unclear. Nonetheless, it is evident from the above studies that, the effects of dietary L-carnitine supplementation differ depending on fish species used, their growth stages, dietary L-carnitine content in diets and water quality parameters.

Effects of L-carnitine on fish lipid metabolism - reducing body fat to improve meat quality

At present, high density in intensive aquaculture, especially in cages cause decreases fish activities. This practice coupled with wide use of low protein and high energy contents in formulated diets, results into a large deposition of fat in the liver and muscle, which impairs liver functions and reduces muscle quality, respectively (Morais *et al.* 2001; Wang *et al.* 2005a). To avoid accumulation of lipids, dietary L-carnitine supplementation has been widely applied to stimulate fatty acid oxidation and regulate lipolysis as described by various studies, which are reported in this section.

Similar to growth performance, the effects of L-carnitine supplementation on lipid content are still contradicting (Table 3). During the past decades, the effects of dietary L-carnitine supplementation on fish lipid metabolism have been studied in different cultured species. Its main effect on lipid metabolism relies on increased fatty acid β-oxidation and balanced acetyl-CoA/CoA ratio (Fig. 2). L-carnitine, as a key factor in the fatty acid oxidation, has been widely applied in aquaculture for reducing body fat mainly by promoting fatty acid β-oxidation (Wang *et al.* 2005a). Previous studies found that both dietary supplementation of L-carnitine with lysine decreased significantly the LCFAs contents such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and other $n-3$ and $n-6$ fatty acids in the liver of red sea bream (Chatzifotis *et al.* 1996). L-carnitine reduced the amount of free fatty acids in liver in rainbow trout indicating an increased fatty acid utilization (Ozório *et al.* 2012). Recently, L-carnitine has also been shown to decrease lipid content in liver and muscle of zebrafish, accompanied by increased concentrations of total and free carnitine in tissues (Li *et al.* 2017a). Meanwhile, L-carnitine supplementation enhanced mitochondrial β-oxidation activities and the expression of CPTI mRNA, whereas it depressed the mRNA expression of adipogenesis-related genes. In a low-carnitine zebrafish model fed with mildronate as a specific carnitine synthesis inhibitor, severe hepatic lipid accumulation with lower efficiency of mitochondrial fatty acids β-oxidation was observed (Li *et al.* 2018). However, the fish had increased mRNA expression of CPTI in the liver. Interestingly, fatty acids β-oxidation efficiencies increased when exogenous L-carnitine was added to the *in vitro* reaction system, suggesting that, the activities of fatty

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Table 3 Effect of L-carnitine supplementation on growth performance and lipid content in cultured fish

Fish species	Dosages of L-carnitine (mg kg^{-1} diet)	Nutrient composition of diets	Growth effect	Change of lipid content of tissues	References
Sea bass (*Dicentrarchus labrax* L.) fingerlings	2000	NR	↑	↓	Santulli and D'Amelio (1986)
Red sea bream (*Pagrus major*) fingerlings	75, 545, 1087, 2088 and 4162	NR	2088 LC: ↑	↓ liver FFAs and L CFAs (20–22C)	Chatzifotis *et al*. (1995)
Red sea bream (*Pagrus major*) fingerlings	2000	Two levels of lysine: 10 and 14 g kg^{-1} diet; 45% crude protein, 14% lipid	LC + 14 lysine: ↑	—; ↓ EPA, DHA and total LCFAs (ΣC_{20-24})	Chatzifotis *et al*. (1996)
Black sea bream (*Sparus macrocephalus*) juveniles	100, 120, 160, 240, 390 and 1100	45% crude protein, 12.6% lipid	100, 120, 160 and 240 LC: ↑; 390 and 1100 LC: ↓	↓ muscle and liver fat	Ma *et al*. (2008)
Hybrid striped bass (*Morone chrysops* ♀ × *M. saxatilis* ♂) juveniles	2.1, 41.0, 212.0 369.7	34.6% crude protein, 6.0% lipid	— ↑	—	Twibell and Brown (2000)
African catfish (*Clarias gariepinus*)juveniles	80 and 660	Three levels of protein energy: non-protein energy ratio (PE:NPE): 0.7, 0.9 and 1.4	660 LC + 0.7 (PE:NPE): ↑ ; ↑ body protein	↓	Ozório *et al*. (2001)
African catfish (*Clarias gariepinus*) fingerlings	125, 245, 450, 980, 1960 and 3920	Two dietary lipid levels: 9.6%and 15.5%; 56% crude protein	500 LC+ 9.6% lipid and 684 LC + 15.5% lipid: ↑	NR	Torreele *et al*. (1993)
Asian catfish (*Clarias batrachus*) fry	250, 500, 750 and 1000	30% crude protein, 3.5% lipid	500 LC: ↑	↓	Desai *et al.* (2010)
Yellow catfish (*Pelteobagrus fulvidraco*) larvae	331 3495	43% crude protein, 9.5% lipid; lysine 35 g kg^{-1} diet	↑ —	↑ ↑	Zheng *et al*. (2014)
Silver perch (*Bidyanus bidyanus*) juveniles	4000	The plant protein sources to replace 0 or 70% of fish meal protein; 10 and 18% lipid	↑	↓	Yang *et al.* (2012)
Rainbow trout (*Oncorhynchus mykiss*)	1000 and 2000	NR	1000 LC: ↑↑; body protein content	1000 LC: ↓	Hajiabadi *et al*. (2009)
Rainbow trout (*Oncorhynchus mykiss*) juveniles	100 and 200	Two levels of ractopamine: 0 and 10 mg kg^{-1} diet; 45% crude protein, 15% lipid	10R + 100LC: ↑; ↑ body protein content	↓ total *n* − 3 PUFAS	Sayedmohammadali *et al*. (2010)
Rainbow trout (*Oncorhynchus mykiss*)	300 and 600	44% crude protein, 20% lipid	600 LC: ↑; ↑ muscle protein content	↑ muscle SFA and MUFA	Dikel *et al*. (2010)
Rainbow trout (*Oncorhynchus mykiss*) juveniles	800	Vitamin C levels: 0, 500, 1000 mg kg^{-1} diet	500/800 (C:L): ↑;↑ protein content	1000/800 (C/L): ↓	Sharifzadeh *et al*. (2017)
Rohu (*Labeo rohita*) fingerlings	250, 500, 750 and 1000	30% crude protein, 6% lipid	500 LC: ↑;	↓	Keshavanath and Renuka (1998)
Beluga sturgeon (*Huso huso*) juveniles	300, 600, 900 and 1200	41% crude protein	300 LC: ↑; 1200 LC:↓	300 LC: ↓	Mohseni *et al*. (2008)
Common carp (*Cyprinus carpio* L.)	50, 100, 150, 200 and 250	NR	100 LC: ↑	NR	Zhao *et al*. (2004)
Common carp (*Cyprinus carpio*)	500 and 1000	34% crude protein, 5 and 10% lipid	↑	1000 LC: ↓	Sabzi *et al.* (2017)
Crucian carp (*Carassius auratus gibelio*) juveniles	50, 100, 150, 200 and 250	NR	200 LC: ↑; ↑ muscle protein and amino acid (improve meat quality)	200 and 250 LC: ↓	Zhang (2009)
	150	32% crude protein, 6% lipid	↑	↓ muscle fat	Ming *et al.* (2013)

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Table 3 (continued)

Fish species	Dosages of L-carnitine (mg kg^{-1} diet)	Nutrient composition of diets	Growth effect	Change of lipid content of tissues	References
Black carp (*Mylopharyngodon piceus*) juveniles					
Carp (*Cyprinus carpio* L.) juveniles	200, 400 and 600	40.5% crude protein, 10.6% lipid	400 and 600 LC: ↑	NR	Focken *et al.* (1997)
Gibel carp (*Carassais auratus gibebio*)	100, 200 and 300	Taurine: 1000, 2000, 3000 mg kg^{-1} diet; 34% crude protein, 6.5% lipid	1000 mg kg^{-1} taurine + 200 LC: ↑	NR	Wang *et al.* (2015)
Tilapia hybrids *O. niloticus* × *O. aureus*) juveniles	150, 300	32% crude protein, 3% lipid; lysine 14.7 g kg^{-1} diet, methionine/cysteine 10.3 g kg^{-1} diet	↑	—	Becker *et al.* (1999)
Tilapia (*Oreochromis niloticus* × *O. aureus*) juveniles	50, 100, 150 and 200	40% crude protein, 5% lipid	150 LC: ↑	↓ muscle fat	Huang *et al.* (2010)
Nile tilapia (*Oreochromis niloticus*) fingerlings	300, 600 and 900 mg kg^{-1} diet	Two lipid levels: 10 and 15%	600 and 900 LC at both lipid levels: ↑; LC+HFD: ↑ tissue protein	—	Azab *et al.* (2002)
Nile tilapia (*Oreochromis niloticus*) juveniles	500	45% crude protein, 3% lipid vitamin C 100 mg kg^{-1} diet	↑	NR	Dikel *et al.* (2003)
Nile tilapia (*Oreochromis niloticus*) juveniles	200, 400, 600 and 800	Three levels of dietary protein: 22, 25 and 28%	↑ body and muscle protein contents	↓	Gang *et al.* (2010)
Mozambican tilapia (*Oreochromis mossambicus*) fry	150, 300, 500, 700 and 900	40% crude protein	↑; ↑ increase body protein content	↓	Jayaprakas *et al.* (1996)
GIFT, *Oreochromis niloticus* juveniles	150 and 300	32% crude protein, 4.5% lipid; methionine 2 g kg^{-1} diet; without fishmeal and fishoil	↑; ↑ liver protein content	150 LC: ↓ liver fat and serum TG	Gou *et al.* (2016)
Japanese flounder (*Paralichthys olivaceus*) juveniles	300, 600, 900, 1200 and 1500	45% crude protein, 13% lipid	1200 LC ↑; ↑ muscle protein	1200 and 1500 LC: ↓ liver and muscle fat	Gao *et al.* (2012)
Mrigal (*Cirrhinus mrigala*) fry	250, 500, 750 and 1000	30% crude protein, 6% lipid	250 LC: ↑	↓	Singh *et al.* (2008a)
Turbot (*Scophthatmus maximus* L.)	200, 400, 600, 800, 1000 and 2000	53.53% crude protein, 12.87% lipid; protein source: fish meal	600 LC: ↑	—	Liu *et al.* (2012)
Cobia (*Rachycentron canadum*) juveniles	100, 200	46.5% crude protein, 10.3% lipid	↑	(200 > 100)↓	Zhou *et al.* (2007)
Zebrafish (*Danio rerio*)	400	35% crude protein, 7% lipid	NR	↓ liver and muscle fat	Li *et al.* (2017a)
Red sea bream (*Pagrus major*) fingerlings	4000	50% crude protein, 10% lipid	—	—	Chatzifotis and Takeuchi (1997)
Black sea bream (*Acanthopagrus schlegel*) juveniles	300 and 1000	43% crude protein, 13% lipid; vitamin C 0.5 g kg^{-1} diet, vitamin E 0.2 g kg^{-1} diet; lysine 2 g kg^{-1} diet, methionine 8 g kg^{-1} diet	—	1000 LC: ↓ liver and serum lipid; ↑ liver PUFA	Peng *et al.* (2010)
Hybrid striped bass (*Morone chrysops* ♀ × *M. saxatilis* ♂) juveniles	3000	Lipid levels: 5%, 10%, 15% and 20%; 40% crude protein	—	—	Gaylord and Gatlin (2000)
Hybrid striped bass (*Morone chrysops* ♀ × *M. saxatilis* ♂) juveniles	500 and 1000	Lipid level: 5 and 10%;	—	1000 LC: ↑intraperitoneal fat ratio	

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Table 3 (continued)

Fish species	Dosages of L-carnitine (mg kg^{-1} diet)	Nutrient composition of diets	Growth effect	Change of lipid content of tissues	References
European seabass (*Dicentrarchus labrax*) adults	300, 1100, 2000 and 3000	42% crude protein, 19% lipid (HFD)	—	—	Dias *et al.* (2001)
Largemouth bass (*Micropterus salmoides*) fingerlings	1000	Three protein/lipid ratios: 39.9%/7.4%, 30.3%/13.9% and 21.5%/19.5%; vitamin C 2 g kg^{-1} diet	—	—	Li *et al.* (2010)
Atlantic salmon (*Salmo salar*) juveniles	4.6, 11.5, 23 mmol kg^{-1} diet	37.7% crude protein, 6.67% lipid	— increase body protein	↓ body fat	Ji *et al.* (1996)
Rainbow trout (*Oncorhynchus mykiss*) adults	500 (1)	1.6 mg kg^{-1} chromium picolinate (Cr-Pic) (2) LC+ 1.6 mg kg^{-1} Cr-Pic (3)	—	Diet (1) and (3): ↑ muscle fat	Selcuk *et al.* (2010)
Rainbow trout (*Oncorhynchus mykiss*) juveniles	15, 200 and 530	44% crude protein, 22% lipid	—	200 LC: ↑ EPA content	Ozório *et al.* (2012); Nunes *et al.* (2014)
Rainbow trout (*Oncorhynchus mykiss*) juveniles	15, 200 and 530	Diploid and triploid rainbow trout	—	— 200 LC: ↑ EPA	Rodehutscord (1995)
Rainbow trout (*Oncorhynchus mykiss*) fingerlings	1000, 2000 and 4000	52% crude protein, 5% lipid; 1% vitamin E 10 g kg^{-1} diet	—; ↑ liver protein content	4000 LC: ↑ liver fat	Chatzifotis *et al.* (1997)
	4000	Three lipid levels 5, 10 and 15%; 40% crude protein; vitamin E 10 g kg^{-1} diet	—	NR	
Channel catfish (*Ictalurus punctatus*) fingerlings	1000	30% crude protein; lysine (L-lysine-HCl): 11, 14 and 17 g kg^{-1} diet	—; ↑ body protein content	↓ liver, muscle and body lipid	Burtle and Liu (1994)
African catfish (*Clarias gariepinus*) juveniles	40 and 600	36% crude protein, 8.5 and 16% lipid (HFD)	—	HFD+600 LC: ↓ mesenteric fat ratio; ↓ PUFAs (22:6*n* − 3, 20:5*n* − 3 and 18:2*n* − 6)	Ozório *et al.* (2003)
African catfish (*Clarias gariepinus*) fingerlings	15 and 1000	Two lipid levels:10 and 18%; 34% crude protein, lysine 11.5 g kg^{-1} diet, methionine 3–5 g kg^{-1} diet	—	↓ liver and muscle *n* − 3 PUFA content	Ozório *et al.* (2010)
Hybrid tilapia adults	NR	Low-fish meal and a high lipid level diet	—	↓mesenteric fat ratio	Yang *et al.* (2009)
Nile tilapia (*Oreochromis niloticus*) fry	250, 500, 750 and 1000	40% crude protein, 6% lipid; methionine 0.5 mg kg^{-1} diet, lysine 0.5 mg kg^{-1} diet	—	↓ liver fat	Erdogan *et al.* (2015)
Hybrid tilapia juveniles	DL-carnitine: 200, 400; L-carnitine: 200	36% crude protein, 6.5% lipid	—	↓ liver fat	Du *et al.* (2002)
Caspian roach (*Rutilus rutilus caspicus*) juveniles	500, 1000 and 2000		—; ↓ body protein	2000 LC: ↑ body lipid	Kordi *et al.* (2012)

Table 3 (continued)

Fish species	Dosages of L-carnitine (mg kg^{-1} diet)	Nutrient composition of diets	Growth effect	Change of lipid content of tissues	References
		38.5% crude protein, 14.3% lipid; methionine 15 g kg^{-1} diet, lysine 15 g kg^{-1} diet			
Large yellow croaker (*Pseudosciaena crocea*) adults	800	44% crude protein, 9.5% lipid	—	↓ serum TG and CH levels and serum FFA; ↓ HSI and VSI	Sang *et al.* (2012)
Turbot (*Scophthalmus maximus*) juveniles	40 and 240	40% crude protein, 13% lipid	—	—	Gonçalves *et al.* (2010)
Red porgy (*Pagrus pagrus*, L. 1758) juveniles	630	52% crude protein, 18% lipid	—	—; ↓ $n-6$ PUFA content	Nogueira *et al.* (2010)
Cobia (*Rachycentron canadum*) juveniles	1500	Two lipid levels: 6 and 14% (HFD);45% crude protein	—	HFD + LC: ↓ body and liver fat	Wang *et al.* (2007)

The symbol ↑ indicates increased; ↓, decreased; —, no change; "NR" not mentioned in the references. HFD, high-fat diet; LC, L-carnitine; FFAs, fatty acids; LCFAs, long-chain fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; TG, triglyceride; CH, cholesterol; HSI, hepatosomatic index; VSI, viscera index.

acids β-oxidation-related enzymes had a compensatory response to the change of the carnitine concentrations in tissues. These results show that, L-carnitine promotes the utilization of LCFAs (20–22 carbon atoms) judging from their reduced content in livers of fish fed on L-carnitine supplemented diets.

Previous studies have indicated that the whole body lipid content in fish diminishes as the concentration of L-carnitine increases in the fish diets. Such results have been reported for beluga sturgeon juveniles (Mohseni *et al.* 2008) and rainbow trout (Hajiabadi *et al.* 2009). Moreover, reduced body or tissues' fat have been reported in a number of fish species reared on diets supplemented with L-carnitine, such as Asian catfish (Desai *et al.* 2010), channel catfish (Burtle & Liu 1994), yellow catfish (Zheng *et al.* 2014), juvenile silver perch (Yang *et al.* 2012), adult hybrid tilapia (*Oreochromis niloticus* × *O. aureus*) (Du *et al.* 2002), Atlantic salmon (Ji *et al.* 1996), cobia juvenile (Zhou *et al.* 2007), rainbow trout (Sayedmohammadali *et al.* 2010; Nunes *et al.* 2014; Sharifzadeh *et al.* 2017), adult yellow croaker (*Pseudosciaena crocea*) (Sang *et al.* 2012), tilapia hybrids (*Oreochromis niloticus* × *O. aureus*) (Huang *et al.* 2010), Nile tilapia fry (Gang *et al.* 2010; Guzmán-Guillén *et al.* 2017), adult crucian carp (Zhang 2009), rohu fingerlings (Keshavanath & Renuka 1998), red sea bream fingerlings (Chatzifotis *et al.* 1996), and zebrafish (*Danio rerio*) (Li *et al.* 2017a).

Although some studies show positive effects of dietary L-carnitine supplementation on reducing lipid content mainly by promoting fat acid β-oxidation, others have indicated contradicting results. It has been reported that dietary L-carnitine supplementation increased lipid deposition in the liver and muscle of yellow catfish through changes in lipid metabolism (Zheng *et al.* 2014) and caspian roach (Kordi *et al.* 2012). The increased lipid content in the liver may be attributed to the up-regulation of the mRNA levels of sterol regulatory element-binding proteins (SREBP), peroxisome proliferator-activated receptor gamma (PPARγ), fatty acid synthase (FAS) and Acetyl-CoA carboxylase alpha (ACCα) and the increased activities of lipogenic enzymes (such as FAS, glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase and malic enzyme) and to the down-regulation of the mRNA levels of the lipolytic gene such as peroxisome proliferator-activated receptor alpha (PPARα) and carnitine palmitoyltransferase I A (CPTI A) (Zheng *et al.* 2014). The increased lipid content in muscle may be attributed to the down-regulation of the mRNA levels of the lipolytic genes CPTI A and adipose triglyceride lipase (ATGL) and the increased activity of lipoprotein lipase. Thus, dietary carnitine influences lipid deposition in a tissue-specific mechanism, probably through different lipid metabolic strategies occurring as a result of competitions between lipolysis and lipogenesis

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and between export and import of lipids from different tissues.

Meanwhile, results showed that supplementation of dietary L-carnitine also had no significant changes in carcass lipid content in hybrid striped bass (*Morone chrysops*♀ × *M. saxatilis*♂) (Gaylord & Gatlin 2000), European seabass (Dias *et al.* 2001), hybrid tilapia (*Oreochromis niloticus* × *O. aureus*) (Becker *et al.* 1999), rainbow trout (Rodehutscord 1995) and European seabass (Dias *et al.* 2001). Similarly, Dias *et al.* (2001) showed that neither total plasma triacylglycerols and cholesterol levels nor tissue lipid content were affected by L-carnitine supplementation. The lack of L-carnitine supplemented diets effects has been related to the ability of the formulated diets to provide the optimum energy/protein ratio, especially since the estimate was based, in part, on reduced tissue lipid concentrations (Gaylord & Gatlin 2000) and increase in the activity of acetyl CoA carboxylase suggesting higher rates of lipogenesis in liver (Dias *et al.* 2001).

Although the crucial role of carnitine in cellular metabolism is to control the influx of LCFAs into the mitochondria for β-oxidation, the underlying mechanism responsible for the effects of dietary carnitine on lipid metabolism is still poorly defined in fish. Variations may be due to different fat sources (Lu *et al.* 2014) and doses L-carnitine used in the diets (Chatzifotis & Takeuchi 1997; Harpaz *et al.* 1999; Yu *et al.* 2008; Ozório 2009; Li *et al.* 2010; Selcuk *et al.* 2010; Xu 2011; Makrecka *et al.* 2014; Zheng *et al.* 2014). Therefore, interactions among these factors probably affect the influence of dietary L-carnitine on modulating fish body fat. It has been hypothesized that, all interactions may regulate the role of dietary L-carnitine in lipid metabolism by influencing the activity of enzymes involved in the process of fatty acid β-oxidation, especially carnitine acyltransferase (CPT) (Chatzifotis & Takeuchi 1997; Lavarias *et al.* 2009; Yang *et al.* 2009, 2012; Dong *et al.* 2014; Zheng *et al.* 2014).

In a nutshell, oxidation of fat provides the highest and most cost-effective energy yield per unit weight of dietary ingredients consumed and metabolized. Dietary L-carnitine promotes fat oxidation and, therefore its addition into the diet for fish presumably results into enhancement of protein-sparing effect and thus lead to better growth on fish fed with diets containing low levels of protein. However, results obtained in lipid metabolism in fish are still contrasting. The inconsistent results may be caused by many factors, such as fish species tested, tissue-specificity effects of dietary L-carnitine content and its doses, different growth stages and dietary nutrients composition.

Effects of L-carnitine on carbohydrate metabolism

Fish have been considered as natural "diabetic" (Harpaz 2005). Glucose metabolism continues to be an agonistic area in many fish species not only in carnivorous species but also in herbivorous and omnivorous species (Polakof *et al.* 2012). Compared with mammals, fish have lower abilities to utilize carbohydrates as energy sources, thus fish cannot use glucose efficiently to produce energy (Kohara *et al.* 2014; Kamalam *et al.* 2017). Nevertheless, carbohydrate is an extensive energy resource for fish and glucose metabolism is essential for specific tissues and/or activities (Polakof *et al.* 2012). Studies in animal models have shown that L-carnitine supplementation improved recovery of ischaemic non-diabetic rats by stimulating both glycolysis during ischaemia and glucose oxidation during reperfusion (Broderick *et al.* 1995a; Al-Odat *et al.* 2015). Carnitine also improved glucose disposal in type 2 diabetic and obese patients (Molfino *et al.* 2010; Galloway *et al.* 2011). L-carnitine administration improved markedly the insulin sensitivity and increased promptly glucose oxidation as fuel (Molfino *et al.* 2010; Galloway *et al.* 2011; Kranenburg *et al.* 2014). The ability of carnitine to improve glucose oxidation is due to an increase in the activity of pyruvate dehydrogenase (PDH), which is depressed in insulin resistant status (Mingrone *et al.* 1999; Kranenburg *et al.* 2014). PDH is a multienzyme complex, which converts pyruvate into acetyl-CoA within the mitochondria, thus, its activity is influenced by the concentration of acetyl-CoA. Carnitine stimulates the export of acetyl groups out of the mitochondria, thus decreases the ratio of acetyl-CoA/CoA and thereby activates PDH, resulting in an increased glucose oxidation (Fig. 2).

In recent years, L-carnitine has attracted the interest of many aquaculture nutritionists due to its potential positive effects on carbohydrate metabolism in fish. Some scientists have found that dietary L-carnitine supplementation regulates carbohydrate metabolism by affecting blood glucose and glycogen content in various tissues (Sharifzadeh *et al.* 2017; Li *et al.* 2018). L-carnitine, as a carrier of LCFAs transporter to the mitochondrial inner membrane, participates in the energy metabolism of fish and maintains normal acetyl-CoA/CoA ratio in mitochondria (Zhang *et al.* 2008). Concurrently, L-carnitine helps to transport ATP out of the mitochondrial inner membrane and regulates gluconeogenesis, glycolysis and ketogenic processes (Felix *et al.* 2001; Ozório 2009; Xu *et al.* 2014). In general, although blood glucose concentration of fish is in a dynamic equilibrium due to the regulation by the nervous and endocrine systems, but it is quite easy to change (Imsland *et al.* 2001). Results in fish have shown that supplementing diets with different levels of L-carnitine increased the plasma glucose concentration in Japanese flounder (*Paralichthys olivaceus*) (Gao *et al.* 2012), common carp (Sabzi *et al.* 2017) and silver perch (Yang *et al.* 2012). In addition, dietary L-carnitine supplementation also increased the activities of PC and glycogen production in

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liver of Atlantic salmon (Ji *et al.* 1996). Similarly, L-carnitine supplementation reduced the utilization of glucose and increased glycogen deposition in zebrafish (Li *et al.* 2017b). In the same study, L-carnitine supplementation increased and decreased the mRNA expressions of gluconeogenesis-related and glycolysis-related genes, respectively (Li *et al.* 2017b). On the contrary, the low-carnitine zebrafish decreased whole body glycogen content, increased glucose metabolism rate and up-regulated the expression of glucose uptake and glycolysis genes (Li *et al.* 2018).

Currently, the mechanism for glucose metabolism after L-carnitine supplementation in fish is not yet clear. However, it is plausible to suggest that the decrease in glucose utilization after L-carnitine supplementation in fish is a mechanism to counteract the increase in fatty acids β-oxidation coupled with reduced acyl-CoA concentration in tissues (Perry & Shulman 2018; Perry *et al.* 2018). During energy homeostasis, the endogenous acetyl-CoA concentration in fish is relatively stable (Li *et al.* 2017b). L-carnitine supplementation promotes the oxidation of fatty acids to produce more acetyl-CoA, ATP and $NADH^+$, which depress the glycolysis pathway (reduce the activities of PDH), thus the acetyl-CoA sourced from other nutrients, especially glucose, decreases correspondingly. Moreover, acetyl-CoA, ATP and $NADH^+$ can be used as the raw materials to reinforce gluconeogenesis, eventually resulting into increased blood glucose level and even tissues' glycogen content. Therefore, it seems that L-carnitine modulates acetyl-CoA/CoA ratio, affects carbohydrate and lipid catabolism and the rate of the Krebs cycle in fish. Thus, carnitine-enhanced lipid catabolism decreases the energy portion sourced from glucose degradation and increases the concentrations of metabolic intermediates, resulting into increased gluconeogenesis and glycogen synthesis in fish (Fig. 2), which is different from that in mammals. However, detailed regulation mechanism of carnitine supplementation on glucose metabolism in fish remains to be determined.

Effects of L-carnitine on protein metabolism

One of the benefits associated with the addition of L-carnitine in fish diets is to increase energy supply from lipid catabolism and "save" protein for energy production (Santulli *et al.* 1990; Ozório *et al.* 2003; Harpaz 2005; Ozório 2009; Chen *et al.* 2011; Yang *et al.* 2012). A number of studies have indicated that dietary L-carnitine reduces lipid content and increases protein content in different fish species, or decreases protein catabolism in tissues and/or whole body, showing a significant protein-sparing effect (Santulli & D'Amelio 1986; Burtle & Liu 1994; Ji *et al.* 1996; Ozório *et al.* 2003). However, the lack of research on protein metabolic pathways in fish makes the relevant mechanisms of dietary L-carnitine supplementation less clear (Azab *et al.* 2002; Gonçalves *et al.* 2010; Li *et al.* 2010; Indiveri *et al.* 2011).

It has been indicated that dietary L-carnitine supplementation increases whole body protein content of fish (Burtle & Liu 1994; Jayaprakas *et al.* 1996; Hajiabadi *et al.* 2009; Sharifzadeh *et al.* 2017), muscles (Zhang 2009; Gao *et al.* 2012; Dong *et al.* 2014; Zheng *et al.* 2014; Novakova *et al.* 2016) and both in whole body and muscles (Gang *et al.* 2010). Also, studies conducted in crucian carp supplemented with L-carnitine showed a significant increase in essential amino acids contents in muscle (Azab *et al.* 2002; Zhang 2009). Indeed, in Atlantic salmon, dietary L-carnitine supplementation increased amino acids concentrations in plasma and liver, especially the three BCAAs, including leucine, isoleucine and valine, and enhanced the protein synthesis capacity, accompanied by the accumulation of protein in muscles (Ji *et al.* 1996). Thus, it is reasonable to suggest that, improved growth performance after L-carnitine supplementation is partly attributed to the increased protein content because growth performance increases as the amount of protein in the diet increases for many fish species.

The increased protein after L-carnitine supplementation maybe attributed to the reduction in the synthesis of endogenous carnitine, which saves *in vivo* methionine and lysine utilization (Fig. 2) and avoids the loss of other amino acids due to imbalance ratio thereby improving their utilization rates (Huan *et al.* 2009; Stålej *et al.* 2010; Dong *et al.* 2014). At the same time, carnitine also enhances the oxidation of fatty acids, which reduces the use of protein for energy supply, and ultimately promote protein deposition (Yu *et al.* 2008; Zhang 2009). In addition to the stimulation of fatty acid oxidation, dietary carnitine might increase carbon flux through PC and decrease branched-chain α-keto acid dehydrogenase complex (BCKDH) by increasing regulatory ratios of acetyl-CoA/CoA and ATP/ADP (Klingenberg 2008; Zhang *et al.* 2008; Ozório 2009). With these changes, L-carnitine treatment can conserve nitrogen by providing more carbon for amino acid biosynthesis, which may block oxidative loss of the BCAAs. Thus, carnitine increases nitrogen savings in the body to spare the utilization of protein and improve growth performance (Fig. 2).

Moreover, it has been reported that dietary L-carnitine supplementation increased the whole body protein content and the hepatic mRNA expression of mammalian target of rapamycin (mTOR) in zebrafish (Li *et al.* 2017a), which is one of the most important regulators of protein synthesis (Wang & Proud 2006). In rainbow trout, L-carnitine affected the expression of mTOR by increasing leucine concentration (Lansard *et al.* 2011). These evidences indicate that dietary L-carnitine supplementation might improve the mRNA expression of mTOR by increasing the leucine

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concentration, which have positive effects on protein synthesis in fish. Therefore, it is reasonable to suggest that L-carnitine-enhanced lipid catabolism is likely to promote protein synthesis by increasing BCAAs which activates mTOR signalling (Fig. 2).

Effects of L-carnitine on nutrients metabolism on crustaceans

Data regarding the effects of L-carnitine on nutrient metabolism on crustaceans are scanty compared to fish, although it has been studied for many years on aquatic animals (Table 4). Results from a few studies conducted indicate that, L-carnitine is an essential nutrient for fatty acids β-oxidation in crustaceans similar to results obtained in fish. Thus, to a certain extent, dietary L-carnitine accelerates the utilization of lipids, alters body composition and regulates growth in crustaceans (Lavarias *et al.* 2009; Safari *et al.* 2015). Moreover, dietary L-carnitine also plays a vital role in crustaceans by regulating mitochondrial acyl-CoA/CoA ratio. Accordingly, it affects the activity of PDH, promotes or inhibits ATP production and regulates energy metabolism (Cai *et al.* 2001; Zhou & Yang 2011).

Results on dietary L-carnitine supplementation in crustaceans have also revealed conflicting results similar to those obtained in fish. L-carnitine supplementation increased growth performance in white prawn (*Penaeus indicus*) (Jayaprakas *et al.* 1996), freshwater prawn (*Macrobrachium rosenbergii*) and Chinese shrimp (*Penaeus chinensis*) (Liu & Zhu 2001) and freshwater prawn post-larvae (Singh *et al.* 2008b). Similarly, dietary L-carnitine supplementation improved survival rate and weight gain, increased feed efficiency and promoted production of good quality Crustacea Palaemonidae (*Macrobrachium borellii*) for sale (Lavarias *et al.* 2009). However, some studies have shown that supplementing crustaceans' diets with dietary L-carnitine have no significant effects on growth and feed utilization of Kuruma prawn (*Marsupenaeus japonicus*) (Yagcioglu & Aktas 2006), juvenile narrow clawed crayfish (Safari *et al.* 2015), tiger shrimp (*Penaeus monodon*) and Pacific white shrimp (*Litopenaeus vannamei*) (Zhou *et al.*, 2004). Moreover, Zhou and Zheng (2004) found that adding dietary L-carnitine at 300 mg kg^{-1} diet in tiger shrimp and 200 to 300 mg kg^{-1} diet in Pacific white shrimp reduced shrimp body fat content.

A few studies have been conducted in shrimps to investigate the effect of dietary L-carnitine supplementation on reducing body fat content and modifying body composition in order to spare protein. However, results obtained are not consistent with those obtained in fish (Cai *et al.*

Table 4 Effect of L-carnitine supplementation on growth performance and lipid content in cultured crustaceans

Crustaceans species	Dosages of L-carnitine (mg kg^{-1} diet)	Nutrient composition of diets	Growth effect	Change of lipid content of tissues	References
Pacific white shrimp (*Litopenaeus vannamei*)	100	40% crude protein, 8% lipid	—	NR	Zhou *et al.* (2017)
	100	42% crude protein, 4% lipid	↑	NR	Cai *et al.* (2001)
	50, 100, 200 and 300	43% crude protein, 6.5% lipid	—	200 and 300 LC: ↓ whole body fat	Zhou and Zheng (2004)
White prawn, (*Penaeus indicus*)	100, 250, 500, 750, 1000 ppm	40% crude protein, 9% lipid	↑500 LC: ↑ whole body protein content	↓ whole body fat	Jayaprakas *et al.* (1996)
Tiger shrimp (*Penaeus monodon*)	50, 100 and 200	40% crude protein, 6.5% lipid	↑ muscle inosine monophosphate content	NR	Wu *et al.* (2008)
	100, 200 and 300	43% crude protein, 6.5% lipid	—	300 LC: ↓ whole body fat	Zhou and Zheng (2004)
Freshwater prawn (*Macrobrachium rosenbergii*) larvae	250, 500, 750 and 1000	38% crude protein, 9% lipid	500 LC: ↑; 500 LC: ↑ whole body protein	↓ whole body fat	Singh *et al.* (2008b)
Freshwater prawn (*Macrobrachium rosenbergii*)	100	NR	↑	NR	Liu *et al.* (1998)
	100 and 200	NR	—	—	Zhou and Yang (2011)
Kuruma prawn (*Marsupenaeus japonicus*) juveniles	300, 600 and 1200	40% crude protein, 12.5% lipid	—; 300 and 600 LC: ↑ muscle protein	300 and 600 LC: ↓ muscle fat	Yagcioglu and Aktas (2006)
Chinese shrimp (*Penaeus chinensis*)	100	NR	↑	NR	Liu and Zhu (2001)

The symbol ↑ indicates increased; ↓, decreased; —, no change; "NR" not mentioned in the references. LC, L-carnitine.

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2001). A study conducted by Zhou and Yang (2011) found that adding L-carnitine at a concentration of 100 mg kg^{-1} or 200 mg kg^{-1} in freshwater prawn diets, did not affect crude fat and crude protein contents both in the whole body and muscle. In Chinese mitten crab (*Eriocheir sinensis*), L-carnitine has been indicated as a possible solution to the precocious maturity experienced in this species similar to its role in mammals. It is postulated that the use of L-carnitine could reduce precocious maturity which diverts energy towards reproduction and promote growth of the crab (Indiveri *et al.* 2011).

In summary, research on dietary L-carnitine application in crustaceans at the moment is neither in-depth nor widely covered. Despite the limited studies conducted, it is clear that, the effect of dietary L-carnitine in crustacean nutrients metabolism and energy utilization is awaiting further research to unveil the contradicting results.

The interactions among L-carnitine, feed composition, metabolism and fish growth

The role of dietary L-carnitine on fish nutrient metabolism ultimately is reflected in fish growth performance and nutrients utilization, yet there are still discrepancies in the results obtained. Numerous studies have shown that factors influencing the effects of dietary L-carnitine supplementation are multifaceted, including feed composition such as lipid or protein levels, (Torreele *et al.* 1993; Gaylord & Gatlin 2000; Wang *et al.* 2005a; Xu 2011) and methionine and lysine contents (Chatzifotis *et al.* 1996; Chen *et al.* 2011). We schematically represent the possible nutritional factors that might affect carnitine effects on nutritional metabolism and growth performance in fish (Fig. 2). Obviously, the body carnitine pool is influenced by the nutritional status. For example, carnitine requirement varies in fish depending on feed composition and energy demands. It has been indicated that, an increasing energy demand increases carnitine requirement (Ozório 2009). Since ectothermic fish are prone to temporal shifts in energy demand in their whole life-cycle, they must be able to regulate most of their physiological processes and maximize performance. It is more likely that under certain situations, when the energy demands have changed, endogenous carnitine synthesis may not be sufficient. Ozório *et al.* (2005) observed a mismatch between carnitine requirement for energy fuelling and carnitine present in African catfish body pool subjected to a swimming burst. Therefore, it is necessary to determine factors responsible for modulating carnitine requirements in fish as discussed in the following section. We expect that, the interactions among L-carnitine, feed composition, metabolism and growth open our understanding on the roles of carnitine in fish.

Diet macronutrients composition

Changes in carnitine requirement are correlated with changes in nutritional status. In humans, plasma carnitine concentration is higher after a high-fat or high-protein diet (Stadler *et al.* 1993). Dietary protein and lipid contents have been shown to affect L-carnitine effects in vertebrates. L-carnitine supplementation was effective in improving body weight (Kita *et al.* 2002) and overall performance (Khadem *et al.* 2006) when proper protein content was provided in chickens. In Nile tilapia, the protein contents in whole body and muscles increased with increasing dietary L-carnitine levels while lipid contents in whole body, muscles and liver decreased (Gang *et al.* 2010). These results demonstrated that L-carnitine supplementation at different protein levels can help improve utilization of fats from the diets, which promotes protein deposition and protein-sparing effect.

Similar to protein levels, L-carnitine supplementation at different levels of lipid in terrestrial animals (Heo *et al.* 2000; Greenwood *et al.* 2001) and fish (Gaylord & Gatlin 2000; Ozório *et al.* 2003) increased plasma and tissue carnitine concentrations as dietary carnitine and dietary fat increased. Moreover, dietary L-carnitine supplementation increased muscle protein content at high lipid level in Nile tilapia (Chatzifotis *et al.* 1995, 1996). Dietary low and high L-carnitine levels improved growth performance of African catfish at low and high lipid levels, respectively (Torreele *et al.* 1993).

Taken together, these results support the idea that, L-carnitine requirement is influenced by dietary compositions. To elucidate in more detail the effect of L-carnitine in fish, future studies are required to assess effects of carbohydrate levels and other nutrients interactions.

Dietary methionine and lysine contents and the vitamin C level

Lysine plays an important role as an essential amino acid and also in carnitine biosynthesis. Lysine content in diets, as one of the precursors of L-carnitine directly affects its synthesis. L-carnitine supplementation in fish diets reduces the use of methionine and lysine as raw materials during L-carnitine synthesis, thereby releasing more methionine and lysine for protein production. Consequently, this lowers requirements for dietary protein and increase body protein content in fish. Several studies have examined the effects of L-carnitine on growth and tissue composition of fish at varying levels of dietary lysine. Burtle and Liu (1994) found that, although carnitine did not cause any clear effect on growth rate in channel catfish, carnitine in combination with lysine reduced visceral fat and whole body lipid content and whole body protein content. Dietary L-carnitine supplementation at high lysine level improved growth and decreased the whole body fat and total LCFAs in tissues in

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Nile tilapia (Soltan *et al.* 2010) and red sea bream (Chatzifotis *et al.* 1996).

Currently, limited studies have been conducted on interactions between methionine and L-carnitine supplementation in fish. The administration of L-carnitine along with methionine improved growth (Kamalam *et al.* 2017; Keramat & Abolfazli 2017) and muscles composition (Keramat & Abolfazli 2017) in rainbow trout. Furthermore, dietary L-carnitine, lysine and methionine supplementation at various levels improved growth and feed utilization, protein content in tissues and survival rates and decreased fat content in Nile tilapia (Soltan *et al.* 2010). The improved growth is related to lysine-sparing effect of carnitine on transport across membranes.

Carnitine biosynthesis does not only need lysine and methionine, but also vitamin C. Thus, the use of both L-carnitine and vitamin C may improve the effects of L-carnitine. Sharifzadeh *et al.* (2017) reported that using vitamin C 500 and L-carnitine 800 mg kg^{-1} diet caused some improvement in growth performance. In addition, they also found that the level of 500/800 vitamin C/L-carnitine had a significant decrease in cholesterol and glucose in blood, and an increase in protein content. Therefore, to a certain extent, vitamin C as an important nutrient required during carnitine synthesis influences the role of carnitine in fish.

Therefore, the effects of L-carnitine on nutrients metabolism in fish is affected by lysine and vitamin C contents in the diets. Future studies should explore the mechanism of dietary L-carnitine on the fish nutrient metabolism by considering other important nutrients required in its synthesis such vitamin B6 and niacin.

Future research strategies on nutritional physiology and application of L-carnitine in aquatic animals

In recent years, extensive studies have been conducted on the application of dietary L-carnitine, as one of the essential nutrients in lipid metabolism in livestock mammals and rodents. In these animals, the mechanisms of actions behind dietary L-carnitine metabolism in nutrition are well established. However, researches on dietary L-carnitine nutrients metabolism in aquatic animals are very limited. Accordingly, there are still several aspects on dietary L-carnitine in aquatic animals' nutrients metabolism which need further studies as indicated in this section.

Mechanism of L-carnitine regulation on energy metabolism in aquatic animals

Fish as ectotherm organisms have different metabolism mechanisms compared with mammals, like rats, pigs and humans. Compared to mammals, most studies conducted on nutrients metabolism in fish show that fish have lower ability to utilize carbohydrates as energy sources (Chatzifotis *et al.* 1996; Chatzifotis & Takeuchi 1997; Becker *et al.* 1999; Gaylord & Gatlin 2000; Knapp *et al.* 2008; Ringseis *et al.* 2009; Indiveri *et al.* 2011; Yang *et al.* 2012; Ying *et al.* 2013; Zheng *et al.* 2014; Skiba-Cassy *et al.* 2016). This is partly because fish are natural "diabetics" and have low ability to utilize glucose for energy production, which is possibly related to metabolic characteristics (Wilson 1994). Consequently, it is necessary to carry out systemic studies on metabolic regulation mechanisms and functions of L-carnitine in energy metabolism from aquatic animals' perspective.

Presently, the nutritional physiology studies on dietary L-carnitine in aquatic animals focus on using growth and body composition as primary response indicators. The regulatory effects of L-carnitine in aquatic animals' energy metabolism system have not been systemically studied. This approach, not only makes harder for aquatic researchers to realize the functions of L-carnitine, but also hinders effective application of dietary L-carnitine in aquatic animals. Subsequently, in order to carry out systemic metabolic regulation exploration on the process and mechanism of dietary L-carnitine supplementation in aquatic animals, future studies should use the results obtained in mammals to investigate the nutrition metabolic mechanisms in aquatic animals by considering their peculiar characteristics.

The relationship between L-carnitine supplementation and carbohydrate levels in fish is fascinating considering their inability to use glucose effectively for energy production. Most studies conducted in fish have indicated that, the activities of many glucose metabolism-related key enzymes such as glucose kinase (GK), phosphofructokinase (PFK) and pyruvate kinase (PK) are not sensitive to the increased dietary carbohydrate content (Tranulis *et al.* 1991; Wilson 1994; Moon & Foster 1995; Polakof *et al.* 2012) compared with mammals (Felix *et al.* 2001; Xi *et al.* 2008; Marcovina *et al.* 2013; Zhang *et al.* 2014). In many fish species, high dietary carbohydrate induces lower growth, excess lipid deposition and decreased stress resistance (Rawles & Gatlin 1998; Kumar *et al.* 2005; Zhou *et al.* 2014). Evidences indicate that increasing lipid catabolism decreases the energy portion sourced from glucose degradation, resulting into increased gluconeogenesis and glycogen synthesis in fish (Ji *et al.* 1996). Reasonably, during energy homeostasis in fish, the endogenous acetyl-CoA concentration is relatively stable such that, the increased lipid catabolism produces more acetyl-CoA for energy production, correspondingly, the portion of the acetyl-CoA sourced from other nutrients, such as glucose, decreases (Li *et al.* 2017a). Moreover, in few fish species, it has been demonstrated that dietary L-carnitine plays

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significant roles in "protein sparing effect" by increasing the BCAAs content in tissues, such as leucine, isoleucine and valine, which effectively affect mTOR signalling (Ji *et al.* 1996; Lansard *et al.* 2011). Therefore, future studies should target different routes to promote carbohydrate/glucose utilization, including exploring the interactions between lipid and carbohydrate metabolism, or exploring the regulatory mechanisms of L-carnitine in protein/amino acids metabolism at different levels. In this way, an in-depth knowledge of dietary L-carnitine mechanisms on biological and functions in systemic energy metabolism in aquatic animals will be acquired. Additionally, this can also provide a solid foundation for research and application of L-carnitine in aquatic animals.

Nutritional regulation of L-carnitine in different fish species

Variations in species and feeding habits have an impact on the effect of dietary L-carnitine on whole body lipid content in fish. Moreover, the concentration of L-carnitine varies in different fish species and tissues (Table 1), which may affect the dosage of L-carnitine supplementation, and its effects on fish. It has been showed that the effects of dietary L-carnitine supplementation in salt water, omnivorous and carnivorous fishes are often more obvious than those obtained in freshwater and herbivorous fishes (Santulli *et al.* 1990; Chatzifotis & Takeuchi 1997; Harpaz *et al.* 1999; Zhang *et al.* 2008; Huan *et al.* 2009; Ozório 2009; Gonçalves *et al.* 2010; Skiba-Cassy *et al.* 2016). Previous studies have indicated that, supplementing diets with the same concentrations of L-carnitine produces different results depending on fish species. This is mainly due to variations in the L-carnitine-dependent lipolytic enzymes activities (mainly CPT) in fish tissues (Dong *et al.* 2014; Zheng *et al.* 2014). Therefore, future studies should combine the functions of energetic metabolism regulators and key enzymes used in metabolic pathways to obtain a better understanding on the interactions among CPT-I, CPT-II, acetyl-carnitine activity and L-carnitine. Presumably, this might be the key reason to explain the controversial results obtained on dietary L-carnitine supplementation in different studies using various fish species.

In addition to combining different energy approaches, methodological improvements are also deemed necessary in order to promote more understanding in L-carnitine research. The use of omics technologies has improved understanding on nutritional metabolism in aquatic animals. A number of researchers have applied transcriptomics (Chen *et al.* 2015a, 2015b; He *et al.* 2015; Ning *et al.* 2016; Liu *et al.* 2018), proteomics (Pei 2010; Chang *et al.* 2017), lipidomics (Hyötyläinen *et al.* 2013; Chen *et al.* 2014) and metabolomics (He *et al.* 2011; Nie & Zhang 2011; Rezzi *et al.* 2013; Sotton *et al.* 2017) in exploring biological characteristics and metabolic regulation pathways in nutritional metabolism in animals. Therefore, these technologies should also be applied to explore the effect and mechanism of dietary L-carnitine on nutritional metabolism in different fish species to explain the controversial results. Besides, pharmacological activation or repression on metabolic sensors by specific activators or inhibitors *in vivo* and *in vitro* is required in future studies involving L-carnitine.

Nutritional functions of L-carnitine in different physiological stages in fish of the same species

Juvenile fishes often have deficiency in L-carnitine because their mechanism for synthesizing it during such a young stage is not well developed. Generally speaking, the amount of L-carnitine synthesized in adult fish can meet the needs for body metabolism. However, adult fish can still be L-carnitine deficient under certain conditions. L-carnitine deficiency may lead to fish body lipid metabolism disorders and other metabolic abnormalities (Kelley *et al.* 1995; Gonçalves *et al.* 2010). Many studies have shown that supplementing L-carnitine in diets exhibits a positive growth-enhancing effect in fry or juvenile fishes. It is well known that, weight gain decreases as individual fish size increases (Musser *et al.* 1999; Dong *et al.* 2006; Yu *et al.* 2008; Huan *et al.* 2009; Zheng *et al.* 2014). This may explain the different results obtained on the effect of dietary L-carnitine supplementation on growth using different sizes of fish in various experiments. However, strong evidences are still lacking to support this observation. Therefore, further studies on growth and metabolism-related genes expressions are needed in order to scrutinize the role of dietary L-carnitine supplementation on growth and lipid metabolism in aquatic animals at different physiological stages. This could lead to better understand the functions and applications of dietary L-carnitine in the whole culture period of a given aquatic animal species.

Effect of dietary composition on L-carnitine nutritional regulation

Currently, some fish nutritionists believe that dietary L-carnitine as a feed additive can achieve protein-sparing effect, promote growth and improve products quality mainly through two mechanisms: 1) saving the use of methionine and lysine as precursors of L-carnitine synthesis; and 2) increasing fatty acid oxidation to efficiently supply energy (Ji *et al.* 1996; Levine *et al.* 2003; Huan *et al.* 2009). However, only a few studies have explored whether these effects would be affected by the corresponding feed ingredients composition. This is likely to be the primary reason for the

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contradicting results obtained in many studies conducted on dietary L-carnitine in aquatic animals.

Although some studies have considered dietary L- carnitine effects accompanied by the content of lysine, vitamin C, protein and lipid levels in the diets in aquatic animals, many other ingredients and the interaction effects have not been studied intensively. For example, fishmeal and fish oils are dominant ingredients in aquafeeds, which supply essential amino acids (lysine and methionine) and fatty acids (eicosapentanoic acid (EPA) and docosahexanoic acid (DHA)) that are deficient in plant proteins and vegetable oils (Hardy *et al.* 2010; Jackson & Shepherd 2010). Besides, fishmeal contains 10 to 20 times more carnitine than plant-based feedstuffs. However, the supply of fishmeal and fish oils has stagnated for several decades, which will eventually not be enough to support the increasing demand for animal diets. Plant protein sources (e.g. soybean meal, cereal by-products and legumes) have been tested during the past decade as fishmeal replacement for several aquatic species (Oliva-Teles *et al.* 2015; Huang *et al.* 2018). However, replacing fishmeal and fish oils in fish feeds with plant-based sources might trigger lack of lysine, methionine and carnitine, which may influence the effect of L-carnitine on fish nutrient metabolism. Consequently, future studies on dietary L-carnitine nutritional functions should focus on the modulatory effects of different sources in aquatic animal diets, including protein, fatty acids and amino acids, vitamin C content, lipid level and other important nutritional factors. This is necessary in order to determine the appropriate amount of dietary L-carnitine added in diverse aquatic diets formulations that would provide its desired physiological nutritional functions under changing dietary formulations.

Effects of L-carnitine on stress resistance in fish through nutrient metabolism regulation

Immunity reactions and resistance to environmental stress have been verified as energy-consuming processes in mammals (Buttgereit *et al.* 2000; Calvo & Mootha 2010; Nunnari & Suomalainen 2012). The high stocking densities, large amounts of supplied feeds and release of high levels of metabolites in intensive fish culture systems often occur in parallel with rapid deterioration of water quality parameters, which can have a negative influence on aquatic animal health. Under such conditions, bacterial infections and ammonia toxicity are known to be common stressors in fish production. Nevertheless, it have been observed that lipid accumulation-related metabolic dysfunctions may induce these stress responses in fish (Jin *et al.* 2013). As stated before, besides having a growth enhancing function, by facilitating lipid utilization as energy source, L-carnitine seems to provide protection of fish against water quality-induced stress (Harpaz *et al.* 1999). It also increases immunocompetence against several bacterial disease and ammonia toxicity (Santulli & D'Amelio 1986; Kloiber *et al.* 1988; Tremblay & Bradley 1992; Schreiber *et al.* 1997; Schlechtriem *et al.* 2004). In any of those cases, feeding carnitine supplements may enhance the ability of cultured fishes to better cope with biotic and abiotic variations, boosting their performance, while enhancing their resistance to disease outbreak.

Recently, dietary L-carnitine has been reported to decrease lipid content in zebrafish tissues, accompanied by decreased and increased pro-inflammatory factor (TNF-α) and anti-inflammatory factor (TGF-β1) mRNA expressions, respectively in muscle, which suggest that enhanced lipid catabolism may decrease inflammation response in order to improve immunity (Li *et al.* 2017a). Furthermore, Nile tilapia fed mildronate, an inhibitor of L-carnitine biosynthesis by γ-butyrobetaine hydroxylase (BBH), had lower survival rate when exposed to *Aeromonas hydrophila* and ammonia nitrogen (Pan *et al.* 2017). This study further showed that, the fish with lower L-carnitine had reduced mitochondrial fatty acid β-oxidation efficiency, which increased liver lipid accumulation. Moreover, low-carnitine fish had decreased immune enzymes activities and anti-inflammatory cytokine genes expressions, accompanied with higher pro-inflammatory cytokine genes expressions. Previously, supplementing dietary L-carnitine in turbot (*Psetta maxima*) exposed acutely to *Streptococcus parauberis* increased the survival rate of fish (Dias *et al.* 2011). Meanwhile, L –carnitine elevated enzymatic antioxidants in tissues in black sea bream (Ma *et al.* 2008), tilapia (GIFT) strain (Gou *et al.* 2016) and common carp (Sabzi *et al.* 2017). Likewise, L–carnitine reduced the contents of lipid peroxidation products in black sea bream (Ma *et al.* 2008) and common carp (Sabzi *et al.* 2017). The mechanisms for decreased lipid peroxidation after L-carnitine supplementation is related to its ability to reduce fat content in tissues by enhancing fatty acids oxidation, which in turn improves antioxidant ability that enhances immunity and improves resistance to bacterial infection (Dias *et al.* 2011; Gou *et al.* 2016). L-carnitine also protected fish against ammonia toxicity in chinook salmon (*Oncorhynchus tschawytscha*) (Tremblay & Bradley 1992) and it decreased plasma ammonia content in tilapia (Yang *et al.* 2009). It is more likely that, L-carnitine provided ammonia toxicity protection by stimulating fatty acid oxidation, which increase energy flux through lipid catabolism and decrease flux through protein utilization.

All these results suggest a protective effect of dietary carnitine supplementation from biotic and abiotic stressors by affecting lipid and protein metabolism. Although the mechanisms of L-carnitine metabolism in immune functions have not been studied extensively in fish, the anti-

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inflammatory effects of L-carnitine and its ability to improve fatty acids β-oxidation, may be a promising strategy to increase stress resistance in fish. Therefore, we propose a hypothesis that, dietary L-carnitine increases the utilization of lipid for energy production and reduces breakdown of amino acids, which depress body lipid peroxidation and promote protein synthesis by inducing less ammonia excretion. Thus, L-carnitine affects stress resistance in fish through nutrient metabolism regulation. However, this hypothesis needs to be verified by further studies on interactions of abiotic and biotic stresses by using *in vivo* and *in vitro* experiments.

Conclusions

Taken together, dietary L-carnitine supplementation in aquatic animal nutrition holds promising results on regulating growth rate to reduce feed efficiency, reducing body fat to improve fillet quality and modulating energy metabolism to provide a protein-sparing effect. However, such dietary L-carnitine nutritional effects in aquatic animals remain controversial in different species. Future studies should explore the effects of dietary L-carnitine supplementation on aquatic animals depending on species, different growth stages, L-carnitine content in diets, water quality parameters and dietary nutritional composition.

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