APPLICATION OF L-CARNITINE AS NUTRITIONAL SUPPLEMENT IN VETERINARY MEDICINE

EZZATOLLAH FATHI[1], RAHELEH FARAHZADI[2,*]

[1] *Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz, Tabriz-Iran*
[2,*] *Young Researchers Elite Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran*

(Received December 18, 2013)

The aim of this review was to investigate the application of L-carnitine in veterinary medicine. Carnitine is a vitamin-like substance that plays an important role in energy and fatty acid metabolism. Its major role appears to be the transport of long-chain fatty acids into mitochondria for oxidation. This compound is found in virtually all cells of higher animals and also in some microorganisms and plants. Clinical application of carnitine holds much promise in a number of disorders, such as diabetes, sepsis, cardiomyopathy, malnutrition, cirrhosis, endocrine disorders, aging and disorders such as Alzheimer's disease, hepatic encephalopathy and other painful neuropathies. Evidence from both animal and human studies supports health-related benefits when used as a therapeutic agent.

Keywords: acetyl-L-carnitine, antioxidant, L-carnitine, oxidative stress.

HISTORY OF CARNITINE

The term “carnitine” is derived from the Latin word “caro”, which means meat. Carnitine was discovered in animal meat in 1905, by Gulewitsch and Krimberg, and it was initially called vitamin BT (1). Its chemical structure was described in 1927, but as late as in 1955, Friedmann and Fraenkel found the basic role of carnitine in the beta-oxidation of fat. Intensive research into carnitine was performed in the 1970s; only a very small amount of L-carnitine (the biologically active stereoisomer) obtained from animal meat was available at that time (2). In the 1980s, the industrial production of L-carnitine was launched, which allowed significant expansion of research, making it possible to think about its use in clinical practice. L-carnitine was shown to have beneficial effects on the heart and

* Corresponding author (Email: r.farahzadi@iaut.ac.ir; Tel: +98-411-3320192; Young Researchers Elite Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran).

skeletal muscles as well as various conditions, such as disorders of the central nervous system, certain types of male sterility and some disorders in newborns (2).

BIOSYNTHESIS AND METABOLISM OF CARNITINE

Carnitine is a vitamin-like substance that is structurally similar to amino acids. Biochemically, it is a small water-soluble quaterner amine (β-hydroxy γ-trimethylaminobutyrate) with a molecular weight of 161.2. Two natural stereoisomeric forms of carnitine are D- and L-carnitine, and between these two forms, only L-carnitine is physiologically active (3). Carnitine is a naturally occurring compound that is obtained mostly from diet *via* both active and passive transport across enterocyte (intestinal cell) membranes (4), especially in red meats and dairy products. It can also be synthesised endogenously from two essential amino acids, lysine and methionine, in the kidney, liver and brain (5). Cardiac and skeletal muscle, harboring the highest concentrations, cannot synthesize carnitine, which has to be therefore acquired from plasma (6, 7). Ascorbic acid, ferrous iron, pyroxidine and niacin are also necessary co-factors, and deficiencies of any of these can lead to carnitine deficiency (8). The bioavailability of L-carnitine varies due to dietary composition – in individuals such as vegetarians, who are adapted to low-carnitine diets, it is higher (66% to 86% of available carnitine) than regular red-meat eaters adapted to high-carnitine diets (54% to 72% of available carnitine) (9). Deviations in carnitine regulation are implicated in complications of diabetes mellitus, hemodialysis, trauma, malnutrition, cardiomyopathy, obesity, fasting, drug interactions, endocrine imbalances and other disorders (8). Although L-carnitine is synthesised in the body, conditions such as stress, disease and physical strain may result in L-carnitine deficiency. The main causes of such conditions include increased production performance and fertility, increased physical performance, stress arising due to improper housing, poor air conditioning, etc. Furthermore, the ban on the use of animal-based meal in animal feeding, which is the major exogenous source of L-carnitine, has resulted in L-carnitine deficiency (2).

FUNCTION OF CARNITINE

L-carnitine serves two considerable functions in energy production: facilitating entry of long-chain fatty acids into mitochondria for utilization in energy-generating processes and removal of short-chain and medium-chain fatty acids that accumulate as a result of normal and abnormal metabolism from mitochondria (10). The former function of carnitine is obligatory: long-chain fatty

acids cannot enter mitochondria independently of translocation as an ester of carnitine. L-carnitine is present in both plasma and tissue as free carnitine, or bound to fatty acids as acylcarnitine derivatives (10). Carnitine participates in cell volume and fluid balancing in all tissues that are affected by the tonicity (iso-, hyper-, hypotonicity) of the extracellular environment (11). Carnitine deficiency has been associated with cirrhosis (5). L-acyl-carnitine has been suggested as a potent, low cost and safe alternative therapy for patients with cirrhosis (12). Carnitine depletion is common in patients hospitalized for advanced cirrhosis and results from three factors: poor intake of dietary carnitine; poor intake of lysine and methionine; and loss of capacity to synthesize carnitine from these two amino acids (8). Sachan *et al*. (13) demonstrated that exogenous carnitine added to the ethanol diet in an experimental rat model significantly reduced lipid accumulation in livers, which were otherwise laden with lipids, suggesting that there is a deficiency of functional carnitine, *i.e*., carnitine which is available for acylation (8). Diet supplementation with lysine can restore carnitine levels (13). It is known that dietary absorption of amino acids is impaired by ethanol, so this could also contribute to carnitine deficiency overall (8).

Evidence is mounting that carnitine supplementation may be beneficial in obesity (5). In obese rats manifesting insulin resistance, carnitine supplementation improved glucose tolerance and increased total energy expenditure (5). Carnitine palmitoyltransferase (CPT-1) is the rate limiting step of the fatty acid oxidation pathway and a target for the treatment of obesity. Pharmacological stimulation of brain CPT-1 was reported to decrease food intake and body weight (14). A negative correlation between free carnitine and both triglycerides and cholesterol indicates that L-carnitine may be utilized under conditions of augmented lipolysis (8).

L-carnitine and acetyl-L-carnitine, an ester of L-carnitine, cross the blood-brain barrier and are widely distributed in the central nervous system. It is postulated from references that these compounds have wide roles in brain metabolism (8). Several studies have suggested that L-carnitine may play a neuroprotective role in hypoxic-ischemic brain injury (2, 15). Recent studies have shown that L-carnitine pre-treatment ameliorated brain injury after hypoxia-ischemia in newborn rats through reducing apoptotic cell death and inhibiting the production of platelet-activating factor (16). Other studies have also shown that acetyl-L-carnitine may be beneficial in reducing the infarct size following focal cerebral ischemia in rats (17). Most recent reports suggest that acetyl-L-carnitine elevates the glucose uptake and the glucose transporter protein expression level, and the acetyl moiety of acetyl-L-carnitine is metabolized for energy in both astrocytes and GABAergic neurons, which may also contribute to its effect of reducing neurotoxicity and neuronal degeneration (18-19). Acetyl-L-carnitine has

been shown to play a therapeutic role in the treatment of dementia (20). An increasing number of studies have demonstrated the efficacy of secondary antioxidants, such as acetyl-L-carnitine, to reduce or to block neuronal death that occurs in the pathophysiology of Alzheimer's disease (8). These studies have suggested that there may be mechanisms beyond antioxidant activities playing a neuroprotective role (21). The use of nutritional antioxidants, such as carnitine/acetylcarnitine, has been advocated to counteract the oxidative stress induced brain damage in Alzheimer's disease (22-23). Similarly, carnitine/acetylcarnitine has been used in the treatment of degenerative neuronal function in older Down's syndrome patients, since upon autopsy it was revealed that almost 100% of these patients over 40 had symptoms of dementia (24). However, acetyl-L-carnitine was not found to be beneficial in young men suffering from Down's syndrome (24).

The cell-protective effect of L-carnitine can be used for inhibiting the genotoxic, mutagenic, and cell proliferative effects of malondialdehyde (MDA), one of the important toxic aldehydes of lipid peroxidation (25). The capacity of L-carnitine to elevate glutathione (GSH) concentration was also shown, and this antioxidant action may be due to the decrease of lipid peroxidation caused by L-carnitine during chronic aflatoxicosis in quails (25). L-carnitine levels in tissues have been found to decline with age (8). Adverse effects of aging are attributed to decreases in mitochondrial function and increases in mitochondrial oxidant production (26). It has been speculated that carnitine and its esters protect cells from oxidative damage, both by inhibiting free-radical propagation and by contributing to the repair of oxidized membrane phospholipids (4). One study indicated that propionyl-L-carnitine protects the ischemic heart from reperfusion injury, perhaps by scavenging free radicals or by preventing their formation by chelating iron necessary for generation of hydroxyl radicals (4). These processes may occur in many cell types, but may be particularly important in the cardiac muscle (8). Moreover, as it is well known, carnitine prevents free radical formation *via* both inhibiting the activity of enzymes involving their generation and inducing antioxidant mechanisms (27). Studies have also reported that L-carnitine affects sperm parameters (sperm count, motility and viability) mainly by increasing the activity of antioxidant enzymes, which is reflected in the increased levels of catalase, superoxide dismutase, reduced glutathione and total antioxidant capacity. These increased levels of antioxidants lead to reduced levels of free radicals available for lipid peroxidation (28). These increased levels of antioxidants lead to reduced levels of free radicals available for lipid peroxidation. In contrast, other studies have reported that L-carnitine had no effect on these sperm parameters (29). The antioxidant effect of L-carnitine may have been due to the role of L-carnitine

in the chelation of free Fe^{2+} ions, with a subsequent reduction in free radical generation or its ability to enhance ATP production, which improves the overall level and activity of antioxidant enzymes in the cell (28). Pharmacologic administration of L-carnitine reduces mortality and metabolic consequences associated with acute ammonium intoxication in mice (10). Carnitine administration may have significant benefit in patients with disorders of ammonia metabolism, including urea cycle defects, chronic valproic acid therapy, liver failure, organic acidemias, and Reye's syndrome (10).

As mentioned above, skeletal and cardiac muscles contain relatively high concentrations of carnitine received from the plasma, since they are incapable of carnitine biosynthesis (8). Carnitine deficiency has been associated with heart failure (5). The mechanisms underlying the effects of L-carnitine in cardiovascular diseases are not well clarified (8). Miguel-Carrasco *et al*. (30) demonstrated in a rat model that chronic administration of L-carnitine reduced blood pressure and attenuated the inflammatory process associated with arterial hypertension. L-carnitine as well as some factors like basic-fibroblast growth factor have been shown to have favorable effects in patients with severe cardiovascular disorders, such as coronary heart disease, chronic heart failure and peripheral vascular disease (31), (49–51). In patients with chronic heart disease, administration of L-carnitine over 12 months led to attenuation of left ventricular dilatation and prevented ventricular remodeling while reducing incidence of chronic heart failure and death (8). Xue and colleagues suggest that the beneficial effects of L-carnitine in cardiovascular disease are due to the resumption of normal oxidative metabolism and restoration of myocardial energy reserves (8).

CONCLUSION

As mentioned in Table 1, the application of L-carnitine in various animals, such as ruminants, pigs, dogs, etc. have been investigated. Carnitine takes part in many functions in organism, such as lipid catabolism, energy production, cardioprotective, gastroprotective, antiapoptotic and neuroprotective properties. Carnitine has beneficial effects on animal performance by enhancing resistance to metabolic diseases, preventing some diseases, strengthening immune system, and playing an important role in metabolic and physiological processes. Different responses to supplementary carnitine are obtained from various studies mainly due to the variations in the species, age, sex, nutrient composition of the diet, levels of L-carnitine in the diet and other environmental conditions.

Table 1

Some research on application of L-carnitine in veterinary medicine

Author names	Year of publication	Title of publication	Animal model	Main results
Center *et al*.	2000	The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral L-carnitine	Domestic cats	Although cats receiving supplemental L-carnitine lost weight at a faster weekly rate than control cats, the conclusion cannot be made that carnitine facilitated loss of body fat and conserved lean tissue mass (32)
Brandsch and Eder	2003	Reproductive performance of rats supplemented with L-carnitine	Sprague-Dawley rats	L-carnitine supplementation does not improve the reproductive performance of rats (33)
Citil *et al*.	2005	Protective effect of L-carnitine against oxidative damage caused by experimental chronic aflatoxicosis in quail (*Coturnix coturnix*)	Quails	L-carnitine brought about the inhibition of lipid peroxidation by enhancing antioxidant capacity in quails with chronic aflatoxicosis (25)
Yalcin *et al*.	2005	Use of L-carnitine and humate in laying quail diets	Japanese quails	L-carnitine supplementation increased egg weight (34)
Waylan *et al*.	2005	Effects of L-carnitine on fetal growth and the IGF system in pigs	Pigs	L-carnitine supplemented to gestating sows altered the IGF system and may affect fetal growth and development (35)
Rajasekar *et al*.	2005	L-carnitine administration prevents oxidative stress in high fructose-fed insulin resistant rats	Wistar rats	The ability to bring a favorable metabolic environment and an antioxidant role could be suggested for the observed benefits of L-carnitine in fructose-fed rats (36)
Kart *et al.*	2006	Effects of L-carnitine on kidney histopathology, plasma and tissue total sialic acid, malondialdehyde and glutathione concentrations in response to gentamicin administration in BALB/C mice	BALB/C mice	L-carnitine may attenuate gentamicin induced nephrotoxicity by improving antioxidant status, and reducing tissular lesions in BALB/C mice (37)
Aydogdu *et al*.	2006	Protective effects of L-carnitine on myoglobinuric acute renal failure in rats	Sprague-Dawley rats	L-carnitine treatment protects against functional, biochemical and morphological

				damage and iron accumulation in glycerol-induced myoglobinuric acute renal failure in rats (38)
Yalçın *et al*.	2006	The effects of dietary supplementation of L-carnitine and Humic substances on performance, egg traits and blood parameters in laying hens	IGH type brown laying hens	L-carnitine alone or in combination with humic substances in diets had no beneficial effects in laying hens (39)
Dokmeci *et al.*	2006	The protective effect of L-carnitine on ionizing radiation-induced free oxygen radicals.	Syrian golden hamsters	L-carnitine with its antioxidant and free radical scavenging properties could play a modula-tory role against the cellular damage produced by free radicals induced by ionizing radiation (40)
Kart *et al*.	2007	Protection through L-carnitine on tissue oxidant status and sialic acid content in tilmicosin-induced alterations in BALB/c mice	BALB/C mice	L-carnitine administration could be attenuated the oxidative stress (41)
Sarica *et al*.	2007	The effects of dietary L-carnitine supplementation on Semen traits, reproductive parameters, and testicular histology of Japanese quail breeders	Japanese quail breeders	The supplementation of dietary L-carnitine at levels of 250 or 500 mg/kg to a basal diet significantly increased sperm viability and decreased multinucleated giant cells per testes in mature male Japanese quail breeders (42)
Neumann *et al*.	2007	Plasma L-carnitine concentration in healthy dogs and dogs with hepatopathy	Dogs	Liver tumors could not be differentiated from moderate or severe hepatitis by measurement of L-carnitine in this study (43)
Jacyno *et al*.	2007	Effect of L-carnitine supplementation on boar semen quality	Pietrain boars	The positive effect of L-carnitine on boar semen quality was observable as early as after one week of its application (44)
Suchý *et al*.	2008	The effect of a diet supplemented with	*Phasianus colchicus*	Results indicated positive effect of the continuous

		L-carnitine on egg production in pheasant (*Phasianus colchicus*)		administration of L-carnitine on egg production in female pheasants in the course of the laying period (2)
Zhai *et al*.	2008	The effect of male and female supplementation of L-carnitine on reproductive traits of white leghorns	White leghorns	Additional studies will be needed to determine whether carnitine-induced increases in yolk fat mobilization in hatchlings affect chick livability during the brooding period (45)
Daşkıran *et al.*	2009	Effects of dietary methionine levels and L-carnitine supplementation on performance and egg quality parameters of layers	White Nick Chick layers	carnitine supplementation did not affect layer performance and egg quality (46)
Kacar *et al*.	2010	The effects of L-carnitine administration on energy metabolism in pregnant Halep (Damascus) goats	Halep goats	Parenteral administration of L-carnitine might be a protective measure against pregnancy toxemia (ketosis) *via* increasing serum glucose concentration in goats with twin pregnancy (47)
Ismail *et al*.	2012	Effect of ginger and L-carnitine on the reproductive performance of male rats	Male albino rats	L-carnitine may be beneficial for improving male sexual performance (28)
Mansour	2013	Effect of L-carnitine on endothelial dysfunction markers in diabetic-irradiated rats	Wistar albino rats	L-carnitine showed a strong antioxidant activity against irradiation-induced lipid peroxidation and has free radical scavenging effects (48)

REFERENCES

1. Arslan C, *L-Carnitine and its use as a feed additive in poultry feeding a review*, ***Revue Méd. Vét.***, **157**, 134–142 (2006).
2. Suchý P, Straková E, Vitula F, *The effect of a diet supplemented with l-carnitine on egg production in pheasant (Phasianus colchicus)*, ***Czech J. Anim. Sci.***, **53**, 31–35 (2008).
3. Daşkıran M, Önol AG, Cengiz Ö, Tatlı O, Sarı M, *Effects of dietary methionine levels and L-carnitine supplementation on performance and egg quality parameters of layers*, ***J. Anim. Feed Sci.***, **18**, 650–661 (2009).

4. Rebouche CJ, *Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism*, ***Ann N. Y. Acad. Sci.***, **1033**, 30–41 (2004).
5. Cave MC, Hurt RT, Frazier TH, Matheson PJ, Garrison RN, McClain CJ, McClave SA, *Obesity, inflammation, and the potential application of pharmaconutrition*, ***Nutr. Clin. Pract.***, **23**, 16–34 (2008).
6. Rebouche CJ, Seim H, *Carnitine metabolism and its regulation in micro-organisms and mammals*, ***Annu. Rev. Nutr.***, **18**, 39–61 (1998).
7. Alshabanah OA, hafez MM, Al-harbi MM, Hassan ZK, Al Rejaie SS, Asiri YA, Sayed-ahmed MM, *Doxorubicin toxicity can be ameliorated during antioxidant L-carnitine supplementation*, ***Oxid. Med. Cell Longev.***, **3**, 428–433 (2010).
8. Flanagan JL, Simmons PA, Vehige J, Willcox MDP, Garret Q, *Role of carnitine in disease*, ***Nutr. Metab.***, **7**, 30–43 (2010).
9. Rebouche CJ, Chenard CA, *Metabolic fate of dietary carnitine in human adults: identification and quantification of urinary and fecal metabolites*, ***J. Nutr.***, **121**, 539–546 (1991).
10. Rebouche CJ, *Carnitine function and requirements during the life cycle*, ***FASEB***, **6**, 3379–3386 (1992).
11. Peluso G, Barbarisi A, Savica V, Reda E, Nicolai R, Benatti P, Calvani M, *Carnitine: an osmolyte that plays a metabolic role*, ***J. Cell Biochem.***, **80**, 1–10 (2000).
12. Shores NJ, Keeffe EB, *Is Oral L-Acyl-Carnitine an Effective Therapy for Hepatic Encephalopathy? Review of the Literature*, ***Dig. Dis. Sci.***, **53**, 2330–3 (2008).
13. Sachan DS, Rhew TH, Ruark RA, *Ameliorating effects of carnitine and its precursors on alcohol-induced fatty liver*, ***Am. J. Clin. Nutr.***, **39**, 738–744 (1984).
14. Aja S, Landree LE, Kleman AM, Medghalchi SM, Vadlamudi A, McFadden JM, *et al*, *Pharmacological stimulation of brain carnitine palmitoyl-transferase-1 decreases food intake and body weight*, ***Am. J. Physiol. Regul. Integr. Comp. Physiol.***, **294**, 352–361 (2008).
15. Wainwright MS, Kohli R, Whitington PF, Chace DH, *Carnitine treatment inhibits increases in cerebral carnitine esters and glutamate detected by mass spectrometry after hypoxia-ischemia in newborn rats*, ***Stroke,*** **37**, 524–530 (2006).
16. Turkyilmaz C, Turkyilmaz Z, Onal E, Atalay Y, Soylemezoglu F, Celasun B, *L-Carnitine pre-treatment reduces apoptotic cell death in seven-day-old rats hypoxia ischemia*, ***Restor. Neurol. Neurosci.***, **28**, 817–824 (2010).
17. Jalal FY, Bohlke M, Maher TJ, *Acetyl-L-carnitine reduces the infarct size and striatal glutamate outflow following focal cerebral ischemia in rats*, ***Ann. N. Y. Acad. Sci.***, **1199**, 95–104 (2010).
18. Muneer PMA, Alikunju S, Szlachetka AM, Mercer AJ, Haorah J, *Ethanol impairs glucose uptake by human astrocytes and neurons: Protective effects of acetyl-L-carnitine*, ***Int. J. Physiol. Pathophysiol. Pharmacol.***, **3**, 48–56 (2011).
19. Scafidi S, Fiskum G, Lindauer SL, Bamford P, Shi D, Hopkins I, McKenna MC, *Metabolism of acetyl-L-carnitine for energy and neurotransmitter synthesis in the immature rat brain*, ***J. Neurochem.***, **114**, 820–831 (2010).
20. Traina G, Bernardi R, Cataldo E, Macchi M, Durante M, Brunelli M, *In the Rat Brain Acetyl-L-carnitine Treatment Modulates the Expression of Genes Involved in Neuronal Ceroid Lipofuscinosis*, ***Mol. Neurobiol.***, **38**, 146–152 (2008).
21. Mancuso C, Bates TE, Butterfield DA, Calafato S, Cornelius C, De Lorenzo A, *et al.*, *Natural antioxidants in Alzheimer's disease*, ***Expert Opin. Investig. Drugs***, **16**, 1921–1931 (2007).
22. Pettegrew JW, Levine J, McClure RJ, *Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression*, ***Mol. Psychiatry***, **5**, 616–632 (2000).
23. Ramassamy C, *Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets*, ***Eur. J. Pharmacol.***, **545**, 51–64 (2006).
24. Pueschel SM, *The effect of acetyl-L-carnitine administration on persons with Down syndrome*, ***Res. Dev. Disabil.***, **27**, 599–604 (2006).

25. Citil M, Gunes V, Atakisi O, Ozcan A, Tuzcu M, Dogan A, *Protective effect of L-carnitine against oxidative damage caused by experimental chronic aflatoxicosis in quail (Coturnix coturnix)*, ***Acta Veterinaria Hungarica***, **53**, 319–324 (2005).
26. Mandavilli BS, Santos JH, Van Houten B, *Mitochondrial DNA repair and aging*, ***Mutat. Res.***, **509**, 127–151 (2002).
27. Derin N, Izgut-Uysal VN, Agac A, Aliciguzel Y, Demir N, *L-Carnitine protects gastric mucosa by decreasing ischemia-reperfusion induced lipid peroxidation*, ***J. Physiol. Pharmacol.***, **55**, 595–606 (2004).
28. Ismail AG, El-Nasharty MA, El-Far AH, Hanan AG, *Effect of ginger and L-carnitine on the reproductive performance of male rats*, ***World Acad Sci. Eng. Tech.***, **64**, 1199–1205 (2012).
29. Zare Z, Eimani H, Mohammadi M, Mofid M, Dashtnavard H, *The effect of orally administered L-carnitine on testis tissue, sperm parameters and daily sperm production in adult mice*, ***Yakhteh Med. J.***, **11**, 382–389 (2010).
30. Miguel-Carrasco JL, Mate A, Monserrat MT, Arias JL, Aramburu O, Vazquez CM, *The role of inflammatory markers in the cardioprotective effect of L-carnitine in L-NAME-Induced hypertension*, ***Am. J. Hypertens.***, **21**, 1231–7 (2008).
31. Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C, *Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular diseases*, ***Ann. N. Y. Acad. Sci.***, **1033**, 79–91 (2004).
32. Center SA, Harte J, Watrous D, Reynolds A, Watson TDG, Markwell PJ, *The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral L-carnitine*, ***J. Vet. Int. Med.***, **14**, 598–608 (2000).
33. Brandsch C, Eder K, *Reproductive performance of rats supplemented with L-carnitine*, ***J. Anim. Physiol. Anim. Nut.***, **87**, 301–307 (2003).
34. Yalçin S, Ergun A, Erol H, Yalcin S, Özsoy B, *Use of L-carnitine and humate in laying quail diets*, ***Acta Vet. Hung.***, **53**, 361–370 (2005).
35. Waylan AT, Kayser JP, Gnad DP, Higgins JJ, Starkey JD, Sissom EK, *et al*., *Effects of L-carnitine on fetal growth and the IGF system in pigs*, ***J. Anim. Sci.***, 8, 1824–1831 (2005).
36. Rajasekar P, Kaviarasan S, Anuradha CV, *L-carnitine administration prevents oxidative stress in high fructose-fed insulin resistant rats*, ***Diabetologia Croatica***, 21–28 (2005).
37. Kart A, Yapar K, karapehlivan M, Tunca R, Ogun M, Citil M, *Effects of L-Carnitine on kidney histopathology, plasma and tissue total sialic acid, malondialdehyde and glutathione concentrations in response to gentamicin administration in BALB/C mice*, ***Revue Méd. Vét.***, **157**, 179–184 (2006).
38. Aydogdu N, Atmaca G, Yalcin O, Taskiran R, Tastekin E, Kaymak K, *Protective effects of L-carnitine on myoglobinuric acute renal failure in rats*, ***Clin. Exp. Pharmacol. Physiol.***, **33**, 119–124 (2006).
39. Yalçın S, Ergün A, Özsoy B, Yalçın S, Erol H, Onbaşılar I, *The Effects of dietary supplementation of L-carnitine and Humic substances on performance, egg traits and blood parameters in laying hens*, ***Asian-Aust. J. Anim. Sci.***, **19**, 1478–1483 (2006).
40. Dokmeci D, Akpolat M, Aydogdu N, Uzal C, Doganay L, Turan FN, *The protective effect of L-carnitine on ionizing radiation-induced free oxygen radicals*, ***Scand. J. Lab. Anim. Sci.***, **33**, 75–83 (2006).
41. Kart A, Karapehlivan M, Yapar K, Citil M, Akpinar A, *Protection through L-carnitine on tissue oxidant status and sialic acid content in tilmicosin-induced alterations in BALB/c mice*, ***Acta Vet. Brno***, **76**, 203–207 (2007).
42. Sarica S, Corduk M, Suicmez M, Cedden F, Yildirim M, Kilinc K, *The effects of dietary L-Carnitine supplementation on Semen traits, reproductive parameters, and testicular histology of Japanese quail breeders*, ***J. Appl. Poult. Res.***, **16**, 178–186 (2007).
43. Neumann S, Welling H, Thuere S, Kaup FJ, *Plasma L-carnitine concentration in healthy dogs and dogs with hepatopathy*, ***Vet. Clin. Pathol.***, **36**, 137–140 (2007).

44. Jacyno E, Kolodziej A, Kamyczek M, Kawecka M, Dziadek K, Pietruszka A, *Effect of L-carnitine supplementation on boar semen quality*, ***Acta Vet. Brno***, **76**, 595–600 (2007).
45. Zhai W, Neuman SL, Latour MA, Hester PY, *The effect of male and female supplementation of L-carnitine on reproductive traits of white leghorns*, ***Poultry Sci.***, **87**, 1171–1181 (2008).
46. Daşkıran M, Önol AG, Cengiz Ö, Tatlı O, San M, *Effects of dietary methionine levels and L-carnitine supplementation on performance and egg quality parameters of layers*, ***J. Anim. Feed Sci.***, **18**, 650–661 (2009).
47. Kacar C, Zonturlo AK, Karapehlivan M, Ari UC, Ögun M, Çitil M, *The effects of L-carnitine administration on energy metabolism in pregnant Halep (Damascus) goats*, ***Turk. J. Vet. Anim. Sci.***, **34**, 163–171 (2010).
48. Mansour HH, *Effect of L-Carnitine on endothelial dysfunction markers in diabetic-irradiated rats*, ***Int J. Toxicol. Appl. Pharmacol.***, **3**, 1–9 (2013).
49. Fathi E, Farahzadi R, Ahmadi-Hamedani M, *Clinicopathological study in an ovine model of experimental acute myocardial infarction*, ***Iranian. J. Vet. Res.***, **14**, 35−41 (2013).
50. Fathi E, Nassiri SM, Atyabi N, Ahmadi SH, Imani M, Farahzadi R, *et al*., *Induction of angiogenesis via topical delivery of basic-fibroblast growth factor from polyvinyl alcohol dextran blend hydrogel in an ovine model of acute myocardial infarction*, ***J. Tissue. Eng. Regen. Med.***, **9**, 697−707 (2013).
51. Fathi E, *Protein expression in myocardium using basic fibroblast growth factor loaded gel in an ovine model*, ***Bulg. J. Vet. Med.***, **16**, 208−216 (2013).