Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Review Article

A Comprehensive Review on L-carnitine: A Promising Nutraceutical

AA Gunjal*, AV Kulkarni, PK Bairagi, VY Chavan

Department of Pharmacology, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Maharashtra, India.

ARTICLE INFO

Article history:

Received: 20 March, 2024

Revised: 02 May, 2024

Accepted: 09 May, 2024

Published: 30 May, 2024

Keywords:

Carnitine, L-carnitine, Nutrition, Health benefits, Supplement.

DOI:

10.25004/IJPSDR.2024.160325

ABSTRACT

L-carnitine (LC), which is a type of quaternary amine, is an essential element for energy metabolism in mammals, plants, and specific bacteria. Originating from the amino acid methionine and lysine, it is primarily synthesized in the kidneys and liver. L-carnitine is a pharmacologically active form of carnitine that plays a vital role in energy generation and the breakdown of fatty acids via β-oxidation in metabolism. Deficiencies in organic cation transporter-2 (OCTN2) can arise due to gene mutations or in conjunction with other conditions like renal or hepatic disorders. Deficiency in carnitine regulation results in several diseases, including cardiomyopathy, cirrhosis, diabetes, endocrine disorders, malnutrition, aging, sepsis, and malnutrition. LC is known for its anti-inflammatory and antioxidant properties. Research indicates that incorporating LC into the diet can ameliorate inflammatory ailments by decreasing the presence of inflammatory agents. Supplementation with LC is particularly useful for individuals with predominant carnitine deficiencies, which can be life-threatening, as well as certain subsidiary deficiencies like organic acid disorders, muscle wasting, and weakness. Moreover, emerging evidence suggests that LC may have therapeutic benefits for various diseases, including renal diseases, liver diseases, neurodegenerative disorders, cardiovascular diseases (CVDs), cancer, diabetes, cachexia, obesity, depression, and epilepsy.

INTRODUCTION

Since the discovery of carnitine, extensive research has been conducted to explore its properties. Current Research has increased our comprehension of carnitine's role in metabolism and its prospective therapeutic uses. This is partially due to the discovery of carnitine as a supplement and treatment for primary and secondary carnitine deficiency.[1]

The widely recognized role of carnitine involves acting as a carrier molecule to facilitate the transportation of long-chain fatty acids into the mitochondrial matrix. Therefore, an inherent connection exists between carnitine and β-oxidation of fatty acid. Carnitine plays a crucial role in energy metabolism due to its promotion of the synthesis of energy from fatty acids and glucose.[2,3] The level of carnitine changes based on body composition, food, and sex. But carnitine is necessary for a healthy diet. The consumption of carnitine through the diet has a positive correlation with plasma carnitine levels. The synthesis of carnitine is a very beneficial process that requires several pathways across multiple parts of the body. Overall, the biosynthesis of carnitine depends on the presence of trimethyllysine within tissue proteins.[4]

Humans obtain carnitine from the diet, and when it is not received from the diet, it is endogenously produced from lysine and methionine. Carnitine is produced in the kidneys, liver, and brain, with approximately 99% of it being found within cells. Its predominant presence is in skeletal and cardiac muscle since these tissues cannot produce it themselves; instead, they uptake it from the bloodstream. Microbes typically break down any unabsorbed carnitine in the gut.[5]

Various pharmacologically active forms of carnitine, such as L-carnitine (LC), L-carnitine L-tartrate (LCLT), L-carnitine fumarate (LCF), acetyl L-carnitine (ALC), propionyl L-carnitine (PLC), etc., have demonstrated utility in assisting patients with diabetes and obesity. These compounds have the potential to treat immunological

***Corresponding Author:** Mr. AA Gunjal

Address: Department of Pharmacology, Dr. D. Y. Patil College of Pharmacy, Pune, Maharashtra, India.

Email ✉: avinashgunjal4247@gmail.com

Tel.: +91-9325064247

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

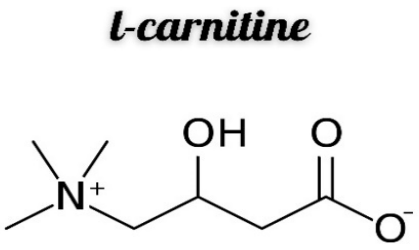

Fig. 1: Structure of L-carnitine (LC)[7]

diseases, neuropathic pain, and nerve conduction and can save the lives of those patients with predominant carnitine deficiency. LC is the pharmacologically active form of carnitine (Fig. 1).[6]

Dietary LC is produced internally by the body and obtained through food consumption. Biosynthesis occurs *via* the utilization of the amino acids methionine and lysine, with lysine acting as the carbon framework for the LC. LC is produced from the 6-N-trimethyl-lysine substrate, while methionine comprises 4-N-methyl groups. The complete process of synthesis of LC is depicted in (Fig. 2).[8,9]

LC has shown potential in the management of various neurological diseases, neuropathic pain, mental conditions, and hepatic encephalopathy.[11,12] Topical LC therapy for dry eyes modulates immunological and proinflammatory responses while providing osmoprotection.[13] LC is considered a dietary supplement for managing cardiovascular diseases, with increasing research suggesting its potential effectiveness in the treatment of obesity, decreasing glucose intolerance, and increasing total energy expenditure.[14]

Materials And Methods

We performed a literature survey by a systematic search method to identify recent literature by using electronic databases such as PubMed, Web of Science, Embase, and Google Scholar. During the literature survey, we used the following keywords: Carnitine, L-carnitine, nutrition, health benefits, and pathology. Original research papers, research reports, and literature reviews written in English were chosen and assessed. Additionally, we reviewed the citations and included any that were missing. Mendeley (reference manager software, version 2.100.0) was utilized to bring all articles identified through the systematic search so that titles and abstracts could be reviewed.

L-Carnitine Deficiencies and Pathological States

Organic cation transporter novel-2 (OCTN2) acts as a transporter for carnitine, relying on sodium for its transport mechanism. The human OCTN2 transporter is primarily located in the heart, kidney, and intestine, with an additional presence in the nervous system, liver, and breast.[15,16]

The primary expression of OCTN2 occurs in endothelial cells within the human heart. Additionally, OCTN2 is found

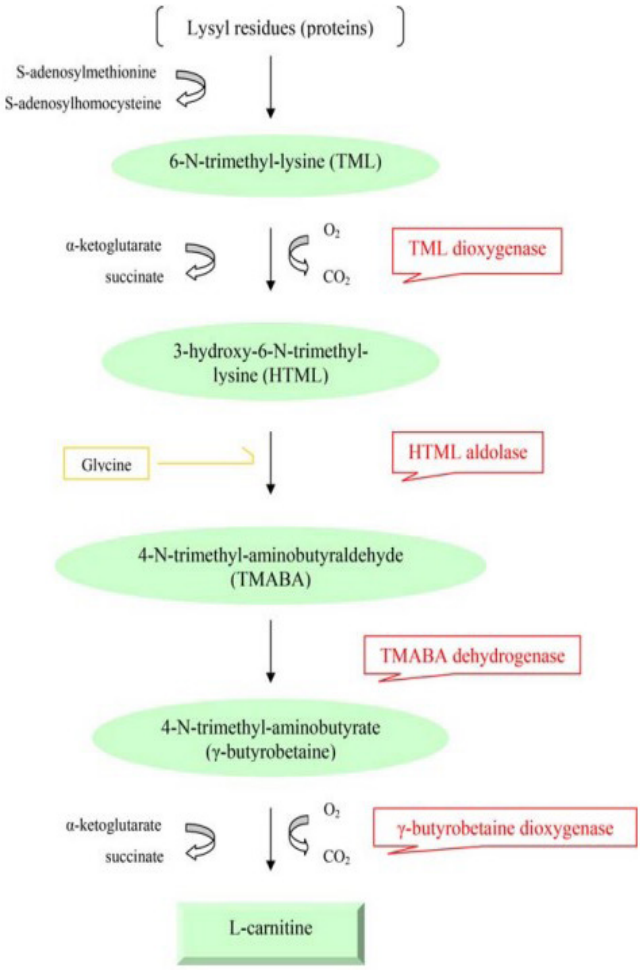

Fig. 2: Pathway of L-carnitine synthesis[10]

on the membrane of the intestine and within the colon.[17] The expression of the OCTN2 gene exhibits variations that may lead to deficiencies and pathological states. Several substrates are available for binding with human OCTN2, such as free LC, ALC, and some organic cations.[18]

ALC inhibits OCTN2-mediated LC transport. Furthermore, cationic medications such as valproate and verapamil prevent OCTN2-mediated absorption of LC in fibroblasts. Levofloxacin and valproate inhibit OCTN2, which is primarily responsible for facilitating LC uptake in the human gut.[19] Cancer patients receiving etoposide therapy may experience OCTN2 inhibition in the kidney tubule.[17]

Two separate cases of carnitine deficiency have been recognized; Nonetheless, discerning between primary and secondary carnitine deficiencies. Primary carnitine deficiency (PCD) is characterized by an autosomal recessive trait where there's a shortage in ferrying carnitine through the cell membrane, specifically *via* the transporter OCTN2. This deficiency arises from a functional mutation in the SLC22A5 gene, which encodes for OCTN2.[20,21] This deficit inhibits tissue uptake and

disrupts renal absorption, resulting in increased carnitine loss through the kidneys. This, in turn, triggers a systemic depletion of carnitine, reducing its accumulation in both the heart and skeletal muscle.[22]

PCD affects 1–5 of the 10,000 people between the ages of 1 and 7 years. PCD impacts three primary tissues/organs: The cardiac muscle, leading to hypoketotic hypoglycemia and subsequently causing progressive cardiomyopathy[23] The central nervous system, as it undergoes encephalopathy, experiences disturbances in its normal functioning.[24]; and the skeletal muscle, which develops episodes of rhabdomyolysis and myoglobinuria (myopathy).[25] Supplementing with LC is crucial, as it can save lives for individuals in need of this treatment.[21]

Secondary carnitine deficiency (SCD) manifests through elevated excretion of acylcarnitine in urine, indicating significant carnitine depletion. SCD arises from various factors such as heightened carnitine depletion (acyl-carnitine), multiple metabolic irregularities, insufficient carnitine intake in the diet, challenges in absorption, Fanconi syndrome (which leads to the loss of free carnitine via renal tubules), and peritoneal dialysis.[26,27] In contrast to PCD, SCD can appear concurrently with other conditions like liver disease, disturbances in fatty acid metabolism, or due to the use of certain therapeutic drugs such as zidovudine, ofloxacin, omeprazole, cefepime, etoposide, and valproic acid.[17] SCD manifests in people with renal tubular diseases, potentially leading to elevated carnitine excretion, and is also prevalent among individuals undergoing hemodialysis.[28]

Nutritional Profile of L-carnitine

The use of dietary supplements is a broad industry and currently, the use of these is expanding rapidly: Each year, plenty of new supplements arrive in the market, provoking a shift in therapeutic frameworks and necessitating adjustments in dietary supplement regulations.[29–31] LC, a crucial nutritional component found in animal food, cannot be adequately synthesized within the body to meet metabolic requirements. Although SCD is more common than PCD, it is also associated with several inherited metabolic disorders and acquired medical conditions, such as those caused by drugs such as zidovudine and valproate. It is also associated with several chronic disorders, such as heart failure, diabetes, and Alzheimer's disease.[32]

There is no specific document that suggests the reference value of LC. As per the guidelines set forth by the United States Food and Drug Administration (USFDA) regulation 21 CFR 170.3(o)(20), L-carnitine (LC) is categorized as a "nutrient supplement." It is recommended for daily intake at levels of up to 3 gm/day or 50 mg/kg/day, assuming an adult weight of 60 kg. Moreover, it has been determined that at these specified intake levels, LC does not pose any adverse effects.[33]

The average daily requirement of LC for an adult is typically estimated to be between 20 to 200 mg, which is met by endogenous synthesis and diet. LC occurs naturally in animal-based foods like meat, fish, milk, and dairy, supplying a minimum of 80% of the required LC.[34] Just like maintaining a balanced diet, incorporating carnitine-rich foods is essential when adding carnitine supplements to your diet.[35] It's crucial to understand that the body absorbs about four times more L-carnitine from meals compared to supplements. Additionally, a high fat intake can produce carnitine and its metabolites.[32]

Health Benefits of L-carnitine

Anti-wasting effect

Muscle wasting, known as atrophy, denotes the reduction in skeletal muscle mass and is increasingly recognized as a prevalent feature across various chronic conditions, encompassing infectious diseases and cancer.[36–38] In chronic illnesses, muscle wasting is commonly known as cachexia and is linked with adipose tissue.[39] The robustness and structural integrity of skeletal muscle play vital roles in metabolism and overall health. Increased muscle degeneration is linked with difficulties in treatment acceptance, unfavorable prognosis, and higher mortality rates. Moreover, it significantly diminishes patients' quality of life, manifesting in muscle atrophy and persistent fatigue.[40]

An experimental investigation clarified the impact of LC supplementation on muscle mass loss to determine whether LC can be used as an anti-wasting agent. Based on research involving animal studies and clinical trials, the addition of LC supplements improves nitrogen balance through mechanisms like promoting protein synthesis by reducing breakdown and suppressing apoptosis (Fig. 3).[41] Nuclear factor-kappa beta (NF-κB) functions as a transcriptional controller for atrogin-1 and MuRF-1. Research on animals has demonstrated that continuous activation of NF-kβ, cytokines, or reactive oxygen species (ROS) enhances the upregulation of atrogin-1 and MuRF-1 in skeletal muscle, leading to the degradation of muscle proteins, contributing to muscle atrophy and deterioration.[42] By suppressing NF-kβ activation, signals of inflammation and atrophy can be prevented, which significantly preserves muscle mass.[43] According to a recent study, administering LC at a dosage of 1-g/kg reduces atrogin-1 and MuRF-1 levels in tumor-bearing rats (Table 1).[44] Activation of caspase-3 stands as a crucial step in the initiation of the apoptosis pathway. Caspases, characterized as cysteine-dependent aspartate proteases, play a crucial role by cleaving diverse proteins.[45]

Current findings clearly show that LC therapy effectively diminishes muscle loss in animals afflicted with cancer cachexia. Researchers observed a decrease in caspase-3 expression within the skeletal muscle of rats modeled with CHF after being administered 50 g/kg b.w. of monocrotaline.[46] The efficacy of combining LC and lipoic acid to halt age-related apoptosis in skeletal muscle fibers

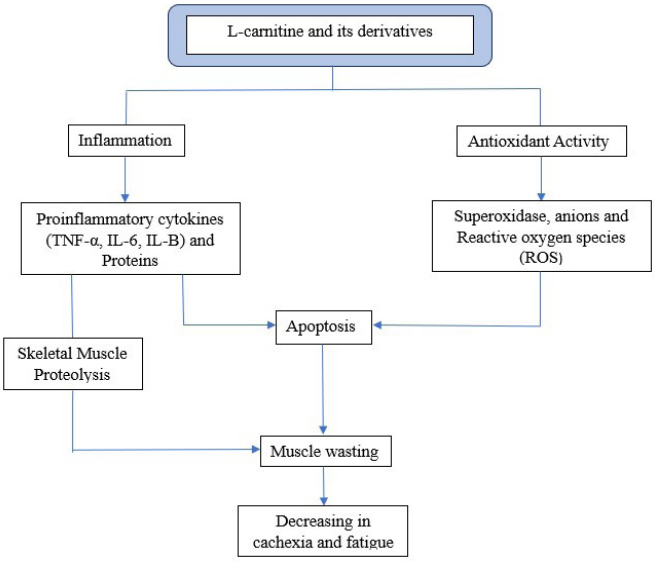

Fig. 3: The protective mechanism of LC in skeletal muscle[41]

of rats was explored.[47] However, current studies indicate that oxidative stress is associated with muscular atrophy.[48]

Neurodegenerative diseases

- *Alzheimer's disease*

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by the gradual breakdown of neurons and synaptic connections in the cerebral cortex, along with certain regions beneath it. This leads to the shrinkage and deterioration of neurons within the frontal, parietal, and temporal lobes.[88,89] The Food and Drug Administration (FDA) has given its approval for the use of LC in various forms, such as powders, liquids, tablets, or capsules, to address primary and secondary carnitine deficiencies. Extensive research, including both *in-vitro* and *in-vivo* studies, has shown no signs of toxicity associated with LC.[90]

LC was administered to healthy individuals at several dosages per day, the range to be from 250 mg to 2 g.[91] Based on 21 randomized, double-blind trials, ALC demonstrated the capacity to either halt cognitive decline or mitigate cognitive impairment. Clinically and statistically substantial improvements in cognitive performance were observed.[92]

The administration of ALC at doses ranging from 2.25 to 3.0 gm/day yielded notable therapeutic effects in individuals with Alzheimer's disease (AD), surpassing both placebo-treated groups and patients with mild vascular dementia (VD).[93] In another experiment, 11 individuals diagnosed with Alzheimer's disease received intravenous administration of ALC at a dosage of 30 mg/kg for ten days. Following this regimen, there was a notable rise in the ALC level in both plasma and cerebrospinal fluid (CSF). This increase, observed after multiple intravenous and oral administrations of ALC, suggests ALC effectively penetrates the blood-brain barrier.[94]

ALC diminishes apoptosis and mitochondrial dysfunction, enhances energy metabolism, restores nerve cell architecture, bolsters memory and creativity, and shields brain cells with its neuroprotective properties.[95]

Numerous studies have demonstrated that acetyl-L-carnitine (ALC) enhances brain function and behavior in elderly individuals and those suffering from Alzheimer's disease. At various doses between 1.5 to 3.0 gm/day, ALC demonstrated enhanced cognitive performance among Alzheimer's patients within the span of 3 to 6 months.[96]

- *Parkinson's disease*

Parkinson's disease (PD) ranks as a prevalent neurological condition in the elderly population, and its prevalence increases as age increases. In Parkinson's disease, there is a reduction in dopaminergic neurons found within the substantia nigra and various regions of the midbrain.[97–99] A recent study indicated that nutraceuticals might delay the onset of neurological diseases. By using these molecules as alternative therapies, fewer prescription medicines are needed.[100–102]

ALC, a metabolic intermediate found naturally, plays a dual role in anabolic and catabolic processes. A research investigation was undertaken to evaluate the novel therapeutic characteristics of ALC compared to those of the 6-hydroxydopamine-induced model and examine a few related mechanisms. For one week, rats with lesions in the intrastriatal region induced by 6-OHDA were administered doses of ALC at 100 or 200 mg/kg/day during the study.[103] ALC decreased MDA levels, enhanced catalase activity, and increased GSH levels. However, ALC decreased nigral DNA fragmentation at both dosages, indicating a consistent marker of cell death reduction. The findings of this study suggest that ALC possesses the capability to inhibit apoptosis, neuroinflammation, astrogliosis, and oxidative stress in Parkinson's disease. These findings suggest that ALC could serve as a viable supplementary treatment approach for Parkinson's disease management.[103]

- *Autism spectrum disorder*

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social interaction. The LC is necessary for the central nervous system to operate properly, particularly for fatty acid metabolism. Studies have demonstrated that individuals diagnosed with ASD exhibit abnormalities in the metabolism of carnitine.[104]

ASD is a complex neurodevelopmental disease frequently identified in early childhood. Therefore, people with ASD must be carefully classified. This clinical cohort might encompass individuals with cognitive impairments, high-functioning abilities, seizures, language disorders, or linked Mendelian genetic conditions. The locus coeruleus in the brain helps in the oxidation of fatty acids, supports

Table 1: Pre-clinical findings: Role of L-carnitine in management of diseases

Diseases	*Compounds*	*Findings*	*References*
Atrophy	L-carnitine	↓ the transcription of genes present in skeletal muscle	(Keller *et al.*, 2012)[49]
	L-carnitine	L-carnitine shields C2C12 myoblast cells from atrophy induced by TNF-α.	(Wu *et al*., 2021)[50]
	Carnitine	Carnitine boosts the activation of myogenic regulatory factors.	(Montesano *et al*., 2015)[51]
	L-carnitine	Enhance the anabolic IGF-1 pathway while inhibiting genes associated with apoptosis and muscle atrophy.	(Keller *et al*., 2011)[52]
	L-carnitine	Reduction in apoptosis is achieved through the anti-inflammatory and antioxidant properties.	(Murata *et al*., 2022)[53]
Alzheimer's disease (AD)	ALC	Mitochondrial membrane potential decline and attenuation in Na+ K+ ATPase functionality, accompanied by reduced mfn1, mfn2, and BCL2 protein concentrations.	(Zhang *et al*., 2015)[54]
	ALC	Increasing the abundance of functional mitochondria while simultaneously decreasing mitochondrial density.	(Aliev *et al*., 2009)[55]
	ALC	Decrease oxygen species (OS) levels within brain tissue to slow down the advancement.	(Suchy *et al*., 2009)[56]
	ALC	Enhancing memory impairment caused by HCV. Decreased Aβ buildup and tau phosphorylation were observed.	(Zhou *et al*., 2011)[57]
Parkinson's disease (PD)	ALC	Boost the generation of mitochondria while reducing the formation of oxygen-derived species.	(Zhang *et al*., 2010)[58]
	ALC	Decrease inflammation of nervous tissue, oxidative stress, increase number of astrocytes, and apoptosis.	(Afshin-majid *et al*., 2017)[59]
	ALC	Reduce astrocyte reactivity, enabling them to uphold neurotransmitter clearance, preserve synapses, and sustain the integrity of the blood-brain barrier.	(Bruks *et al*., 2019)[60]
	ALC	Activating microglia and astroglia prevents the loss of tyrosine hydroxylase and reduce dopamine transporter levels in the brain.	(Acosta *et al*., 2020)[61]
Depression	ALC	Elevate the concentration of artemin (ARTN) in the prefrontal cortex, and spinal cord.	(De Cesare mannelli *et al*., 2011)[62]
	ALC	Reduce the metabolism of glucose into lactate while simultaneously elevating the concentrations of serotonin and noradrenaline.	(Smeland *et al*., 2012)[63]
Epilepsy	L-carnitine	Decrease in caspase-3 and β-catenin expression, coupled with an increase in heat shock protein 70 (Hsp70) levels.	(Hussein *et al*., 2018)[64]
Obesity	L-carnitine	The lipid profile was normalized, resulting in a decrease in body weight, albumin, and alanine transaminase levels.	(Esmail *et al*., 2021)[65]
	L-carnitine	L-carnitine mitigated the adverse changes in gene expressions related to lipid metabolism	(Tao *et al*., 2015)[66]
Cardiovascular risk	Carnitine	Decrease the concentrations of lipofuscin and monoamine oxidase within the cardiac muscle.	(Savita *et al*., 2007)[67]
	L-carnitine	Elevated plasma malondialdehyde levels correlate with reduced oxidative stress.	(O Brain *et al*., 2010)[68]
	Carnitine	Serum levels of homocysteine and natriuretic peptide have shown a significant increase.	(Strilakou *et al*., 2013)[69]
Renal disease	L-carnitine	Significant increase in levels of Alanine transaminase, urea, creatinine, and uric acid.	(Toussan *et al*., 2014)[70]
	Propionyl L-carnitine	Reduce serum TNF-α levels alongside downregulation of ATM-Kinase expression, while also suppressing Caspase-3 expression. Concurrently, enhances the expression of Bcl2 mRNA.	(Ganai *et al*., 2014)[71]
	L-carnitine	Enhancing renal function, cognitive performance, and mitigating damage.	(Abu Ahmed *et al*., 2016)[72]
	L-carnitine	Improving the renal urinary concentration process.	(Gao *et al*., 2017)[73]

	L-carnitine	Reducing the influence of maternal factors on renal development requires implementing thorough genetic adjustments from the moment of birth.	(Stangenberg *et al*., 2019) [74]
	L-carnitine	The anti-inflammatory properties alleviate cell death.	(Zheng *et al*., 2021)[75]
Liver disease	L-carnitine	Shielding hepatic tissue from oxidative harm during the reperfusion phase following ischemic injury in rats through the administration of L-carnitine.	(Cekin *et al*., 2013)[76]
	L-carnitine	The decrease in L-carnitine reabsorption induced by clozapine, achieved through inhibiting or down-regulating renal OCTN2, plays a role in liver lipid metabolic disorder.	(Wang *et al*., 2019)[77]
	L-carnitine	Enhance liver cell resilience against IRI-induced damage, inflammation, and reduce nitric oxide (NO) levels.	(Eldamarawi *et al*., 2022) [78]
Diabetes	L-carnitine	Enhanced capacity to tolerate glucose as assessed through the oral tolerance test.	(Yoshikawa *et al*., 2003) [79]
Anti-oxidant activity	L-carnitine	Reduction of hepatic and renal oxidative stress rendering it potentially efficacious.	(Guzman *et al*., 2013)[80]
	ALC	ALCAR effectively lowers oxidative stress.	(Bayrak *et al*., 2020)[81]
Anti-inflammatory activity	ALC	PPARγ levels rise while levels of p-NF-kB and the NLRP3 inflammasome decline.	(Samin *et al.*, 2021)[82]
	L-carnitine	L-carnitine demonstrates anti-inflammatory property by reducing the levels of phosphorylated NF-kB and COX-2.	(Jiang *et al*., 2015)[83]
Anti-cancer activity	L-carnitine	Prevention of lipid metabolism	(Silverio *et al*., 2012)[84]
	L-carnitine	L-carnitine exhibits its protective effects in cancer cachexia.	(Jiang *et al*., 2015)[83]
Sexual function	L-carnitine	Treating somatic cell nuclear transfer (SCNT) embryos with LC during *in-vitro* maturation (IVM) enhances their developmental competence.	(You *et al*., 2012)[85]
	L-carnitine	L-carnitine shows promise as an antioxidant compound that may enhance both the rate and quality of embryo development.	(Ghanem *et al*., 2015)[86]
	ALC	Enhancing blastocyst formation in oocytes and boosting mitochondrial volume in adipose tissue.	(Reader *et al.*, 2015)[87]

acetylcholine synthesis, and safeguards against cellular and neuronal harm.[105]

The diagnosis and management of ASD are performed by analyzing acyl-carnitines in dried blood spots and determining LC in serum or plasma. A lack of LC (Lipid Compound) regulation or its deregulation in autism spectrum disorder (ASD) is linked to irregularities in various other metabolic pathways, including respiratory chain complex activity (mitochondrial dysfunction) and the Krebs cycle. Supplementation with LC helps ASD patients treat their behavioral and cognitive issues.[106] About 35 patients who underwent six months of LC treatment showed notable enhancements in ASD symptoms.[107]

- *Depression*

Depression is a prevalent and devastating mental health disorder with unresolved etiology and pathophysiology. Numerous antidepressant drugs are available, but many people with depression do not respond to them, leading to the development of novel antidepressant medications with different mechanisms of action. Animal studies suggest that ALC exhibits promise as a novel antidepressant medication, offering a distinct mechanism of action.[108]

ALC demonstrated greater efficacy compared to a placebo (PBO) in addressing depression across four randomized controlled trials (RCTs). It has been shown in two RCTs to be more effective over a placebo treatment of dysthymia and in further trials to be equally beneficial in treating dysthymic disorders as amisulpride and fluoxetine.[108] ALC plays vital roles, including enhancing acetylcholine synthesis, facilitating acetyl-CoA absorption into mitochondria, transmembrane phospholipid synthesis, and safeguarding neurons against excessive cellular damage.[109]

- *Epilepsy*

Epilepsy is marked by recurrent seizures, and abnormal, excessive, and coordinated electrical discharge in brain cells is characteristic of epileptic seizures. Disturbances in the metabolism and equilibrium of glutamate and GABA, the principal excitatory and inhibitory neurotransmitters, respectively, are involved in the pathogenesis of epilepsy.[110] The main goal of most available pharmaceutical treatments is to reduce neuronal excitability and prevent seizures. Many patients show resistance to these therapies and several adverse consequences. Temporal lobe epilepsy

(TLE) stands out as the predominant form of drug-resistant epilepsy in adults. An increasing amount of evidence from TLE studies points to significant metabolic alterations in neurons and astrocytes. According to a review, therapies that increase mitochondrial metabolism enhance astrocyte-neuronal connections.[111]

The materials that are being examined are the heptanoate triglyceride triheptanoin and the natural transport molecule ALC. Both contribute acetyl moieties to the tricarboxylic acid cycle for oxidation. Yet, heptanoate offers an additional advantage by supplying propionyl-CoA. This compound can undergo carboxylation to form succinyl-CoA, facilitating anaplerosis.[112]

Obesity

Obesity or being overweight occurs when there's an excessive buildup of fat in the body, often linked with metabolic issues, posing significant health risks. It has been demonstrated that using LC supplements can reduce blood and hepatic lipid levels, alleviate fatty liver, and reduce obesity caused by an HFD.[113]

One study examined the impact of LC on obesity resulting from irregular eating schedules. Body weight development and extra weight from epididymal fat resulting from delayed feeding were significantly reduced after an 8-week study with LC delivery. Furthermore, LC supplementation led to a reduction in the blood levels of glutamic oxaloacetic transaminase (GOT) and triglycerides (TGs), both of which had been notably elevated due to irregular eating patterns.[114]

In one experiment, nicotinamide riboside and LC together improved liver metabolism and liver steatosis and reduced obesity. This research aimed to investigate whether a combination therapy comprising nicotinamide riboside and LC could mitigate liver damage induced by obesity. These medications have the potential to boost the transportation of fatty acids across mitochondria while also elevating NAD+ levels, crucial for both the TCA cycle and β-oxidation processes. An HFD reduced the plasma levels of LC, which returned to normal. COMBI therapy significantly mitigated the increase in body weight induced by a fatty diet, diminished the expansion of fat mass, and notably alleviated hepatic steatosis despite both groups consuming the same amount of food and engaging in similar levels of physical activity.[115]

LC therapy decreased the serum AI, ALT, and, ultimately, body weight. Rats fed a fatty diet exhibited liver steatosis on histopathological examination, a condition reduced by LC. Overall, the present research demonstrated that LC effectively mitigated metabolic abnormalities in the livers of rats exposed to a fatty diet.[116]

Cardiovascular risk

Globally, an estimated 25 to 30 million individuals are affected by cardiac disorders, primarily with chronic heart failure (CHF). CHF manifests through myocardial infarction (MI), ventricular systolic dysfunction, and diminished cardiac muscle contraction, impacting blood circulation.[117] Common treatments for cardiac arrest include β-blockers, Ca-channel antagonists, ACE inhibitors, angiotensin, and corticosteroid receptor antagonists.[118] These medications enhance the circulation of blood and the delivery of oxygen to the heart muscles, cause vasodilation and decrease blood pressure and vascular resistance. Depending on the patient's needs and condition, the medications can be taken individually or together. On the other hand, prolonged use of these drugs has been linked to adverse hepatotoxic/hemologic effects, such as hyperkalemia and renal failure.[119]

Propionyl and acetyl-LC are the two most studied types of LC and help to reduce the production of harmful metabolites that are created during coronary thrombosis. Therefore, LC has been proposed as a remedy for various heart conditions, such as diabetes, hypercholesterolemia, toxic myocardial injury, coronary infarction, cardiopulmonary arrest, and reperfusion injury.[120] Meta-analysis revealed that LC significantly reduces the risk of cardiovascular disease. The results showed that using LC supplements decreased angina pectoris pain, ventricular dysfunction, and arrhythmia, which led to a reduced likelihood of heart attack and mortality.[121]

Renal disease

Patients suffering from end-stage renal disease (ESRD) are interested in LC because of LC deficits in hemodialysis patients due to reduced renal synthesis and losses during dialysis.[122] Consequently, several symptoms observed in uremic patients, such as fatigue, cardiomyopathy, anemia, and skeletal and muscular weakness, have been connected to carnitine shortages.[123] Regular administration of carnitine is not recommended for uremic patients.[124]

Carnitine metabolism problems in individuals with ESRD undergoing peritoneal dialysis (PD) may be caused by various factors, including insufficient dietary intake, intestinal absorption issues, buildup of metabolic byproducts, decreased renal production, and prolonged exposure to dialysis. Dialysis technique and peritoneal membrane function may have an impact on the metabolism of carnitine in individuals diagnosed with Parkinson's disease. Patients with higher peritoneal transport rates showed greater metabolic activity of carnitine compared to those with lower rates. Moreover, acetylcarnitine levels were lower in APD-treated patients than in CAPD-treated patients. APD manifests with extended and increased volume stay times, potentially aiding in the elimination of carnitine molecules.[125]

The serum triglyceride levels remained unchanged, and the mean plasma carnitine content increased significantly.[126]

Many observational studies have indicated a link between lipid metabolism issues in people with Parkinson's disease and carnitine. Kosan and colleagues investigated the impact of administering oral LC to a group of 20 volunteers

over 30 days, focusing on its effects on PD.[127]

A study was conducted to investigate the role of LC in methotrexate (MTX)-induced hepatic damage and renal damage. MTX-treated lambs with LC exhibited notable elevations in catalase, GSH, and other biochemical markers and a decrease in the blood levels of urea, creatinine, and MDA levels compared to the total protein levels in the self-healing and MTX groups. The histopathological results confirmed the ability of carnitine to reduce liver and kidney toxicity. This could suggest that using LC medicine during MTX chemotherapy has benefits and can lessen the harm that MTX causes to the kidneys and liver (Table 2).[128]

Liver disease

The LC plays a crucial part in maintaining liver function due to its impact on lipid metabolism. Evidence suggesting that individuals with PCD may develop fatty liver disease, potentially due to decreased levels of LC in the serum and liver, underscores the significance of LC in maintaining liver health.[141]

Furthermore, studies indicate that LC treatment may help NAFLD patients have decreased levels of hepatic fat as well as the liver enzymes AST and ALT. LC increases PDH flow and improves insulin sensitivity. Research indicating a reduction in intrahepatic fat and improved liver enzyme levels following the consumption of LC suggests that LC could potentially serve as a beneficial supplement in either bolstering or delaying the advancement of NAFLD.[142]

Obese rats fed a prolonged fatty diet experienced a reduction in plasma LC levels when given OHC. However, the impacts of LC therapy were found to be reversible. In another study, rats induced with diabetes mellitus through streptozotocin and administered LC for one month exhibited enhanced liver enzyme, alongside a reduction in plasma TG levels.[143]

In a research trial, the levels of fatty acids and overall carbohydrate oxidation in 13 individuals with chronic liver disease increased during LC treatment. Conversely, there was a notable decrease in the oxidation of fatty acid and protein.[144]

Antidiabetic activity

Administration of carnitine reduced insulin resistance in mice subjected to a high-fat diet (HFD). and the injection of carnitine decreased insulin resistance without influencing the intake or weight of the mice. In mice with diabetes and obesity, carnitine improved urine excretion, circulation levels of acyl-carnitine, and insulin-induced glucose metabolism. A hyperinsulinemic-euglycemic clamp technique was employed to assess the impact of carnitine infusions on glucose metabolism in individuals without health complications. This increase was attributed to a nonoxidative pathway that promotes glycogen

Table 2: Clinical findings: Role of L-carnitine in management of diseases

Study design	*Outcomes*	*Reference*
Randomized controlled trials	L-carnitine reduces body weight and fat mass.	(Talenezhad *et al*., 2020)[129]
Double-blinded randomized trial	There was no observable impact on the strength of skeletal muscles or circulating markers in healthy women.	(Sawicka *et al*., 2018) [130]
Randomized controlled trials	Supplementing with L-carnitine exhibited positive hepato-protective effects by reducing levels of circulating liver enzymes.	(Askarpour *et al*., 2020)[131]
Randomized trial (Pilot study)	L-carnitine may serve as a therapeutic supplement for individuals with COVID-19.	(Talebi *et al*., 2022) [132]
Randomized controlled trials	Patients afflicted fatty liver exhibit a decrease in AST, ALT and TG levels.	(Abolfathi *et al*., 2020)[133]
Double-blinded randomized trial	Research findings indicate that L-carnitine does not demonstrate any added benefit for severe acute malnutrition (SAM).	(Alam *et al*., 2024) [134]
Double-blinded randomized trial	Using L-carnitine alongside risperidone may improve the treatment of irritability symptoms.	(Nasiri *et al*., 2023) [135]
Double-blinded randomized trial	Improving cardiovascular health by reducing oxidative stress and inflammatory markers.	(Nachvak *et al*., 2020) [136]
Randomized controlled trials	L-carnitine shows promise in enhancing various indicators such as INR, creatinine (Cr) levels, ALT levels, lactate levels, calcium (Ca) levels, albumin (Alb) levels, and total protein levels.	(Yahyapoor *et al*., 2023)[137]
Randomized controlled trials	During major depressive episodes (MDEs), there's a notable decline in the metabolic activity of mitochondria converting l-carnitine to ALC.	(Ait *et al*., 2023)[138]
Randomized controlled trials	L-carnitine potentially yields favorable impacts on lipid profile, particularly in reducing LDL cholesterol.	(Asbaghi *et al*., 2020) [139]
Randomized controlled trials	ALC enhances functional and neurological outcomes likely attributed to its anti-inflammatory property.	(Mazdeh *et al*., 2022) [140]

storage.[145] In T2DM patients, treatment with carnitine improved glucose oxidation and glycogen storage.[146] It has been suggested that type 2 diabetes mellitus may be treated with carnitine compared to those without such conditions.[147]

Brain mitochondrial swelling and subsequent neuronal cell death are caused by severe hypoglycemia. LC was investigated in male Wistar rats for its potential to reduce the effects of hypoglycemic shock on the brain.[148]

By preventing the rise of oxidized glutathione and averting mitochondrial dysfunction within the hippocampal area, LC significantly reduced the risk of neuronal injury. Additionally, LC stopped ROS production and lowered the mitochondrial membrane potential in hippocampal neural cells. These findings demonstrate that the LC maintains mitochondrial activity, thereby shielding the hippocampus from neuronal damage caused by hypoglycemia.[148]

Antioxidant activity

A study was conducted to examine how LC affects the renal epithelial cells of rats administered with leptin causing the hallmark features reminiscent of obesity. Leptin increased nitrotyrosine levels, boosted NOX2 expression, and escalated superoxide anion (O2) production through NADPH oxidase activation, facilitated by the PI3K/Akt pathway.

However, once leptin was administered, there was a decrease in H_2O_2 levels and NOX4 expression. Additionally, leptin increased the mRNA levels of proinflammatory factors and influenced the expression of antioxidant enzymes such as catalase and SOD. All changes caused by leptin were reversed by pretreatment with LC. Ultimately, preincubation with LC mitigated the oxidative damage and inflammation generated by leptin administration in NRK-52E cells.

Remarkably, LC restored the release of hydrogen peroxide, the product of NOX4, and enhanced NOX4 expression, suggesting that NOX4 may protect against renal damage caused by leptin. An oval spore-induced increase in OS in cells was examined in another study to determine the impact of LC pretreatment. Multiple oxidative stress markers were assessed in the liver, including lipid peroxidation and protein oxidation, alongside enzymatic activities such as catalase and superoxide dismutase. The study's conclusions showed that food supplementation with LC had positive antioxidant effects on the OS condition of the fish.[149]

Table 3: Marketed formulations of L-carnitine for disease management.[164]

Brand name	*Content*	*Dosage form*	*Uses*	*Side effects*
Carnitor	L-carnitine	Tab. 500 mg, Inj. 1 mg/5 mL	Carnitine deficiency, cellular energy production, boost immunity, reduce myopathy	Nausea, vomiting
Lacarnit	L-carnitine	Tab. 500 mg, Inj. 1 mg/5 mL	Carnitine deficiency, antioxidant activity, boosts immunity	Headache, nausea, vomiting
Carnisure	L-carnitine	Tab. 500 mg	Carnitine deficiency	Carnitine deficiency
Vernace	L-carnitine	Tab. 500 mg	Carnitine deficiency	Headache, nausea, vomiting
Carnimac	L-carnitine	Tab. 500 mg	Carnitine deficiency	Nausea, vomiting
Carni-Q	L-carnitine	Tab. 500 mg	Nutritional deficiency	Insomnia, heartburn, headache
Levocarnil	L-carnitine	Tab. 500 mg	Carnitine deficiency	Nausea, vomiting
Maxnuron-LC	L-carnitine, L-arginine, vitamin E, and methylcobalamine	Tab. 500 mg	Anti-oxidant, red blood cell (RBC) formation	Headache, nausea, vomiting
Ovafuel	L-carnitine L-tartrate, alfacalcidol, Co-enzyme Q10, omega 3 fatty acid, L-arginine, lycopene	Cap.	Treatment of female infertility, Irregular menstrual cycle, anti-oxidant activity	Headache, nausea, vomiting
Ulticozim-LC	Co-enzyme Q10, L-carnitine, methylcobalamine, and lycopene	Tab.	Healthy cardiac & cognitive function, ↓ cholesterol, and maintain blood pressure (BP)	Nausea, vomiting
Ferpil-M, Pepson	L-carnitine	Tab. 1000 mg	Treatment of male infertility	Headache, nausea, vomiting,
Ubimarc-LC	L-carnitine,	Tab. 500 mg	Carnitine deficiency	Nausea, vomiting

Table 4: Clinical studies regarding the effect of L-carnitine.[165,166]

Title of study	*Type of study*	*Health condition*	*Intervention name/Test drug*	*Location*
Effect of Rejiyana (Acetyl-L-carnitine and Agmatine) in major depressive disorder.	Interventional (Clinical Trial)	Major depressive disorder, recurrent, moderate	Rejiyana (Acetyl-L-carnitine and Agmatine)	Asha Hospital, Telenghana
The Effects of Levocarnitine on Recovery in Children Afflicted by Complicated Severe Acute Malnutrition.	Interventional (Clinical Trial)	Unspecified severe protein-calorie malnutrition	Syp. Levocarnitine	UCMS and GTB Hospital, Delhi
Assessing the Effectiveness and Safety of Mac Q10 Plus in Men with Infertility	PMS	Male infertility, unspecified	MacQ10 Plus	Omega Hospital (A unit of Shembeker Hospitals Pvt. Ltd.) Maharashtra
Evaluation of the Effectiveness of Carnipure AAS on Body Composition, Muscle Thickness, and Strength Development in Male Individuals without Health Complications	Interventional (Clinical Trial)	Muscle hypotrophy	Dietary Supplement: Carnipure AAS, Creatine monohydrate	Florida, United States
Examining the Impact of Levocarnitine on Liver Protection During Chemotherapy for Leukemia or Lymphoma	Interventional (Clinical Trial)	Acute lymphoblastic leukemia	Drug: Calaspargase Pegol, Dietary Supplement: Levocarnitine	Anaheim, California, United States
Minimizing Liver Damage from Asparaginase in Acute Lymphoblastic Leukemia Patients Through Levocarnitine Administration	Interventional (Clinical Trial)	Acute lymphoblastic leukemia, hepatotoxicity	Levocarnitine	California, United States
Optimizing Adolescent Alcohol Treatment with Acetyl-L-Carnitine	Interventional (Clinical Trial)	Alcohol use disorder	Acetyl-l-carnitine	Island, United States
Levocarnitine for Dry Eye in Sjogren's Syndrome	Interventional (Clinical Trial)	Sjogren's syndrome, Keratoconjunctivitis Sicca	Levocarnitine	Tennessee, United States

Anticancer activity

Cancer encompasses a range of conditions marked by the body's cells growing uncontrollably (abnormal cell growth) with the potential to spread to other parts of the body. Other terms used for cancer are neoplasm, benign tumor, and malignant tumor. Cancer cachexia (CC) manifests as a progressive decline in weight and decreased synthesis of energy. Due to unusually low levels of LC in muscle tissue, the efficient mitochondrial β-oxidation of long-chain fatty acids isn't conducted in individuals with CC.[150]

In mice, LC improves CC, mainly through the PPAR-associated carnitine palmitoyltransferase pathway. Some indications show that LC reduces cachectic symptoms. Oral administration of 9 mg/kg/day LC showed improvement in cachexia and metabolic parameters in rats with cancer-induced cachexia.[151] Researchers investigated how administering LC affected genes and proteins linked with hepatic fat metabolism in rats with cachectic tumors. Wistar rats were administered 1 g/kg of LC or saline. Hepatic lipid metabolism is protected by LC in tumor-bearing rats, suggesting that supplementation may be helpful in patients grappling with cachexia.[152]

Scientists have thoroughly explored the connection between carnitine and cancer through both experimental and clinical studies. Chang and colleagues postulated that the antioxidative qualities of LC might suppress the development of liver cancer in Long-Evans cinnamon rats.[153] By preventing mitochondrial fatty acid import in malignant cells, Laboratory studies have demonstrated that LC possesses the potential to inhibit the proliferation of colon cancer cells.[154] According to researchers, acetyl-LC may help to prevent chemotherapy-induced neuropathy, which is observed in patients receiving ifosfamide.[155]

Anti-inflammatory activity

A study was conducted to examine how LC affects on inflammatory agents like prostaglandin E2 (PGE2) and nitric oxide (NO), generated through the activation of cyclooxygenase-2 (Cox-2), as well as proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β, and tumor necrosis factor (TNF-α).[156]

These proinflammatory cytokines and inflammatory mediators initiate the generation of reactive oxygen species (ROS), prompting neutrophil infiltration and culminating in ischemia-reperfusion injury. Fortunately, T/D rats administered with either 1000 or 5000 mg/kg BW of proxeed plus (PP) for durations of four hours or seven days displayed impressive anti-inflammatory properties, evidenced by notable decreases in the levels