Novel progress in the application of the small molecule drug carnosine for the treatment of several diseases (Review)

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Abstract. Carnosine is a dipeptide composed of β-alanine and L-histidine, linked by peptide bonds, and is widely distributed in muscle tissue, the central nervous system (including the brain) and various other organs. As an endogenous bioactive molecule, carnosine plays a crucial role in cellular metabolism and physiological regulation. In recent years, advancements in molecular biology, biochemistry and pharmacology have gradually unveiled the multiple biological functions of carnosine, leading to increased interest in its potential applications for disease therapy. Carnosine exhibits considerable antioxidant and anti-glycation properties, while also demonstrating unique pharmacological effects related to neuroprotection, anti-inflammatory responses and immune regulation. These attributes position carnosine as a significant intervention with therapeutic value across various pathophysiological processes associated with different diseases. This review systematically summarizes recent progress on the application of carnosine in disease therapy, focusing on its mechanisms of action and therapeutic roles in neurodegenerative diseases, metabolic disorders, cardiovascular diseases, several types of cancer and ophthalmic conditions. By reviewing existing studies on this topic, this review aims to further explore the diversity of carnosine's roles along with potential mechanisms involved in disease treatment. Ultimately, it aims to provide a theoretical foundation and direction for future research.

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Contents

1. Introduction

Since its discovery in the early 20th-century, the biological function of carnosine has increasingly garnered interest (1). One of the most significant functions of carnosine is its antioxidant effect (2). Oxidative stress serves as a common pathological basis for numerous diseases (3). By scavenging free radicals, chelating metal ions and enhancing endogenous defenses, carnosine reduces oxidative stress (4). It further inhibits lipid peroxidation, protein oxidation and DNA damage, thereby preserving cellular integrity (4-7). Furthermore, the anti-glycation properties of carnosine offer novel insights into the prevention and treatment of diabetes mellitus and its complications by inhibiting the formation of advanced glycation end products (AGEs) (8,9). The accumulation of AGE is closely associated with diabetes, cardiovascular disease and aging; carnosine competes with sugars to bind proteins to reduce AGEs formation by inhibiting glycosylation processes (10). In terms of neuroprotection, carnosine demonstrates potential therapeutic value for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (11). AD is characterized by β-amyloid protein (Aβ) deposition along with neuronal loss. Studies have shown that carnosine can inhibit Aβ aggregation and toxicity while reducing oxidative damage and inflammation in neurons, thus delaying AD progression (12,13). PD is a neurodegenerative disorder characterized by the loss of dopaminergic neurons. Evidence indicates that carnosine may protect these neurons from damage induced by oxidative stress and inflammatory

responses; consequently, it has the potential to delay the progression of PD (14-16). Carnosine exerts anti-inflammatory and immunomodulatory effects by suppressing pro-inflammatory mediators and regulating immune cell activity, supporting its potential in chronic inflammatory and autoimmune diseases (17-20). Research demonstrates that carnosine can inhibit the secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), among other inflammatory mediators, thereby reducing inflammation (21-24). Furthermore, carnosine also plays a role in regulating immune cell functions such as those of macrophages and T cells, enhancing the body's overall anti-inflammatory capacity (25).

In the treatment of cancer, the role of carnosine is also gradually revealed (26). Carnosine may delay cancer progression by reducing oxidative stress and inflammation in tumor cells, while also inhibiting proliferation and migration, and inducing apoptosis. In addition, carnosine protects normal cells from damage caused by oxidative stress and inflammatory responses, thereby reducing side effects in cancer treatment (18,27).

Although carnosine has shown a wide range of potential applications in disease therapy, it still faces several challenges for clinical use. First, carnosine has low bioavailability *in vivo* and is readily degraded by enzymes, which affects its efficacy (28). Studies have explored various strategies to address this. Nanotechnology-based delivery systems, such as liposomes and polymeric nanoparticles, have been developed to protect carnosine from rapid hydrolysis by carnosinase and to facilitate targeted delivery to specific tissues. For instance, liposomal encapsulation has been shown to enhance the stability of carnosine (29). In addition, derivatization and conjugation strategies (such as cyclodextrins and trehalose) have been employed to enhance the stability of carnosine against carnosinase-mediated degradation as well as its pharmacological activity (30). Secondly, the efficacy of carnosine is dose-dependent, and high doses may result in certain side effects (31,32). In addition, the current clinical research data on carnosine remain insufficient and there is a lack of large-scale clinical trials on this drug. Therefore, it is necessary to improve the bioavailability and stability of carnosine through chemical modification or nanotechnology and develop novel carnosine-based drugs. Similarly, when combined with precision medicine, a personalized carnosine treatment program may be feasible to improve efficacy and reduce side effects. In addition, conducting large-scale clinical trials to verify the safety and effectiveness of carnosine in disease treatment is also an important direction for future research. By systematically reviewing the multiple biological functions of carnosine and its application in the treatment of diseases (Fig. 1), this review aims to provide comprehensive theoretical support and practical guidance for researchers in related fields and promote the wider application of carnosine in the medical field.

2. Biological function of carnosine

Antioxidant effect. Carnosine is a powerful antioxidant capable of scavenging free radicals [such as reactive oxygen species] through a variety of mechanisms to protect cells from oxidative stress (33). Oxidative stress is a common pathological basis for a variety of diseases such as neurodegenerative diseases, cardiovascular diseases and cancer, and the antioxidant effects of carnosine provide a scientific basis for its application in these diseases (34-37). Studies have shown that carnosine can inhibit lipid peroxidation, protein oxidation and DNA damage, thereby protecting the structural and functional integrity of cells (4,38). The antioxidant effect of carnosine is primarily achieved through several mechanisms (Fig. 2): i) Direct removal of free radicals: Carnosine can react directly with free radicals to neutralize their activity, thereby reducing the damage of free radicals to cells (12,14,39). Free radicals are the primary mediators of oxidative stress, capable of attacking cell membranes, proteins and DNA, leading to the destruction of cell structure and function. Carnosine, through its histidine residues in its molecular structure, can effectively trap and neutralize free radicals, thereby protecting cells from oxidative damage. ii) Chelating metal ions: Carnosine can bind to metal ions (such as copper and iron) and inhibit the oxidation reaction catalyzed by metal ions (40-43). Metal ions play an important role in oxidative stress, which can catalyze the formation of free radicals and the oxidation reaction. Carnosine can form stable complexes with metal ions through carboxyl and amino groups in its molecular structure, thus inhibiting the oxidation reaction catalyzed by metal ions and reducing the generation of free radicals. iii) Enhancing the endogenous antioxidant system: Carnosine can enhance the levels of endogenous antioxidants such as glutathione (GSH) in the cell, thereby improving the antioxidant capacity of the cell (24,44). GSH is one of the most important antioxidants in the cell, which can directly remove free radicals and participate in the regulation of redox reactions. Carnosine enhances the function of the intracellular antioxidant system by promoting the synthesis and regeneration of GSH, thereby improving the resistance of cells to oxidative stress.

In addition, carnosine can further enhance the antioxidant capacity of cells by regulating the activity of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase (GPx). These antioxidant enzymes can catalyze the breakdown and removal of free radicals, thereby protecting cells from oxidative damage. By regulating the activity of these enzymes, carnosine can effectively reduce the damage to cells caused by oxidative stress (45,46).

Anti-glycation. Carnosine has been shown to play a significant role in the field of anti-glycation, effectively inhibiting the non-enzymatic reaction of proteins and sugars (glycation reaction), thereby reducing the formation of AGEs (8). Glycosylation is a non-enzymatic reaction between proteins, lipids or nucleic acids and reducing sugars, and the accumulation of AGEs in the body is closely associated with a variety of diseases, such as diabetes, cardiovascular disease and age-related diseases (47-50). The anti-glycation effect of carnosine is of great significance in delaying aging and preventing diabetic complications (such as vasculopathy and neuropathy), and its mechanism primarily includes the following aspects: i) Inhibition of glycosylation: Carnosine can compete with sugars to bind proteins, thereby inhibiting the occurrence of glycosylation. At the heart of the glycosylation reaction is the reduction of sugars (such as glucose) with free amino groups in proteins (such as lysine and arginine residues) to form unstable Schiff bases, which,

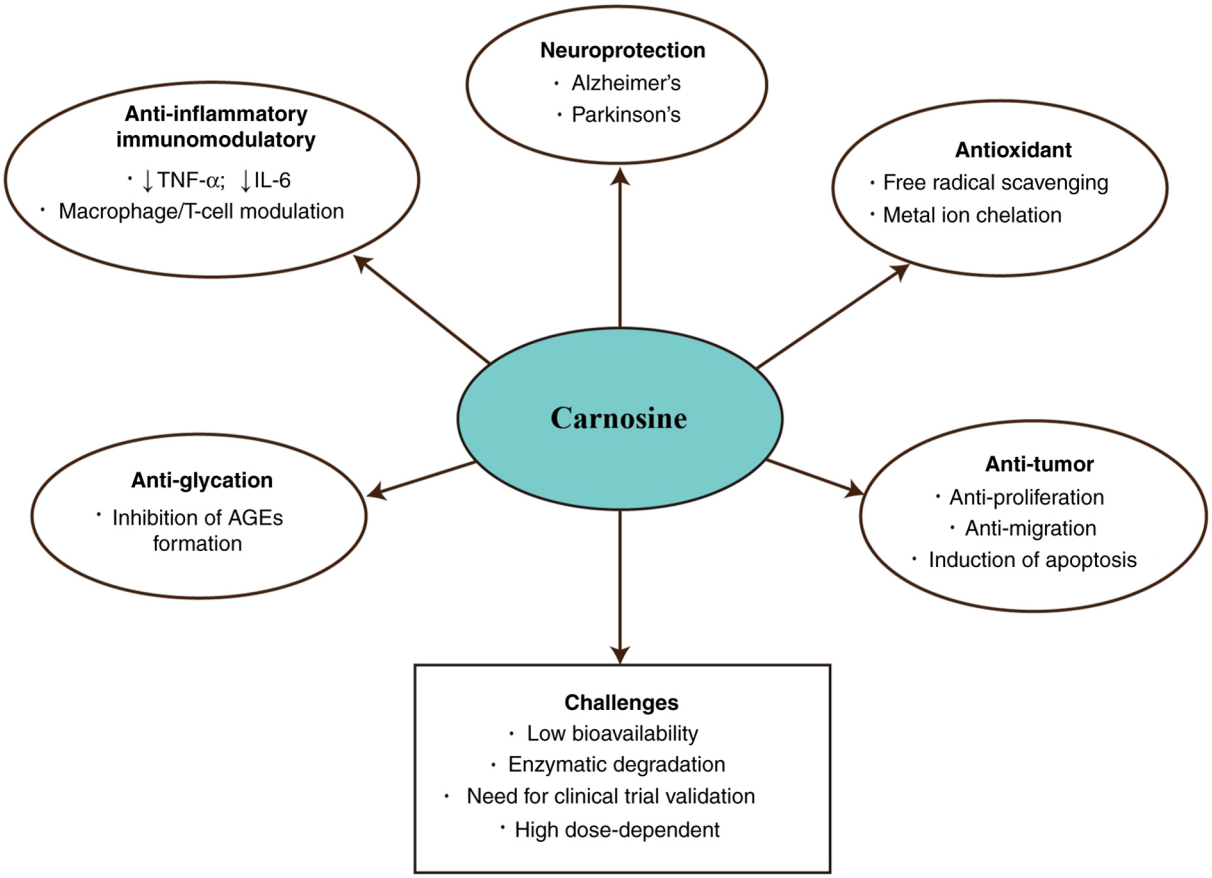

Figure 1. The diverse biological activities of carnosine and perspectives on challenges. AGEs, advanced glycation end products.

in turn, rearrange into stable AGEs. Carnosine, through the amino and carboxyl groups in its molecular structure, can compete with sugars to bind the free amino group of proteins, blocking the initial step of the glycosylation reaction, thereby reducing the production of AGEs (8,51). ii) Elimination of AGE precursors: Carnosine can eliminate the precursor substances of AGEs, such as α-dicarbonyl compounds (such as methylglyoxal and glyoxal), thereby reducing the formation of AGEs. α-dicarbonyl compounds are important intermediates in glycation reactions, which are highly reactive and can rapidly bind to proteins to form AGEs. Carnosine blocks the AGE formation pathways by binding to these highly active intermediates and neutralizing their reactivity (52). iii) Protection of protein function: Carnosine can protect the structure and function of proteins and reduce the damage of the glycosylation reaction to protein function. Glycosylation can lead to protein cross-linking, structural changes and loss of function, which can affect the normal physiological function of cells (53,54). By binding to proteins, carnosine stabilizes their conformation and prevents protein denaturation caused by glycosylation. In addition, carnosine can also repair certain proteins that have been glycated, restoring their function. iv) Regulation of AGE receptor signaling pathway: Carnosine can also reduce the toxic effects of AGEs on cells by regulating the signaling pathway of AGE receptors (RAGEs). AGEs induce inflammation and oxidative stress-related signaling pathways by binding to RAGE, leading to cell damage. Carnosine can inhibit the binding of AGEs and RAGE, and block the activation of downstream signaling pathways, thus reducing the damage of AGEs to cells (55).

The anti-glycation effect of carnosine is particularly important in the prevention and treatment of diabetes and its complications. Long-term hyperglycemia in diabetic patients accelerates the glycosylation reaction, leading to the accumulation of AGEs in blood vessels, nerves and kidneys, which can lead to diabetic complications (such as diabetic nephropathy, retinopathy and neuropathy). Carnosine can effectively delay the progression of diabetic complications by inhibiting the glycation reaction and clearing the precursors of AGEs. In addition, the anti-glycation effect of carnosine is also of great value in the field of anti-aging. The accumulation of AGEs is one of the important signs of aging and is closely related to age-related diseases such as skin aging, arteriosclerosis and cognitive decline. By reducing the formation of AGEs, carnosine can delay the aging process and improve age-related functional decline.

Neuroprotective effect. Carnosine exerts neuroprotective effects in neurodegenerative diseases (such as AD and PD) by targeting multiple pathological processes, including oxidative stress, inflammation, neurotransmitter imbalance and abnormal protein aggregation (56,57). The primary mechanisms of the neuroprotective effect of carnosine are as follows: i) Antioxidant effect: Carnosine can clear free radicals in neurons and reduce the damage of neurons caused by oxidative

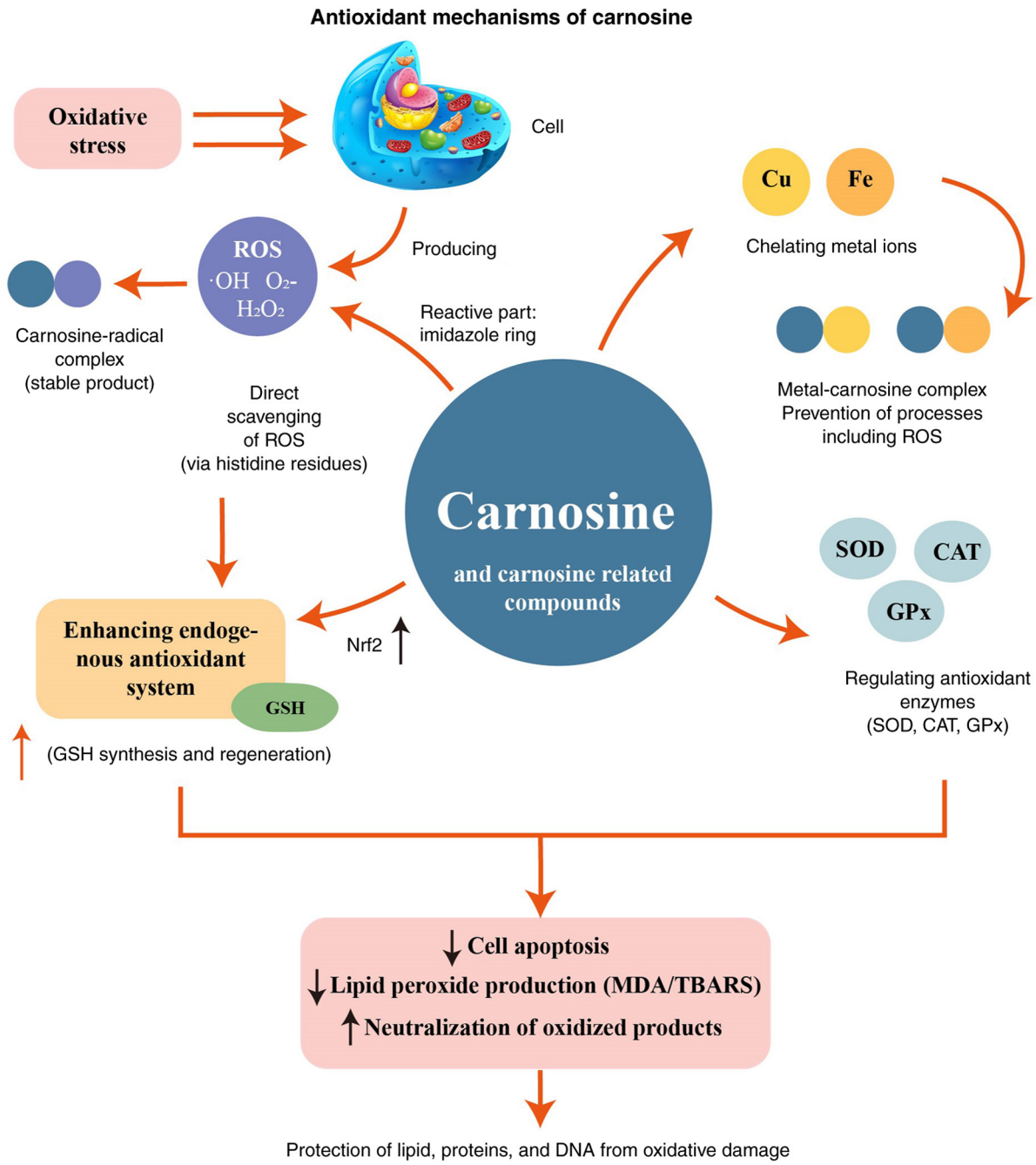

Figure 2. Antioxidant mechanisms of carnosine. ROS, reactive oxygen species; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; GPx, GSH peroxidase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances.

stress (58-61). In addition, carnosine can chelate metal ions (such as iron and copper), inhibiting oxidation reactions catalyzed by metal ions, thereby further reducing oxidative stress (27,40). ii) Anti-inflammatory effect: Carnosine can inhibit the inflammatory response of neurons (such as the NF-κB pathway) and reduce the damage caused by inflammatory factors (such as TNF-α, IL-1β and IL-6) to neurons (62). In addition, carnosine can also regulate the activity of microglia and astrocytes, inhibit their overactivation and further relieve neuroinflammation (63-65). iii) Regulation of neurotransmitters: Carnosine can regulate the release and metabolism of neurotransmitters, thereby protecting the function of neurons (66). Imbalances in neurotransmitters such as dopamine, glutamate and γ-aminobutyric acid are important pathological features of neurodegenerative diseases. For instance, in PD, loss of dopaminergic neurons leads to decreased dopamine levels, and in AD, the excitotoxicity of glutamate exacerbates neuronal damage (67). Carnosine regulates the synthesis, release and degradation of neurotransmitters and maintains the balance of neurotransmitters, thereby protecting the function of neurons (68). In addition, carnosine can also inhibit the excitatory toxicity of glutamate and reduce the damage caused by the overexcitation of neurons (69). iv) Inhibition of abnormal protein aggregation: Carnosine can inhibit the aggregation of abnormal proteins in neurodegenerative diseases, such as Aβ in AD and in PD (70,71). The aggregation of these abnormal

proteins can form toxic aggregates, which result in neuronal dysfunction and death. Carnosine protects neurons by binding to these abnormal proteins, inhibiting their aggregation and toxicity. v) Promotion of the expression of neurotrophic factors: Carnosine can promote the expression of neurotrophic factors (such as brain-derived neurotrophic factor) and enhance the survival and regeneration ability of neurons (72). Neurotrophic factors play an important role in the growth, differentiation and repair of neurons, and carnosine can further play a neuroprotective role by upregulating their expression.

Anti-inflammatory and immunoregulatory effects. Carnosine has been shown to play a significant role in anti-inflammatory and immune regulation. It can regulate the function of the immune system through several mechanisms and enhance the anti-inflammatory capacity of the body, so it has important value in the treatment of inflammation-related diseases. Inflammation is the body's defense response to injury or infection, but an excessive inflammatory response can lead to tissue damage and disease. Carnosine exerts its anti-inflammatory and immunomodulatory effects by inhibiting the release of inflammatory factors, regulating the function of immune cells and protecting tissues from inflammatory damage. The primary mechanisms of carnosine's anti-inflammatory and immunomodulatory effects are as follows: i) Inhibition of inflammatory factors: Carnosine can inhibit the release of inflammatory factors (such as TNF-α, IL-6 and IL-1β), thereby reducing the inflammatory response (21). Inflammatory factors are key molecules mediating the inflammatory response and their excessive release can lead to tissue damage and disease progression. Carnosine reduces the transcription and release of inflammatory factors by inhibiting the activation of inflammatory signaling pathways, such as the NF-κB pathway (73). For instance, in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, carnosine can significantly reduce the levels of TNF-α and IL-6, thereby reducing inflammatory symptoms (73). ii) Regulation of immune cells: Carnosine can regulate the function of immune cells (such as macrophages, T cells and neutrophils) and enhance the body's anti-inflammatory ability. Macrophages are key cells in the inflammatory response, releasing a large number of inflammatory factors. Carnosine reduces the inflammatory response by regulating the polarization of macrophages and promoting their transformation from pro-inflammatory (M1 type) to anti-inflammatory (M2 type) (58,74). In addition, carnosine can regulate the differentiation and function of T cells, inhibit the activity of pro-inflammatory type 17 T-helper cells, and enhance the function of regulatory T cells, thereby maintaining immune balance (75,76). iii) Protection of tissue: Carnosine can protect the tissue from the damage of the inflammatory response to maintain the normal function of the tissue. Inflammatory response can lead to tissue oxidative stress, cell apoptosis and fibrosis. Carnosine, through its antioxidant effect, clears free radicals in inflammatory sites and reduces tissue damage caused by oxidative stress (77). In addition, carnosine can inhibit inflammation-mediated apoptosis and protect the survival of tissue cells (65). For instance, in inflammatory diseases such as myocarditis and hepatitis, carnosine can significantly reduce tissue damage and improve organ function (78,79). iv) Regulation of inflammatory mediators: Carnosine can regulate the production of inflammatory mediators [such as nitric oxide (NO) and prostaglandin], thereby reducing inflammatory response (80,81). NO is an important mediator in inflammatory response and its overproduction can lead to tissue damage. Carnosine reduces the production of NO by inhibiting the expression of inducible NO synthase, thereby alleviating inflammatory damage (72). In addition, carnosine can also inhibit the activity of cyclooxygenase-2, reduce the production of prostaglandins and further alleviate the inflammatory response (82). v) Promotion of tissue repair: Carnosine can promote tissue repair after inflammation and accelerate the healing of injured tissue. The attenuation of inflammatory response and tissue repair are important steps in the treatment of inflammatory diseases. Carnosine enhances tissue regeneration by promoting cell proliferation and migration. For instance, in models of skin lesions and ulcers, carnosine significantly accelerated wound healing and reduced scarring (17).

3. Application of carnosine in disease treatment

Studies have demonstrated that carnosine exhibits significant protective effects across multiple disease systems (Fig. 3). In neurodegenerative disorders such as AD and PD, carnosine is implicated in mitigating oxidative stress and protein aggregation. Its role in diabetes, particularly in preventing complications like diabetic nephropathy, has also been recognized. Furthermore, carnosine contributes to cardiovascular health by alleviating conditions like atherosclerosis and myocardial ischemia-reperfusion injury. In oncology, its antioxidant, anti-inflammatory and anti-tumor properties provide a promising adjunct in cancer therapy. Additionally, carnosine shows potential in protecting against age-related eye diseases including macular degeneration and cataract. These diverse applications highlight carnosine's multifunctional nature and establish a strong rationale for exploring its clinical relevance in greater depth.

Neurodegenerative diseases

AD. AD is a common neurodegenerative disease characterized by Aβ deposition and loss of neurons, leading to progressive decline in cognitive function (83). Studies have shown that carnosine plays an important role in the treatment of AD and can delay the progression of the disease through multiple mechanisms. First, carnosine can bind to Aβ, inhibiting its aggregation and toxicity, thereby reducing the damage caused by Aβ to neurons (84). Abnormal aggregation of Aβ is one of the core pathological features of AD and its toxicity can lead to neuronal dysfunction and death. Secondly, carnosine, through its powerful antioxidant effect, can clear free radicals in neurons and reduce the damage of neurons caused by oxidative stress (63). Oxidative stress plays a key role in the pathogenesis of AD, where excess free radicals attack the lipid membranes, proteins and DNA of neurons, leading to the destruction of cell structure and function. In addition, carnosine can also inhibit the inflammatory response of neurons and reduce the release of inflammatory factors (such as TNF-α and IL-6), thus reducing inflammatory damage to neurons (28). Neuroinflammation is

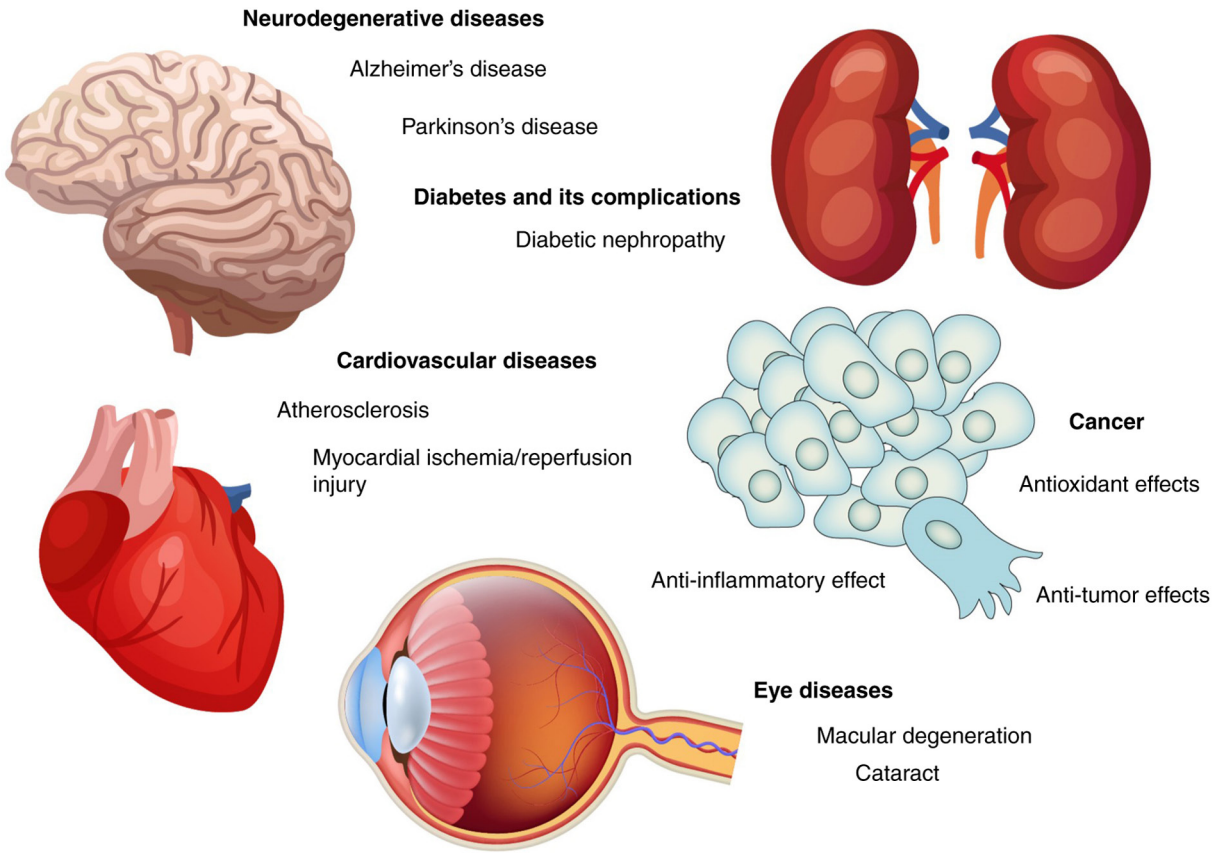

Figure 3. Multiple applications of carnosine in disease treatment.

another important pathological feature of AD, and excessive release of inflammatory factors aggravates neuronal damage and cognitive decline.

PD. PD is a neurodegenerative disease characterized by loss of dopaminergic neurons, characterized by motor dysfunction and cognitive decline (85). Studies have shown that carnosine plays an important role in the treatment of PD and can delay the progression of the disease through a variety of mechanisms. Firstly, carnosine, through its powerful antioxidant effect, can clear free radicals in dopaminergic neurons and reduce the damage of neurons caused by oxidative stress (86). Oxidative stress is one of the core pathological mechanisms of PD. Free radicals generated during dopamine metabolism attack neurons, leading to the destruction of cell structure and function. Secondly, carnosine can inhibit the inflammatory response of dopaminergic neurons and reduce the release of inflammatory factors (such as TNF-α and IL-6), thereby reducing inflammatory damage to neurons (87). Neuroinflammation plays an important role in the pathogenesis of PD, and excessive release of inflammatory factors can aggravate neuronal injury and motor dysfunction. In addition, carnosine can regulate the release and metabolism of dopamine and maintain the balance of neurotransmitters, protecting the function of dopaminergic neurons. The imbalance of dopamine metabolism is an important pathological feature of PD. Experimental studies report that carnosine ameliorates motor deficits in PD models, associated with increased dopamine or dopamine metabolite levels (88).

Diabetes and its complications

Diabetes. Diabetes is a metabolic disease characterized by high blood sugar, and long-term high blood sugar can lead to a variety of complications, including vascular disease, and neuropathy and kidney disease (89). Studies have shown that carnosine plays an important role in the treatment of diabetes and can delay the progression of complications through multiple mechanisms. Firstly, carnosine, through its anti-glycation effect, can inhibit the non-enzymatic reaction between proteins and sugars and reduce the formation of AGEs (90). The accumulation of AGEs is a core pathological mechanism of diabetic complications, which can lead to vascular sclerosis, neurological dysfunction and glomerular injury. Secondly, carnosine, through its powerful antioxidant effect, can clear free radicals and reduce the damage of blood vessels and nerves caused by oxidative stress (77). Oxidative stress plays a key role in the pathogenesis of diabetes complications, as excess free radicals attack vascular endothelial cells and nerve cells, leading to their dysfunction and structural destruction. In addition, carnosine can directly protect blood vessels and nerves from the damage of hyperglycemia and maintain their physiological function. For instance, carnosine inhibits hyperglycemia-induced apoptosis of vascular endothelial cells and neurofibrosis, and thus delays the progression of diabetic complications (91).

Diabetic nephropathy. Diabetic nephropathy is one of the major complications of diabetes, characterized by glomerular sclerosis and progressive decline in kidney function, which may eventually lead to end-stage renal disease (92). Studies

have shown that carnosine plays an important role in the treatment of diabetic nephropathy and can delay the progression of the disease through multiple mechanisms. First, carnosine can clear free radicals in the glomeruli and reduces damage caused by oxidative stress to the glomeruli (93). Oxidative stress is one of the core pathological mechanisms of diabetic nephropathy. Free radicals induced by hyperglycemia attack glomerular cells, leading to the destruction of their structure and function. Secondly, carnosine can inhibit the inflammatory response of the glomeruli and reduce the release of inflammatory factors (such as TNF-α and IL-6), and thus reduces inflammatory damage to the glomeruli. Chronic inflammation plays an important role in the pathogenesis of diabetic nephropathy. Excessive release of inflammatory factors may aggravate glomerular sclerosis and renal function decline (94,95). In addition, carnosine can directly protect the structure and function of the glomeruli, inhibit apoptosis and fibrosis induced by hyperglycemia, and delay the deterioration of renal function (96,97). For instance, carnosine can reduce the thickening of the glomerular basement membrane and the expansion of the mesangial matrix, maintaining glomerular filtration function (98).

Cardiovascular diseases

Atherosclerosis. Atherosclerosis is a type of cardiovascular disease characterized by lipid deposition and chronic inflammatory response in blood vessel walls, and is the primary pathological basis of cardiovascular and cerebrovascular events such as myocardial infarction and stroke (99). Studies have shown that carnosine plays an important role in the treatment of atherosclerosis and can delay the progression of the disease through multiple mechanisms. First, carnosine, through its antioxidant effect, clears free radicals in the blood vessel wall and reduces oxidative stress damage to vascular endothelial cells (100). Oxidative stress is one of the core pathological mechanisms of atherosclerosis. Oxidative modification of low-density lipoprotein promotes the formation of foam cells and lipid deposition in blood vessel walls. Secondly, carnosine can inhibit the inflammatory response of the blood vessel wall and reduce the release of inflammatory factors, thereby reducing the damage of inflammation to the blood vessel wall (74). Chronic inflammation plays a key role in the pathogenesis of atherosclerosis, with excessive release of inflammatory factors exacerbating vascular endothelial dysfunction and plaque formation. In addition, carnosine can directly protect the structure and function of the blood vessel wall, inhibit the abnormal proliferation and migration of vascular smooth muscle cells and thus maintain the normal physiological function of blood vessels (101).

Myocardial ischemia-reperfusion injury. Myocardial ischemia-reperfusion injury is one of the primary complications in the treatment of myocardial infarction. Its pathological process involves several complex mechanisms such as oxidative stress, inflammation and apoptosis, which ultimately lead to the dysfunction and death of cardiomyocytes (102). Studies have shown that carnosine plays an important role in the treatment of myocardial ischemia-reperfusion injury and can alleviate myocardial injury through multiple mechanisms. Firstly, carnosine, through its antioxidant effect, clears free radicals in cardiomyocytes and reduces oxidative stress damage to cardiomyocytes (103-105). During ischemia-reperfusion, a large number of free radicals are produced, which attack the lipid membrane, protein and DNA of cardiomyocytes, destroying cell structure and function. Secondly, carnosine can inhibit the inflammatory response of cardiomyocytes and reduce the release of inflammatory factors, thus reducing inflammatory damage to cardiomyocytes. Inflammatory response plays a key role in ischemia-reperfusion injury. Excessive release of inflammatory factors can aggravate apoptosis and necrosis of cardiomyocytes. In addition, carnosine can directly protect the structure and function of cardiomyocytes, inhibit apoptosis and mitochondrial dysfunction, and thus maintain the systolic and diastolic functions of myocardium (7).

Cancer

Antioxidant and anti-inflammatory effects. The occurrence and development of cancer are closely related to oxidative stress and inflammatory response, which not only promote the proliferation and metastasis of cancer cells, but also lead to damage to normal tissues (106). Research has shown that carnosine plays an important role in cancer treatment, delaying cancer progression and reducing treatment side effects caused by treatments through multiple mechanisms. First, carnosine, through its antioxidant effect, can clear free radicals in cancer cells and reduce oxidative stress damage to cancer cells (107). Oxidative stress plays a key role in the development and progression of cancer, and excess free radicals can damage DNA, leading to genetic mutations and carcinogenesis. Secondly, carnosine can inhibit the inflammatory response of cancer cells and reduce the release of inflammatory factors, thus reducing the promoting effect of inflammation on cancer cells (108). Chronic inflammation is an important driver of cancer, and excessive release of inflammatory factors will promote the formation of the tumour microenvironment and invasion of cancer cells. In addition, carnosine protects normal cells from damage caused by oxidative stress and inflammatory responses, reducing side effects caused by cancer treatments such as radiation and chemotherapy. For instance, carnosine reduces the oxidative damage to normal tissues caused by radiotherapy and the toxicity of chemotherapy drugs to healthy cells (109,110).

Anti-tumor effect. Studies have shown that carnosine exerts anti-tumor effects in preclinical settings, including *in vitro* and animal models, where it inhibits the proliferation and migration of cancer cells and induces apoptosis through various mechanisms. However, its application in cancer therapy has not yet entered routine clinical practice, and current evidence mainly derives from experimental studies. To date, only limited clinical investigations have been reported, and further trials are required to clarify its translational potential. First, carnosine inhibits the proliferation of cancer cells and slow the growth of tumours (2). The mechanism involves regulating the expression of cell cycle-related proteins, such as inhibiting Cyclin D1 and upregulating cyclin suppressor proteins (such as p21), and thus blocking the proliferation cycle of cancer cells (111). Secondly, carnosine can inhibit the migration of cancer cells and reduce metastasis of tumours (112). Carnosine reduces the invasion and migration of cancer cells by inhibiting the activity of matrix metalloproteinases and downregulating molecules associated with

epithelial to mesenchymal transition, such as N-cadherin and vimentin (113,114). In addition, carnosine can induce apoptosis of cancer cells and reduce tumor volume (115). The mechanisms include activation of mitochondria-dependent apoptotic pathways, upregulation of pro-apoptotic proteins (such as Bax) and downregulation of anti-apoptotic proteins (such as Bcl-2), thus promoting the programmed death of cancer cells (116).

Ocular diseases

Cataract. Cataract is an ocular condition characterized by the opacity of the lens, and its occurrence is closely related to oxidative stress and glycation reactions, which eventually lead to vision loss and even blindness (117). Studies have shown that carnosine plays an important role in the treatment of cataracts and can delay the progression of the disease through multiple mechanisms. First, carnosine, through its antioxidant effect, clears free radicals in the lens and reduces oxidative stress damage to lens proteins and lipids (118). Oxidative stress is one of the core pathological mechanisms of cataracts, and excessive free radicals attack the lens cells, leading to protein denaturation and lipid peroxidation. Secondly, carnosine can inhibit the glycation reaction of the lens and reduce the formation of AGEs (119). The accumulation of AGEs can lead to cross-linking and structural changes in lens proteins, which can lead to opacity. In addition, carnosine can directly protect the structure and function of the lens, maintaining its transparency and refractive properties. For instance, carnosine stabilizes the conformation of lens proteins, preventing their denaturation and aggregation (120).

Macular degeneration. Macular degeneration is an ocular disease characterized by damage to the macular area of the retina (121). The pathological process involves multiple mechanisms such as oxidative stress, inflammatory response and vascular abnormalities, which ultimately lead to loss of central vision. Studies have shown that carnosine plays an important role in the treatment of macular degeneration and can delay the progression of the disease through multiple mechanisms. Firstly, carnosine, through its antioxidant effect, clears free radicals in the retina and reduces the damage of retinal pigment epithelial cells and photoreceptor cells caused by oxidative stress (122,123). Oxidative stress is one of the core pathological mechanisms of macular degeneration, in which excess free radicals attack retinal cells, leading to their dysfunction and death. Secondly, carnosine inhibits inflammatory responses in the retina and reduces the release of inflammatory factors, thus reducing inflammatory damage to the retina. Chronic inflammation plays a key role in the pathogenesis of macular degeneration, with excessive release of inflammatory factors exacerbating retinal cell apoptosis and vascular abnormalities. In addition, carnosine can directly protect the structure and function of the retina, inhibit the degeneration of retinal pigment epithelial cells and the loss of photoreceptor cells, and maintain the normal physiological function of the retina (124,125).

Clinical evidence and research limitations. To provide a balanced and comprehensive overview, the clinical studies investigating carnosine and its derivatives across different disease contexts are summarized in Table I (90,126-155). At present, existing clinical studies on carnosine can mainly be categorized into three groups based on the form of administration: i) Carnosine alone; ii) complexes containing carnosine; and iii) carnosine as an adjunct therapy. Most studies are randomized controlled trials, predominantly small-scale in design. The administered dosage ranges from 400 mg to 4 g, with an observation period of 2-3 months. The therapeutic effects vary across different diseases, as detailed in Table I. The table includes both positive and negative findings, thus addressing not only the reported therapeutic benefits but also inconclusive or contradictory outcomes. There are certain limitations in the research on carnosine: First, certain studies report contradictory results. Second, several studies lack endpoints with direct clinical relevance. Additionally, carnosine was often administered in combination formulations, making it difficult to isolate its individual effects. Finally, larger, well-designed clinical trials are required to confirm its efficacy across different disease contexts. Overall, the current clinical evidence remains limited in scale and rigor, underscoring the need for larger, well-controlled trials to establish the therapeutic value and safety profile of carnosine in human disease.

Dose-response and safety profile

Dose-response. Preclinical studies have explored a range of carnosine dosages across various disease models, typically between 50-500 mg/kg body weight in rodents, depending on the route of administration and experimental design. However, in certain cases, the dosage can be as low as 10 mg/kg, or even reach ≥1,000 mg/kg (156,157). In neurodegenerative models, oral or intraperitoneal doses of 100-250 mg/kg have shown significant antioxidative and anti-aggregation effects (158,159). In cardiovascular models, the effective treatment doses vary. A dose of 250 mg/kg significantly reduces oxidative stress in the myocardium of mice with isoproterenol-induced myocardial infarction, whereas a dose of 10 mg/kg is used to modulate the circadian resetting of clock genes in the rat heart (157,160). In clinical trials, carnosine is currently administered at doses ranging from 500 mg to 2 g/day. In a 14-week study on prediabetes and type 2 diabetes for glycemic control, oral supplementation with 2 g/day of carnosine significantly reduced blood glucose levels at 90 and 120 min during an oral glucose tolerance test, as well as the total area under the glucose curve (126). In patients with major depressive disorder receiving 400 mg of L-carnosine twice daily, symptoms showed significant improvement compared to the control group (149).

Safety profile. The majority of studies suggest that oral carnosine is safe within the commonly used dose range (0.1-2 g) (161). However, certain studies reported a higher incidence of adverse events compared to placebo (30 vs. 14%) (152). Despite this, the adverse effects were generally mild and manageable, indicating that carnosine supplementation is overall well-tolerated.

4. Discussion

As a naturally occurring dipeptide, carnosine has shown wide potential for the treatment of diseases due to its multiple biological functions (such as antioxidant, anti-glycation, neuroprotective, anti-inflammatory and immunomodulatory). Its advantage lies in its multi-target mechanism of action,

Table I. Summary of clinical trials of carnosine in various diseases.

A, Carnosine

Study design	Disease	Participant	Dosage	Results	(Refs.)
RCT	T2DM	43 adults with prediabetes or T2DM	2 g/day, 14 weeks	Decreased blood glucose and total glucose area under the curve	(126)
RCT	T2DM	30 nondiabetic individuals with overweight and obesity	2 g/day, 12 weeks	Lower fasting insulin, insulin resistance and 2 h glucose/insulin	(127)
RCT	T2DM	54 patients	1 g/day, 12 weeks	Lowered fasting glucose, TGs, AGEs, TNF-α without changes in sRAGE, IL-6, IL-1β	(90)
RCT	T2DM	49 adults with prediabetes or well-controlled T2DM	2 g/day, 14 weeks	No difference in cytokine and adipokine changes between groups	(128)
RCT	Diabetic nephropathy	40 patients	2 g/day, 12 weeks	Urinary TGF-β significantly decreased	(129)
Secondary analysis	Musculoskeletal conditions	49 participants with prediabetes or T2DM without musculoskeletal conditions	2 g/day, 14 weeks	No improvement in muscle strength, body composition or bone health	(130)
RCT	ASCVD	49 adults with prediabetes or well-controlled T2DM	2 g/day, 14 weeks	No improvement in cardiovascular or metabolic risk factors	(131)
Secondary analysis	Obesity	22 overweight or obese healthy adults	2 g/day, 12 weeks	Partial normalization of serum adipokines	(132)
RCT	Dyslipidemia	24 overweight and obese adults	2 g/day, 12 weeks	Potential benefits on plasma lipidome	(133)
Prospective, single-group interventional trial	ASD	31 children aged 3 to 6 years with mild to moderate ASD	10-15 mg/kg twice a day for 2 months	Ineffective for managing ASD in children	(134)
RCT	Sleep disorders in autism	43 patients aged 4 to 16 years	500 mg/d, 2 months	Improved sleep disturbances, especially duration and parasomnias	(135)
Post-hoc analysis	Cognitive abilities	299 participants	2 g/day, 12 weeks	Significant cognitive improvements in the youngest age group	(136)
Case report	Multiple sclerosis	3 patients	2 g/day, 8 weeks	Reduced symptom presence and severity	(137)
RCT	Schizophrenia	100 patients	400 mg for 12 weeks, then 800 mg from week 13 to study end	Attention scores improved but negative symptoms unchanged	(138)
Controlled and cross-over study	Not available	14 male athletes	4 g/day, 14 days	Antioxidant protection	(139)

Table I. Continued.

A, Carnosine

Study design	Disease	Participant	Dosage	Results	(Refs.)
RCT	Oxaliplatin-induced peripheral neuropathy	65 patients	500 mg/day, 3 months	Neuroprotection effect	(140)

B, Carnosine complex

Study design	Disease	Participant	Content	Results	(Refs.)
RCT	Sarcopenia	59 participants	Hydroxy-methyl-butyrate, carnosine and magnesium	Improved muscle mass and function	(141)
RCT	MCI	54 subjects	Anserine/ carnosine	Possible protective effect against cognitive decline in APOE4(+) MCI subjects	(142)
RCT	Radiotherapy-related dysphagia	40 patients	Zinc-L-carnosine	Prevented radiotherapy-related dysphagia and reduced steroid use	(143)
RCT	UC	28 patients with active UC	Zinc-carnosine chelate compound	Zinc-carnosine enema may accelerate mucosal healing	(144)
Non-RCT	Pressure ulcer	42 patients with stage II-IV pressure ulcers	Carnosine and its zinc complex	Accelerated pressure ulcer healing	(145)
RCT	Primary open angle glaucoma	22 patients	Food supplement containing carnosine	Further intraocular pressure reduction; pattern electroretino-gram amplitude and foveal sensitivity improved	(146)

C, Carnosine adjunct therapy

Study design	Disease	Participant	Dosage	Results	(Refs.)
RCT	Diabetic nephropathy	90 patients	1 g/day, 12 weeks	Improved oxidative stress, glycemic control and renal function	(147)
RCT	CHF	50 patients with stable CHF and severe left ventricular systolic dysfunction	500 mg/day, 6 months	Improved exercise performance and quality of life in stable CHF added to conventional therapy	(148)
RCT	Major depressive disorder	58 patients	400 mg twice a day, 6 weeks	Carnosine + citalopram improved symptoms	(149)

Table I. Continued.

C, Carnosine adjunct therapy

Study design	Disease	Participant	Dosage	Results	(Refs.)
RCT	OCD	44 patients with moderate to severe OCD	500 mg twice a day, 10 weeks	Significant reduction of symptoms as adjuvant to fluvoxamine	(150)
RCT	Schizophrenia	63 patients	1 g twice a day, 8 weeks	Reduced primary negative symptoms as an add-on to risperidone	(151)
RCT	Schizophrenia	75 symptomatically stable adults	2 g/day, 3 months	Potential adjunct for executive dysfunction; more adverse events	(152)
RCT	Attention-deficit/hyperactivity disorder	56 drug-free children and adolescents aged 6-17 years old	400 mg twicea day, 8 weeks	Carnosine + methylphenidate may benefit children	(153)
RCT	ASD	70 drug-free children aged 4-12 years	400 mg twice a day, 10 weeks	Improved hyperactivity/noncompliance as an adjunctive therapy to risperidone; no effect on irritability	(154)
RCT	ASD	67 children aged 3-6 years with mild to moderate ASD	10-15 mg/kg twice a day, 2 months	No improvement in CARS2-ST, ATEC, BEARS or 6-GSI scores	(155)

TG, triglycerides; AGEs, advanced glycation end-products; APOE, apolipoprotein E; sRAGE, soluble receptor for AGEs; ASD, autism spectrum disorder; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; MCI, mild cognitive impairment; UC, ulcerative colitis; CHF, chronic heart failure; OCD, obsessive-compulsive disorder; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; ASCVD, atherosclerotic cardiovascular disease; IL-1β, interleukin-1β.

which can simultaneously act on multiple pathological links such as free radicals, inflammatory factors and glycation reaction, thus playing a comprehensive protective role in a variety of diseases. For instance, in neurodegenerative diseases, carnosine is not only able to clear free radicals from neurons and reduce oxidative stress, but also inhibits inflammatory responses and regulates neurotransmitters, thereby delaying disease progression. In diabetes and its complications, carnosine reduces the formation of AGEs by inhibiting the glycation reaction and antioxidant effects, and protects blood vessel and nerve function. In addition, carnosine has also demonstrated significant therapeutic effects in cardiovascular diseases, cancer and ocular diseases, showing its broad therapeutic prospects. Another significant advantage of carnosine is its high safety profile. As an endogenous substance, carnosine has a clear metabolic pathway in the body, fewer side effects and is suitable for long-term use (162). This gives carnosine a unique advantage in the treatment of chronic diseases such as diabetes, AD and atherosclerosis.

However, although carnosine has shown notable potential in the treatment of diseases, its practical application still faces certain challenges and limitations. First, the low bioavailability of carnosine is one of the major factors limiting its clinical application (30). Carnosine is easily degraded by enzymes (such as carnosinase) in the body, resulting in a short half-life and difficulty in reaching effective concentrations in target tissues. Secondly, the efficacy of carnosine is dose-dependent, and high doses may result in certain side effects, such as gastrointestinal discomfort or metabolic burden. In addition, the current clinical data on carnosine remain insufficient; most studies are still in the basic experimental stage and there is a lack of translational or large-scale, multi-center clinical trial data (Table I). Thus, carnosine faces certain scientific and normative hurdles before it can be adopted for clinical use.

Despite these challenges, the future prospects of carnosine in disease treatment remain promising. First, the bioavailability and stability of carnosine can be improved through pharmacochemical modification or nanotechnology. For instance, combining carnosine with carrier molecules or developing sustained-release formulations can extend its action time *in vivo* and increase the drug concentration in target tissues (29). Second, combining the concept of precision medicine and developing a personalized carnosine treatment program can further improve the treatment effect and reduce side effects. For instance, genetic testing and metabolomics analysis are used to screen out patient populations that are sensitive to carnosine therapy and optimize dosage and administration. In addition, carnosine combined with other drugs or therapies also has broad prospects. For instance, in cancer treatment, carnosine can be used in combination

with chemotherapeutic drugs or immunotherapy to reduce the side effects of treatment through its antioxidant and anti-inflammatory effects while enhancing anti-tumor effects. In neurodegenerative diseases, carnosine can be used in combination with neurotrophic factors or anti-inflammatory drugs to play a synergistic therapeutic role.

In the future, large-scale clinical trials are key for establishing the clinical application of carnosine. Through multi-center, randomized controlled clinical trials, the safety and efficacy of carnosine in different diseases can be systematically evaluated to provide a scientific basis for its clinical application. In addition, further research on the mechanism of carnosine and exploring its novel targets and novel means in the treatment of diseases will also open up new directions for its application. For instance, studying the role of carnosine in epigenetic regulation, mitochondrial function repair and immune microenvironment regulation may provide new ideas for its application in complex diseases such as cancer and autoimmune diseases.

5. Conclusion

As a natural dipeptide with multiple biological functions, carnosine has shown wide application potential in the treatment of diseases. In the present review, the research progress on carnosine for neurodegenerative diseases, diabetes and its complications, cardiovascular diseases, several types of cancer and ophthalmic diseases was systematically reviewed, highlighting its unique mechanism of action in antioxidant, anti-glycation, neuroprotective, anti-inflammatory and immunomodulatory aspects. Combining basic experiments and clinical studies, carnosine not only provides novel ideas for the treatment of several complex diseases, but also lays the foundation for its application in precision medicine and personalized therapy. However, despite significant advances in carnosine research, issues such as its bioavailability, dose optimization and long-term safety in clinical applications still need to be further explored. In the future, carnosine may play a greater role in disease treatment through pharmacochemical modification, nanotechnology and combined application with other therapeutic means. Similarly, large-scale, multicenter clinical trials will be a key step in moving carnosine from the laboratory to the clinic. Overall, carnosine research will not only provide a novel strategy for disease treatment, but may also serve as a model for the development and application of natural active substances.

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Authors' contributions

CF conceived the present review. CF and YH designed the review. YH, DX and LX wrote the manuscript, conducted the literature investigation and interpreted the related literature, and prepared the figures. YH, ZN and DX critically analyzed the key knowledge in the present review. LX, CS and DX edited and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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