Table S1

Study characteristics (continued)

Author, year	Country	Sample size (Control / Intervention)	Patient Population	Comorbidities	Mechanism of action
Studies in cancer patients					
Magdy R et al. (2018)	Egypt	31/30	Colorectal cancer	Nil	L-carnosine exerted a neuroprotective effect against OIPN in colorectal cancer patients by targeting Nrf-2 and NF-κB pathways.
Kitagawa J et al. (2020)	Japan	47/41	AML, ALL, Chronic mylogenous leukaemia, B-lymphoblastic leukaemia, Malignant lymphoma, Multiple myeloma, Myelodysplastic syndromes and others with HSCT	Not mentioned	Animal models of stomach cancer and colon cancer showed that PZ inhibits the production of inflammatory cytokines, including TNF-α, IL-1β, IL-6 and MMP-2, and induces an anti-inflammatory effect and immune responses via inhibition ofNF-κB. All of those cytokines and signal molecules are considered to be involved in the pathogenesis of chemotherapy-induced oral mucositis. Additionally, PZ inhibits the production of ROS and induces IGF-1, a polypeptide that plays an important role in gastric epithelial wound repair.
Studies in cardiovascular disease patients					

Lombardi C et al. (2014)	Italy	25/25	HF	CAD, HTN, DM, Dyslipidaemia, COPD, AF, CRT	An increase in muscle L-carnosine levels may improve contractility and reduce fatigue. Other mechanisms include regulatory effects on myocardialCa^{2+} levels, an increase in sensitivity of Ca^{2+}-release channels and of the contractile apparatus, with favourable effects on cardiac contractility and function. Thus, carnosine is potentially useful as an addition to standard therapy of the patients with HF. L-carnosine may involve an increase in Ca^{2+}sensitivity of the contractile apparatus in both type I and type II fibres that directly increase muscle force. L-carnosine has also favourable effects on Ca^{2+} homeostasis which may allow an improvement in cardiac function.
Yoshikawa F et al. (2019)	Japan	26/24	ST elevation MI (Primary acute MI)	Not mentioned	Its mechanism of action is believed to involve oxygen radical scavenging, antioxidation, and acceleration of wound healing. Accumulating evidence suggests that PZ exerts gastric mucosal cytoprotection and promotes ulcer healing through multiple mechanisms including antioxidant activity. Furthermore, it has recently been reported that the zinc derivative, PZ induces the mobilization of mesenchymal stem cells and the mRNA

					expression of IGF - 1 in vascular endothelial cells to protect injured gastric tissue or skin. Zinc has been shown to have an effect on myocardial ischemia/reperfusion
Studies in diabetes mellitus patients					
Federici A et al. (2015)	Italy	25/25	T2DM and moderate-to-severe foot skin dryness	Not mentioned	Arginine is an important substrate for NO production and arginine supplementation improves microcirculation in diabetes. Finally, urea and carnosine could favourably interfere with the formation and accumulation of AGE.
Houjeghani S et al. (2017)	Iran	22/22	T2DM	Not mentioned	A probable mechanism responsible for the hypoglycaemic property of L-carnosine is its ability to act as a precursor of histamine, to regulate the autonomic nervous system via the H3 receptor. A proof for such a receptor-mediated mechanism originates from the similar hypoglycaemic effects evoked by L-histidine and histamine. On the other hand, L-carnosine is capable of inhibiting glycation of proteins thus haemoglobin glycation was suppressed by L-carnosine intake. The anti-glycating mechanism may account for the meaningful reduction in serum AGEs,

					since L-carnosine supplementation resulted in improved control of fasting blood sugar. L-carnosine contributes to an anti-inflammatory effect is its inhibitory effect on AGEs formation which in turn suppresses inflammatory response, activated by NF-κB, and consequently attenuating TNF-α release.
Karkabounas S et al. (2018)	Greece	82	T2DM	Not mentioned	The absence of studies that provide solid evidence for a direct glucose lowering action of thiamine, we concluded that the reduction of FBG in the supplementation group was an effect possibly caused by ALA and carnosine application. Carnosine might act indirectly by promoting the enhancement of the endogenous antioxidant system activity.
Siriwattanasit N et al. (2021)	Thailand	20/20	T2DM	HTN, Dyslipidaemia, CAD, Chronic lung Disease	Carnosine has many biological qualities that can slow CKD progression and prevent diabetic nephropathy from developing. One of the proposed mechanisms is that it inhibits the synthesis of TGF-β. It has been hypothesized that individuals with two copies of the CNDP1 Mannheim have lower activity of plasma carnosinase, leading to higher plasma carnosine concentrations and a lower risk of diabetic

					nephropathy. One study has shown that oral carnosine supplementation could reduce albuminuria and urinary alpha-1 microglobulin level in T1DM
Studies in neurodegenerative disorder patients					
Chengappa KN et al. (2012)	USA	37/33	Schizophreniaor schizoaffective disorder	Not mentioned	The exact mechanisms that underlie cognitive dysfunction in schizophrenia remain elusive, glutamate excitotoxicity and NMDA receptor hypo function combined with impaired cellular antioxidant defences offer testable possibilities for improving executive dysfunction. L-carnosine taken together with the impaired cellular anti-oxidant defences and dysfunctional glutamatergic modulation reported in persons with schizophrenia make carnosine a promising candidate drug for enhancing cognitive performance.

Budzen S et al. (2014)	Poland	25/26	Patients should be at least 65 years old. Also, the subjects should not be engaged in any physical exercises programme for at least 1 year	Nil	According to cell studies using neurons, carnosine prevents cell death.β-alanine supplementation increases the carnosine level in skeletal muscles among the elderly and improves their exercise capacity. Anserine could also be used therapeutically due to it's slower than carnosine degradation by plasma. Carnosine imply that it is an anti-aging agent, and various nutritional supplement manufacturers claim its benefits in treating neurodegenerative diseases, such as AD.
Hisatsune T et al. (2016)	Japan	20/19	Elderly people	Not mentioned	Carnosine is an endogenous dipeptide consisting of β-alanine and histidine, present in the millimolar range in skeletal muscle and in the hundred micromolar range in the vertebrate brain. Carnosinehas many biochemical functions, including buffering, metal ion chelating, antioxidant, and anti-glycation activities, and a wide variety of physiological functions, mainly in excitable cells, including skeletal, cardiac, and smooth muscle cells, and nerve cells.
Katakura Y et al. (2017)	Japan	30/30	Elderly people	Not mentioned	The mechanism underlying the preservation of verbal episodic memory in elderly people, as evaluated by the WMS-LM. Normal aging is associated with an increase

					in inflammatory chemokines, such as eotaxin 1, in the blood, and this elevation is related to cognitive decline.
Ghajar A et al. (2018)	Iran	30/30	Schizophrenia	Not mentioned	NMDA modulatory activity of l-carnosine might be associated with significant improvement observed in negative symptoms. The mechanism of action and functions of carnosine in the brain however, anti-oxidant, NMDA modulatory, glutamatergic, and histaminergic effects are proposed. Anti-inflammatory mechanisms are becoming of interest in treating neuropsychiatric disorders including schizophrenia.
Masuoka N et al. (2019)	Japan	25/25	CDR was utilized to adopt subjects from outpatients. gloCDR score of all participant candidates was 0.5 at the baseline	Not mentioned	Anserine/carnosine supplements are ingested, these peptides directly and/or indirectly resulted in the protection of the degenerative cellular changes of brain microvascular pericytes which can be triggered by the accumulation of amyloid-beta peptides; however, further studies are required to determine the precise mechanisms by which ACS affects brain function in APOE4 (+) individuals.

OIPN=Oxaliplatin -induced peripheral neuropathy, Nrf-2 = human nuclear factor erythroid 2- related factor; NF-κB = human nuclear factor-kappa B; AML= Acute myeloid leukaemia, ALL= Acute lymphoid leukaemia, HSCT= Hematopoietic stem cell transplantation; PZ = Polaprezinc; TNF-α = Tumor necrosis factor-alpha; IL-1β =interleukin-1β; IL-6= interleukin-6; MMP-2= matrix metalloproteinase-2; NF-κB= nuclear factor-kappa light-chain-enhancer of activated B cells, ROS=reactive oxygen species, IGF-1= insulin like growth factor-1; CAD= coronary artery disease; HTN=Hypertension, DM=Diabetes mellitus, COPD= chronic obstructive pulmonary disease; AF= Atrial fibrillation; CRT= ; HF= Heart failure; Ca(2+)= calcium; MI=Myocardial Infarction; T2DM= Type 2 diabetes mellitus; NO= Nitric Oxide; H3 receptor= Histamine-3 receptor; FBG= Fasting blood glucose; ALA= α-lipoic acid; CKD= Chronic kidney disease; CNDP1= Carnosine Dipeptidase;T1DM= Type 1 Diabetes mellitus; NMDA= N-Methyl-D-aspartic acid; AD=Alzheimer disease; WMS-LM= Wechsler memory scale–logical memory; CDR = Clinical Dementia Rating; gloCDR= global Clinical Dementia Rating; ACS = Anserine and Carnosine Supplementation; APOE4= Apolipoprotein E4.