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Review

Influence of Oxidative Stress-Mediated Inflammation on the Pathogenesis of Reproductive Disorders: Exploring the Benefits of Carnosine for Prevention and Treatment of Endometriosis

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Abstract

Endometriosis is a chronic pathological condition characterized by the growth of endometrial-like tissue outside the uterine cavity and is frequently associated with severe pain, persistent inflammation, and fibrosis within the pelvic region and other parts of the body. The exact causes of endometriosis are not clear, but an innate or adaptive immune response defect has recently been suggested as a factor in the disease's development. Carnosine is a natural dipeptide formed by the ligation of β-alanine and L-histidine and characterized by a multimodal mechanism of action that includes antioxidant and anti-inflammatory activities. Carnosine has also been shown to modulate glucose, nucleotide, and lipid metabolism as well as the response of immune cells, all processes that play a key role in the context of endometriosis. Despite numerous reviews published on the structure, role, function, and biological activities of carnosine in preclinical and clinical settings, none have focused on its therapeutic potential for the prevention or treatment of reproductive disorders, including endometriosis. In this review, after a brief introduction to the pathogenesis and pathophysiology of endometriosis, we focus on the use of carnosine for the management of reproductive disorders, concluding with its ability to modulate specific cellular and molecular mechanisms closely related to endometriosis. Given the central role of oxidative stress and inflammation across several reproductive disorders, carnosine may represent a promising therapeutic candidate not only in endometriosis, but also in broader reproductive health contexts.

Keywords: reproductive health; endometriosis; carnosine; inflammation; oxidative stress; iron overload; immune system phenomena; macrophage polarization; microglia; neuroprotection

1. Introduction

Endometriosis is a chronic, estrogen-dependent gynecological disease affecting approximately 10–15% of women of reproductive age. It is characterized by the presence of ectopic endometrial-like tissue (glands and stroma) outside the uterine cavity, most commonly within the pelvic region, and is associated with symptoms such as dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility [1]. The pathological lesions are associated with significant morbidity, a detrimental impact on quality of life, and considerable socioeconomic burden [2]. An increasing body of evidence has highlighted the pivotal role of oxidative stress and inflammation in the pathogenesis of endometriosis (Fig. 1) [1,3].

Oxidative stress occurs in the presence of an imbalance between reactive oxygen species (ROS) and antioxidant defenses, leading to oxidative damage and promoting a pro-inflammatory microenvironment. In particular, retrograde menstruation introduces erythrocytes and heme into the peritoneal cavity; their breakdown generates free iron, which catalyzes the formation of ROS via Fenton reactions, thereby damaging peritoneal tissues and contributing to lesion establishment and progression [1,4]. In addition, immunologic dysfunctions, such as impaired natural killer (NK) cells clearance and the accumulation of activated macrophages, sustain both oxidative stress and inflammation. Activated macrophages phagocytize erythrocyte debris and release pro-oxidant and pro-inflammatory

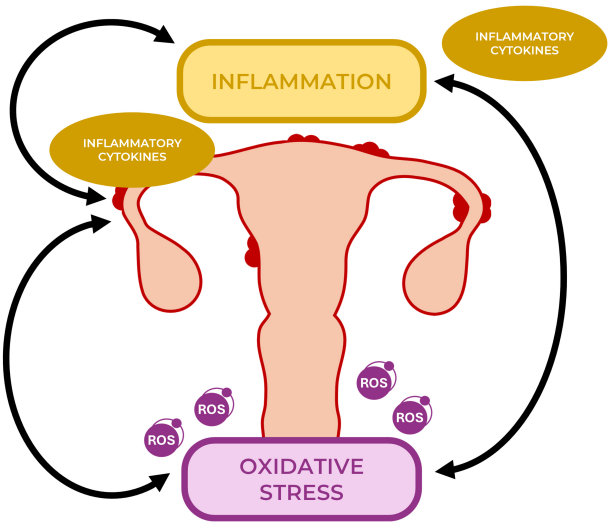

Fig. 1. Oxidative stress and inflammation in the pathogenesis of endometriosis. Oxidative stress and inflammation are key contributors to the pathogenesis of endometriosis. The excessive production of reactive oxygen species (ROS) and the release of inflammatory cytokines create a self-perpetuating cycle that exacerbates disease progression.

mediators, which further exacerbate this pathologic cycle (Fig. 1) [5,6]. Given the complex interplay between oxidative stress, inflammation, and immune dysregulation, targeting oxidative pathways represents an important strategy for reducing both symptomatic burden and lesion progression. In this context, the naturally occurring dipeptide carnosine (β-alanyl-L-histidine) emerges as a promising therapeutic agent. In fact, carnosine exhibits a robust antioxidant activity along with anti-inflammatory, metal-chelating, and anti-glycating properties. Additionally, it modulates metabolic and immune processes that overlap significantly with pathogenic mechanisms implicated in endometriosis [7,8]. While endometriosis is the primary focus of this review, the oxidative and inflammatory landscape explored is also relevant in other reproductive disorders such as polycystic ovary syndrome (PCOS) and male infertility, suggesting potential broader implications for carnosine-based interventions.

2. Molecular Pathogenesis and Key Mechanisms of Endometriosis

Understanding the multifactorial etiology of endometriosis is essential to identify therapeutic targets. Among the different theories, the major hypotheses explaining lesion formation are represented by retrograde menstruation, iron overload, and immune dysfunction linked to oxidative stress and inflammation.

The most widely accepted theory of retrograde menstruation and implantation, originally postulated by Sampson in the 1920s, suggests that menstrual debris flows backward through the fallopian tubes into the peritoneal cavity, allowing viable endometrial cells to implant and proliferate on peritoneal surfaces [9,10]. Although retrograde menstruation occurs in many women, the differential progression to endometriosis is thought to depend on additional factors such as iron overload and immune alterations [11]. Retrograde bleeding delivers erythrocytes and heme into the peritoneal cavity; their breakdown leads to the accumulation of free iron, which is responsible for the generation of harmful oxidative species through Fenton reactions [4]. Different studies demonstrate significantly elevated levels of free iron and ferritin in the peritoneal fluid of women with endometriosis compared to controls, with levels correlating with disease severity [12–14]. In addition, ferritin-loaded macrophages in lesions represent a further marker of iron deposition level. The resulting iron overload and ROS production cause oxidative damage, induce lipid peroxidation, and may trigger ferroptosis in peritoneal and follicular cells, potentially contributing to infertility [15–18]. ROS accumulation damages lipids, proteins, and DNA within peritoneal and ectopic tissues [19]. Studies have demonstrated increased oxidative biomarker levels (including malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG)) in peritoneal and follicular fluids of affected women [3,20–22]. Further, oxidative damage to mitochondria triggers mtDNA leakage, activating innate immune sensors like the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS–STING) pathway, which promotes autophagy and enhances the invasive and migratory capacity of ectopic stromal cells [23,24].

Regarding the immunologic aspect of the disease, in women with endometriosis, immune surveillance mechanisms appear deficient [25,26]. Key findings include reduced NK-cell cytotoxicity, altered macrophage activation, and an inflammatory peritoneal microenvironment [11,27]. This dysfunction impairs clearance of ectopic endometrial cells, promotes pro-oxidant and pro-inflammatory cytokine release (including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)), and allows the persistence of implants, which exacerbate oxidative stress and lesion progression [28–30]. In this context, a retrospective study conducted on females with reproductive failure and a history of endometriosis shows that peripheral NK cytotoxicity was significantly reduced, while it was observed an increased infiltration of uterine $CD68^{+}$ macrophages [31]. The activity of NK cells is regulated through the signals from their receptor NK group 2D (NKG2D), which represents an activating C-type lectin-like NK cell receptor involved in the elimination of transformed cells. After the binding to the related ligands, NKG2D triggers a cytotoxic response that activates NK cells [32]. Paradoxically, it has been reported that increased levels of soluble NKG2D ligands in the serum of cancer patients generate an inhibitory action on NK cells, which seems to be related to a strategy for cancer cells to avoid immune surveillance [33]. The importance of NKG2D ligands in the disease pathogenesis was demon-

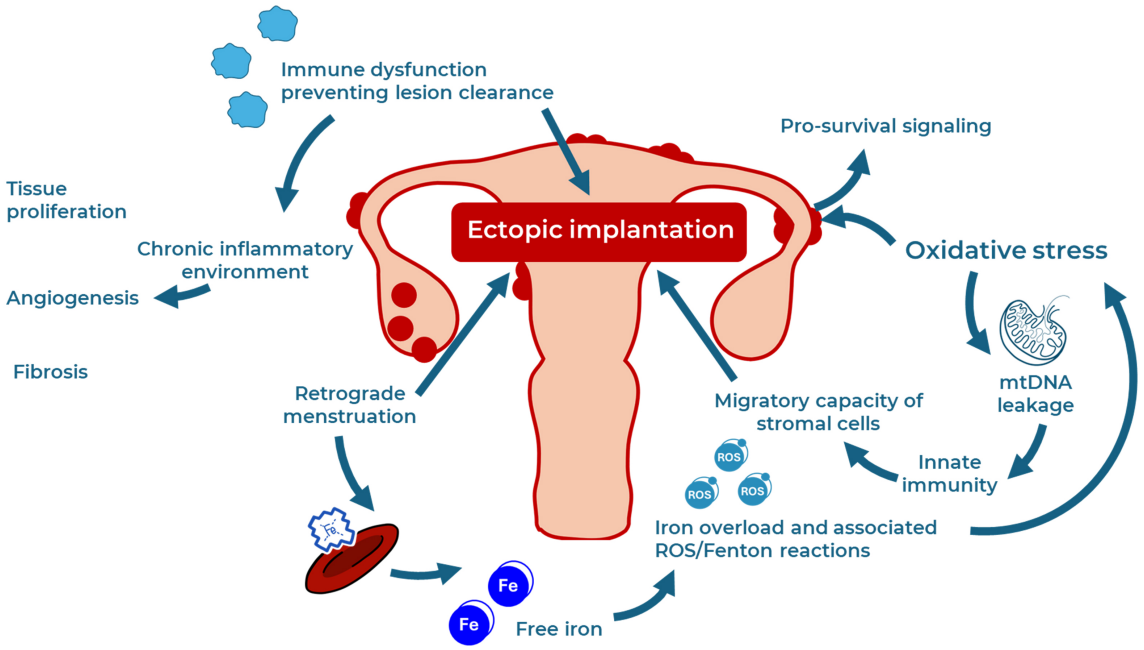

Fig. 2. Multifactorial etiology of endometriosis. Multiple mechanisms contribute to the etiology of endometriosis. These include ectopic implantation through retrograde menstruation, iron overload with consequent ROS generation and Fenton reactions, and immune dysfunctions that hinder lesion clearance. Oxidative stress further amplifies cellular damage, leading to mitochondrial DNA leakage that sustains stromal cell migration via innate immune activation. Additionally, oxidative stress promotes pro-survival signaling in ectopic cells. The resulting chronic inflammation drives tissue proliferation, angiogenesis, and fibrosis, all hallmarks of endometriosis pathogenesis.

strated in a prospective study conducted on endometriosis patients in which increased levels of NKG2D ligands in peritoneal fluid were associated to a reduced expression of these factors in ectopic endometrial cells surface, leading to an evasion from NK cells recognition [32]. The combined effects of immune dysfunction, iron-induced ROS production, and oxidative damage create a vicious cycle (Fig. 2).

Macrophages play a complex and multifaceted role in the development and progression of endometriosis [34]. In endometriotic lesions, macrophages exhibit altered phenotypes and functions, contributing not only to impaired clearance of menstrual debris but also to the establishment of a chronic inflammatory microenvironment that supports ectopic tissue survival and immune evasion [34]. In this context, macrophages are not able to manage damaged erythrocytes, but contribute to ROS and cytokine production [35]. These factors activate signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinases (MAPK), and cGAS–STING, which promote angiogenesis, tissue proliferation, and fibrosis, all hallmarks of lesion establishment and progression in the context of endometriosis [36–38]. In particular, ROS activate MAPKs such as ERK, p38, and JNK, leading to cellular senescence, enhanced stromal proliferation, and inflammatory gene expression, thus contributing to lesion maintenance [21,39–42]. Moreover, the reduced expression of antioxidant enzymes, such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT), has been reported in serum and peritoneal fluid, reflecting systemic and local depletion of antioxidant defenses [43–46]. This imbalance results in elevated levels of oxidative byproducts such as 8-isoprostane (8-iso-PGF2α) and advanced oxidation of protein products, further amplifying oxidative injury [47]. The overall result is a microenvironment characterized by chronic inflammation, oxidative stress, and immune evasion that supports the persistence of endometriotic implants (Table 1) [48].

This complex interplay underlines why oxidative stress and iron chelation are considered promising therapeutic targets, and why agents like carnosine, with both antioxidant and metal-chelating functions, deserved detailed exploration in this disease context.

3. Preclinical Insights Into the Therapeutic Potential of Carnosine in Endometriosis

Carnosine is a naturally occurring dipeptide composed of β-alanine and L-histidine, found at high concentration in excitable tissues such as skeletal muscle and brain. It exerts multiple physiological effects, including pH buffering, antioxidant, anti-inflammatory, metal-chelating, anti-glycating, and immunomodulatory activities, all properties which can be useful to counteract the oxidative stress and inflammation characterizing endometriosis [49–52].

Although direct studies in endometriosis models are not yet published, research in non-reproductive oxidative stress models offers a very solid mechanistic relevance.

Table 1. Molecular mechanisms involved in endometriosis pathogenesis.

Pathway	Component	Effect
ROS and lipid peroxidation	MDA, 8-iso-PGF2α	Endothelial dysfunction, pain, infertility
Iron overload	Free iron, ferritin, Fenton reactions	ROS production, ferroptosis
Antioxidant depletion	Thiols, GPX, SOD, catalase, total antioxidant capacity	Sustained oxidative damage
Signaling	NF-κB, MAPKs, cGAS–STING	Lesion growth, senescence, inflammation
Immune dysfunction	$\downarrow$ NK cytotoxicity, $\uparrow$ macrophage activation	Inadequate lesion clearance

MDA, malondialdehyde; GPX, glutathione peroxidase; SOD, superoxide dismutase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinases; cGAS–STING, cyclic GMP-AMP synthase-stimulator of interferon genes; NK, natural killer.

Carnosine has been reported to directly scavenge a variety of ROS, such as superoxide anion and hydroxyl radicals, and react with α,β-unsaturated aldehydes produced during lipid peroxidation [50,53]. It also enhances the activity of endogenous antioxidant enzymes, boosting cellular defenses [8]. In a zebrafish embryo model exposed to titanium dioxide nanoparticles, carnosine significantly reduced ROS production, inhibited stress marker expression (70 kDa-HSP (Hsp70), and metallothioneins), and protected against DNA and protein damage without affecting development [54]. Similarly, in intestinal stem cells challenged with mycotoxin deoxynivalenol, carnosine activated the Kelch-like ECH-associated protein 1 (Keap1)/Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling axis, enhancing antioxidant defenses, promoting cell survival, and preserving mucosal integrity [55]. Studies on mice oral mucosa cells treated with *tert*-butyl hydroperoxide demonstrated that carnosine lowered ROS levels, controlled DNA damage (8-OH-dG, γH2A.X), downregulated senescence markers ($p21^{Waf1}$), and attenuated activation of the Nrf2/heme oxygenase-1 (HO-1) pathway [56]. Furthermore, the preservation of GPX, the key enzyme preventing lipid peroxidation, appears pivotal to carnosine's protective effect; in fact, in ischemia-reperfusion models, carnosine increased GPX4 expression, decreased iron-induced lipid peroxidation, and inhibited ferroptosis [57]. As chelator of divalent transition metal ions, carnosine binds metals like Cu^{2+} and Fe^{2+}, preventing Fenton reaction and iron-catalyzed ROS production [51,58]. Inflammation in endometriosis is largely driven by ROS-mediated activation of NF-κB pathway, leading to elevated pro-inflammatory cytokines, angiogenesis, fibrosis, and lesion growth. Carnosine has been shown to downregulate NF-κB signaling and to reduce pro-inflammatory mediators, such as TNF-α and IL-6, across multiple cell types, mitigating chronic inflammation [59–62].

While the above-mentioned models and carnosine modulatory activity are not directly related to the reproductive system, they illustrate carnosine's capabilities in protecting against oxidative damage in diverse cell types. Given the established role of oxidative stress, mitochondrial damage, and iron-driven ROS in endometriosis, these mechanisms offer a strong rationale for exploring carnosine in both *in vitro* and *in vivo* endometriosis models.

Despite this, some preclinical studies evaluating carnosine relevance in different female reproductive contexts are available and provide encouraging insights into its potential for endometriosis management through reduction of oxidative stress and inflammation. In an *in vivo* study conducted on female rats exposed to electromagnetic field, closely related to oxidative stress development, DNA damage, and deterioration of the structure and function of the cells, carnosine demonstrated the ability to prevent the loss of primordial and primary follicles, also maintaining the follicle diameter [63]. Additionally, carnosine supplementation during pregnancy in mice enhanced maternal and fetal antioxidant status, with increased SOD and GPX activity and reduced MDA in offsprings, indicating improved redox balance in reproductive tissues [64]. This evidence provides proof of concept about carnosine potential in preserving female fertility by protecting ovarian reserve and enhancing antioxidant defenses under oxidative challenge (Fig. 3).

3.1 Carnosine in Models of Iron-Induced Cellular Stress

As previously discussed, iron overload plays a pivotal role in promoting oxidative stress through Fenton chemistry, a process relevant to endometriosis and other chronic inflammatory conditions. Carnosine, due to its imidazole group, exhibits significant iron-chelating properties, which contribute to its antioxidant and cytoprotective effects. Mozdzan *et al.* [65] demonstrated that carnosine effectively chelates Fe^{2+} and Cu^{2+} ions and reduces hydroxyl radical generation *in vitro*, suggesting that its metal-binding capacity could attenuate iron-driven oxidative damage. Similarly, results provided by Kang showed that carnosine and its analogues (e.g., homocarnosine) prevent DNA damage induced by ferritin and H_2O_2, further underlining a protective role against iron-mediated ROS generation [66]. These findings are further supported by recent *in vivo* studies. In a mouse model of chronic kidney disease with iron overload, carnosine administration reduced non-heme iron accumulation in tissues and lipid peroxidation levels, while improving redox balance and hemoglobin content [67]. The authors proposed the formation of Fe^{2+}-GSH-carnosine ternary complexes as a mechanism of detoxification. A different study reported that oral carnosine administration was able to mitigate the adverse

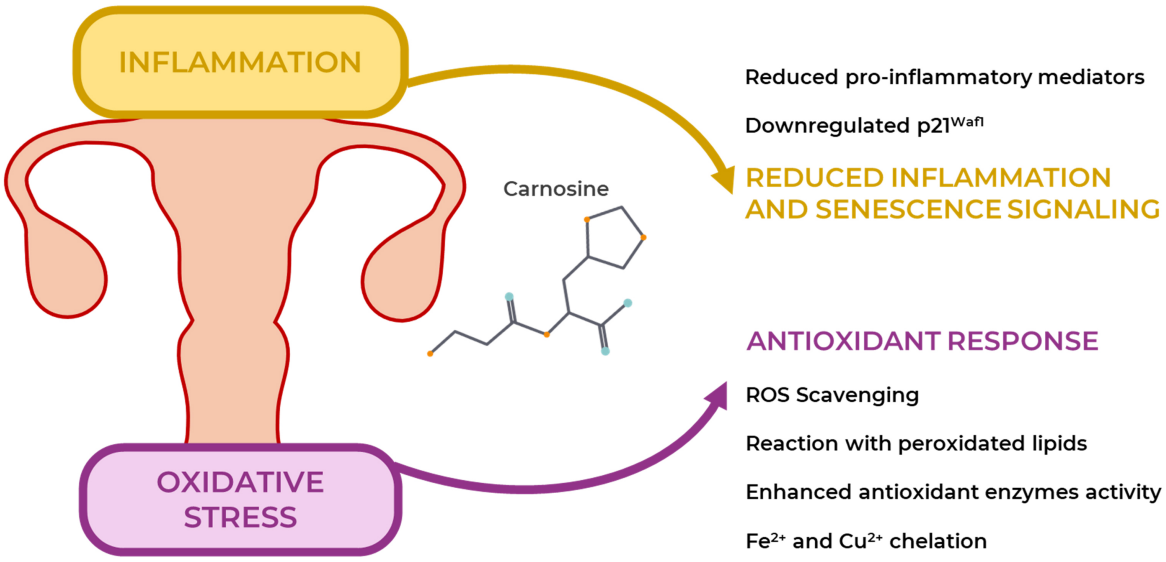

Fig. 3. Carnosine properties in reproductive disorders. Carnosine has shown promising results in counteracting two key features of reproductive disorders: inflammation and oxidative stress. It scavenges ROS, prevents the oxidation of lipids, proteins, and DNA, activates endogenous antioxidant responses via different enzymes and chelates metal ions such as Fe^{2+} and Cu^{2+}. It reduces inflammation by suppressing proinflammatory mediators and senescence-associated signaling through the downregulation of $p21^{Waf1}$.

cardiac remodeling associated with diet-induced obesity in a mouse model of enhanced lipid peroxidation (GPX4 deficient mice). In this context, carnosine significantly reduced iron levels and suppressed collagen-cross-linking in myocardial tissue, strengthening its well-known antifibrotic activity [68]. Collectively, these studies suggest that carnosine may offer therapeutic benefits in disorders involving iron overload by chelating labile iron, preventing hydroxyl radical formation, and activating endogenous antioxidant pathways. This mechanism may be particularly relevant in endometriosis, where excess of iron and the related oxidative stress sustain lesion persistence and infertility [69].

3.2 Carnosine Modulation of Macrophage Activity and Innate Immune Responses

Carnosine exerts significant immunomodulatory effects on macrophages, influencing both oxidative stress and inflammatory signaling [70–72]. In lipopolysaccharide (LPS) + interferon-γ (IFN-γ)-activated M1 macrophages, carnosine treatment led to a plethora of beneficial effects [73]. The dipeptide was able to reduce the production of ROS and nitric oxide (NO), downregulate the expression of inducible nitric oxide synthase (iNOS) and NADPH oxidases (Nox1/2), and suppress pro-inflammatory cytokines, while increasing anti-inflammatory mediators including interleukin-10 (IL-10) and transforming growth factor-β1 (TGF-β1). Moreover, carnosine treatment decreased the levels of lipid peroxidation product MDA, and restored the expression of antioxidant enzymes (GpX, SOD and CAT), while increasing the expressions of Nrf2 and HO-1, significantly ameliorating the antioxidant status of the cells, and promoting the phenotypic switch towards the M2 state [73]. In a further study employing RAW 264.7 macrophages exposed to amyloid-β (Aβ) oligomers, carnosine protected against oxidative and nitrosative stress, reducing ROS, NO, and peroxynitrite levels, a mechanism linked to decreased cell death and apoptosis [52]. Carnosine's ability to modulate macrophage phagocytosis and clearance functions under oxidative challenge were further demonstrated in studies showing stimulated removal of senescent fibroblasts and keratinocytes [74]. The authors stated that this effect involves the upregulation of CD36 and the receptor for advanced glycation end products (RAGE) expression, probably stimulated by carnosine via the activation of the AKT2 signaling pathway. Although direct evidence on NK cell modulation is limited, it is plausible that by reducing macrophage-derived pro-inflammatory signals, carnosine may indirectly influence macrophage-NK cross-talk and innate immune surveillance. In this context, a study was conducted on mice under restraint stress, showing a subsequent reduction of spleen index and number of spleen lymphocytes, including NK cells, whose cytotoxic activity was abolished [75]. Still in the context of NK modulation, oral administration of carnosine ameliorated stress-evoked immunocompromise through spleen lymphocyte number maintenance, thus restoring the classic activity for NK cells, pivotal players in immune responses against pathogens and tumors [75]. Beyond its role in modulating macrophage activation and NK activity, carnosine also appears to influence adaptive immune components. In a study evaluating human peripheral blood-derived $CD4^+$ T lymphocytes, the treatment with carnosine extended their replicative lifespan, while also reducing levels of oxidative DNA [76]. These findings confirm the evidence that carnosine can modulate innate immune cell activity, including suppressing pro-inflammatory cytokine secretion by macrophages,

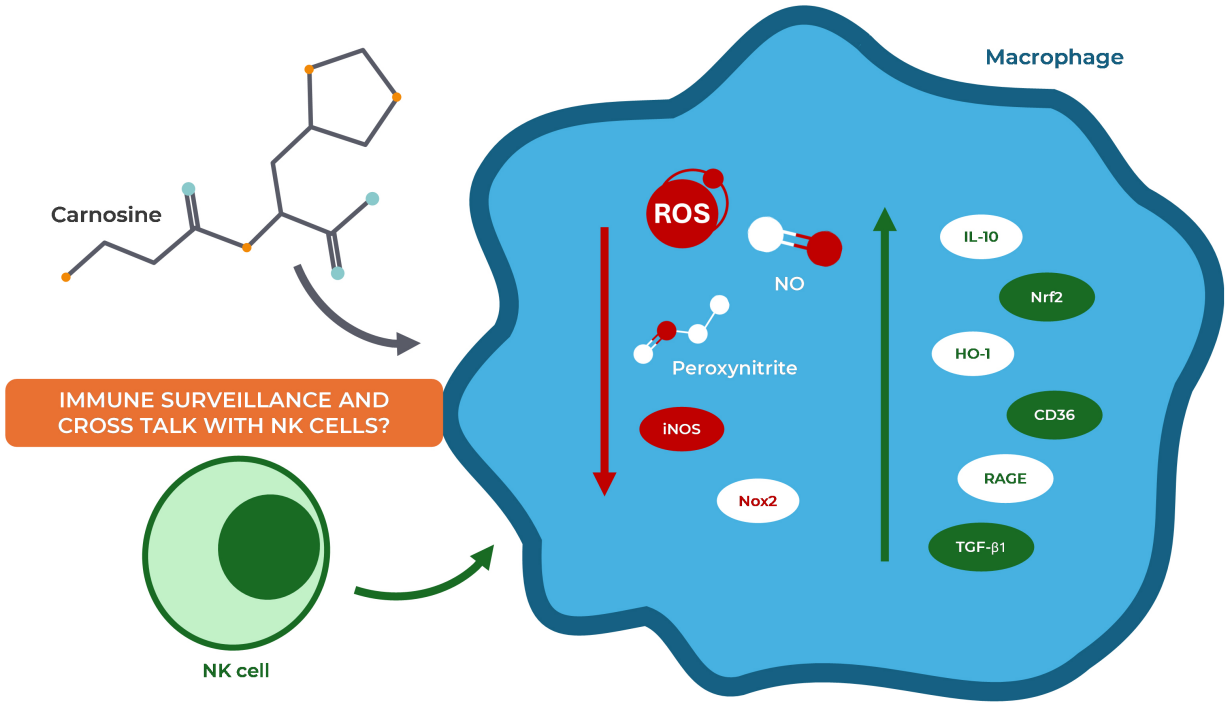

Fig. 4. The role of carnosine in immune response. Carnosine modulates macrophage activity by reducing the production of ROS, NO, and peroxynitrite. It attenuates inflammation by downregulating iNOS and Nox2 expression, while enhancing the anti-inflammatory response through the upregulation of IL-10, Nrf2, HO-1, CD36, RAGE, and TGF-β1. Carnosine may also support immune surveillance by promoting crosstalk between macrophages and NK cells. NO, nitric oxide; iNOS, inducible nitric oxide synthase; Nox2, NADPH oxidase 2; IL-10, interleukin-10; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; HO-1, heme oxygenase-1; RAGE, receptor for advanced glycation end products; TGF-β1, transforming growth factor-β1.

and highlight its potential to restore immune homeostasis in inflammatory contexts (Fig. 4).

Given that endometriosis is characterized by a dysregulated immune response, including defective clearance of ectopic endometrial cells, aberrant macrophage polarization, and impaired T cell and NK cell activity, carnosine's immunomodulatory effects may offer therapeutic benefit by rebalancing both innate and adaptive immune components within the peritoneal microenvironment.

3.3 Glial Cells as Regulator of Fertility: The Role of Carnosine

Beyond the well-established peripheral mechanisms, recent evidence suggests that neuroinflammation and central nervous system regulation may also represent underappreciated contributors to reproductive disorders. In the context of endometriosis, which is frequently associated with central sensitization and chronic pelvic pain, exploring the role of glial cells provides a novel point of view to understand how neuroimmune interactions may influence fertility. In particular, an alternative approach to addressing fertility challenges in women has been recently proposed by Desroziers [77], who highlighted an interesting and unconventional link between glial cells and PCOS. In her review, Desroziers [77] underscores how glial cells, including astrocytes and microglia, can structurally and functionally modulate neurons related to the gonadotropin-releasing hormone (GnRH), allowing increased pulsatile or release of GnRH via morphological remodeling of glial processes. In PCOS-like animal models, abnormal neuronal wiring, related to increased GABAergic synaptic inputs to GnRH neurons, correlates with impaired synaptic pruning and suggests a potential, although not yet fully elucidated, role for glial-mediated shaping of neural circuits. This concept leads to a captivating hypothesis that glial dysfunction may contribute to neuroendocrine dysregulation in PCOS by allowing enhanced excitatory input persistence to GnRH neurons, driving LH hypersecretion and the resultant hormonal and ovarian symptoms [77,78]. Interestingly, carnosine exerts multiple modulatory effects on glial cells that could be linked to these mechanisms. In a study on human HMC3 microglial cells, carnosine significantly reduced NO production and improved mitochondrial ATP/ADP ratio [79]. When the same human cells were challenged with a pro-oxidative and pro-inflammatory stimulus represented by the combination of LPS and ATP, results obtained by HPLC analysis reported the ability of carnosine to modulate ROS production and restore the basal energy metabolism of the glial cells [80]. Moreover, in BV-2 murine microglial cultures challenged with Aβ, carnosine lowered reactive oxygen/nitrogen species, suppressed the gene expression of iNOS, Nox1/Nox2, and

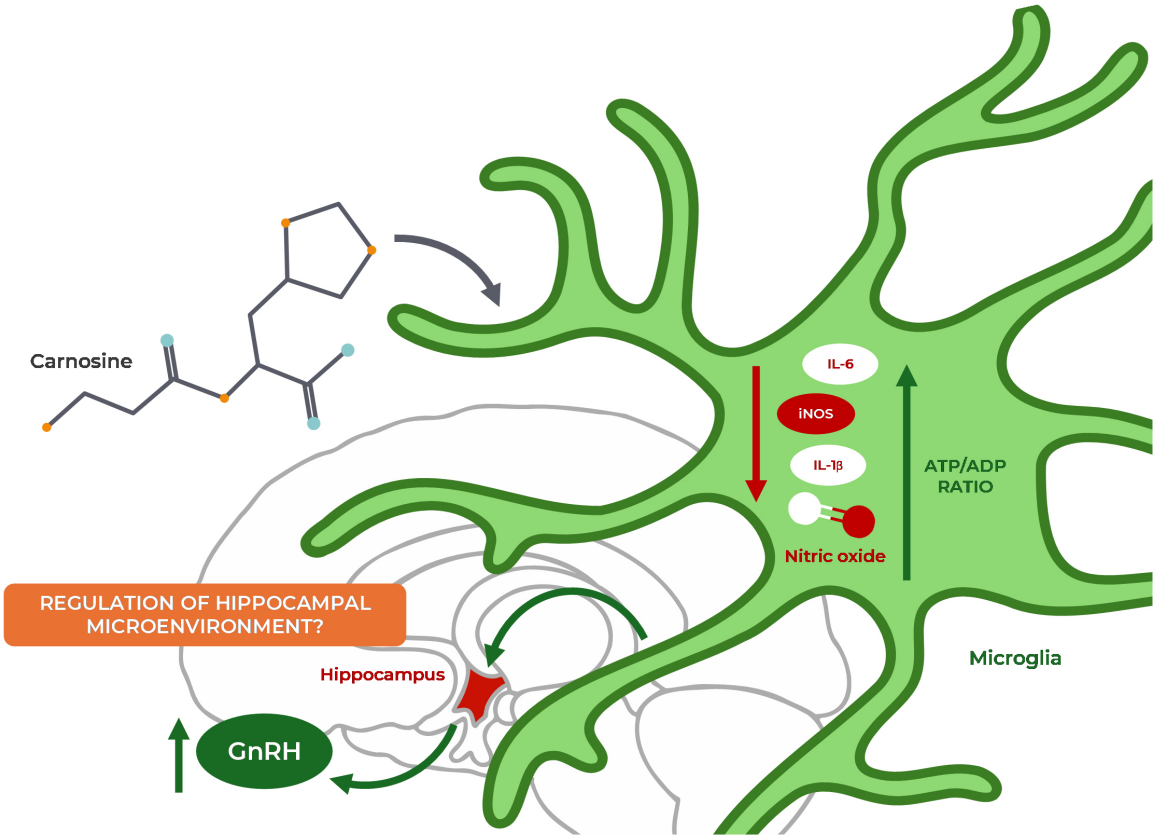

Fig. 5. Proposed mechanisms linking carnosine, microglial regulation, and fertility. Carnosine is a promising regulator of fertility due to its antioxidant and anti-inflammatory effects on microglia. It reduces the production of pro-inflammatory cytokines (IL-6, IL-1β) and enzymes such as iNOS, while lowering NO levels. At the same time, it increases the ATP/ADP ratio, thereby enhancing cellular energy status. Moreover, carnosine may help stabilize the glial microenvironment surrounding GnRH neurons, supporting hormone-driven neuronal communication through the release of GnRH. IL-1β, Interleukin-1β.

pro-inflammatory cytokines (interleukin-1β (IL-1β), IL-6, IFN-γ), while rescuing IL-10 and TGF-β1 levels, highlighting its anti-inflammatory and glial-regulatory actions [81] (Fig. 5).

The same model was also employed to assess the transcriptional regulatory activity of carnosine on glial cells in Aβ-induced stress conditions, in which the dipeptide was able to upregulate the expression of CXCL2, an anti-inflammatory mediator, and rescue the level of markers related to the phagocytic activity, including CD11b, CD68, and TNF-α. Moreover, carnosine counteracted the down-regulation Aβ-induced of CX3C motif chemokine receptor 1 (CX3CR1), the receptor for fractalkine, which is essential for neuron-microglia interactions [82]. Additionally, further evidence emphasizes carnosine's ability to modulate microglia and astrocyte activity, to reduce oxidative, nitrosative, and inflammatory stress, and to support glial-driven metabolic cooperation with neurons [83]. In this context, a model of primary rat mixed glia cultures, composed of both microglia and astrocytes, was recently used to confirm the ability of carnosine to counteract the Aβ oligomers-induced oxidative stress and inflammation [84]. Single-cell analyses of cellular responses to oligomers' treatment revealed massive ROS and NO production and the separation of cell population in distinct clusters, all parameters rescued and/or counteracted by carnosine. By doing so, carnosine may stabilize the glial microenvironment surrounding GnRH neurons, promoting proper synaptic pruning, neurotransmitter regulation, and hormone-driven neuronal communication. This offers an interesting mechanistic hypothesis: by modulating glial cell health and function, carnosine could indirectly restore physiological GnRH pulsatility and ameliorate PCOS-related neuroendocrine disorders (Fig. 5). Given the central role of glial cells in neuroimmune and neuroendocrine regulation, these findings, along with carnosine's well-known neuroprotective properties, may also highlight its broader relevance in neuro-rehabilitation contexts, in which restoring glia-mediated signaling could represent a promising therapeutic target.

3.4 Unique Features of Endometriosis and Potential Implications for Carnosine

Endometriosis exhibits several disease-specific features that differentiate it from other chronic inflammatory and oxidative disorders. Lesions are strongly estrogen-

dependent, with aberrant hormone signaling leading to proliferation and survival of ectopic endometrial cells [85]. Moreover, the progressive fibrotic remodeling of peritoneal lesions, mediated by excessive extracellular matrix deposition and myofibroblast activation, represents a distinctive hallmark of endometriosis [86–88]. In parallel, the immune microenvironment is characterized by impaired NK cell cytotoxicity, altered macrophage polarization, and sustained release of pro-inflammatory cytokines such as TNF-α and IL-6, all contributing to lesion persistence and infertility [5,6,89–91]. Of note, chronic pelvic pain and central sensitization also highlight the contribution of neuroinflammation and glial dysfunction to the disease pathophysiology [92–94].

These features provide a rationale to hypothesize specific mechanisms through which carnosine might exert beneficial effects in endometriosis. Beyond its antioxidant and metal-chelating activities, carnosine shows antiglycating properties that could attenuate fibrotic progression by limiting advanced glycation end-products and tissue stiffening [68,95]. Its immunomodulatory action on macrophages and cytokine release may help restoring immune surveillance within endometriotic lesions [73,96]. Furthermore, evidence of carnosine's ability to regulate glial activation and neuroinflammatory signaling strengthen its potential role in alleviating pain and neuroendocrine alterations disease-associated [50,97]. Although direct studies in endometriosis are lacking, these unique disease-specific aspects point to potential multimodal mechanisms through which carnosine may act, encouraging further research.

4. Antioxidant and Cytoprotective Actions of Carnosine in Male Reproductive Health

While the focus has been on female reproductive disorders so far, it is important to underline that oxidative stress, immune dysregulation, and metabolic imbalance are also major features of male infertility. These shared pathogenic pathways suggest that carnosine's antioxidant and cytoprotective effects may extend beyond female contexts, providing benefits in male reproductive health as well. In particular, male infertility is classically related to oxidative insults to spermatozoa, leading to decreased motility, DNA fragmentation, and mitochondrial dysfunction [98]. In different preclinical models of reproductive toxicity in male animals, carnosine demonstrated protective effects via antioxidant and anti-glycating pathways. For instance, in male rats treated with cyclophosphamide hydroxydaunomycin, oncovin, and prednisone (CHOP), a combination of chemotherapeutics commonly used to induce gonadotoxicity in experimental models, carnosine supplementation preserved testicular function, reduced lipid peroxidation, and decreased oxidative DNA damage [99]. Carnosine was also tested in a different model of testicular toxicity induced by sodium valproate, in which the dipeptide, along with Coenzyme Q10 co-administration, was able to increase the levels of reproductive hormones such as testosterone, FSH, and LH in serum, thereby increasing the levels of biochemical parameters such as SOD, GPX, and catalase [100]. Additionally, carnosine was shown to mitigate testicular aging induced by galactose exposure through its anti-glycating and ROS-scavenging properties [101]. Further support for carnosine's cytoprotective role in the male reproductive system derive from a model of malnutrition-induced hypogonadism, where rats fed with a protein-deficient diet exhibited severe reductions in testicular weight, sperm count and viability, along with hormonal imbalances and increased pro-inflammatory and apoptotic markers in testicular tissue [102]. Carnosine administration reversed these alterations by restoring antioxidant defenses and anti-inflammatory activity. Similarly, in a model of lead (Pb)-induced reproductive toxicity, characterized by increased oxidative stress, mitochondrial dysfunction, and poor sperm parameters, carnosine supplementation alleviated these alterations, confirming its protective role for mitochondria and redox homeostasis [103]. Beyond animal models, carnosine has also demonstrated promising results in human sperm manipulation contexts. When added during semen processing, carnosine improved mitochondrial activity and beat-cross frequency (BCF), supporting its potential in assisted reproduction technologies [104]. These beneficial mitochondrial effects were reproposed and assessed in studies on quail sperms, where carnosine, present in seminal plasma, improved different motility parameters after *in vitro* storage, suggesting an innovative and critical function of imidazole dipeptides in sperm preservation [105]. This function appears significantly relevant in semen cryopreservation, where oxidative stress is a critical factor. In stallion semen, higher carnosine levels were associated with better tolerance to cooling and freezing, and with reduced MDA levels, proving that carnosine was effective in removing lipid peroxidation products. These findings suggest that carnosine may act as a natural buffer against cryo-induced oxidative insults, potentially enhancing sperm resistance during biotechnological processes [106]. This evidence confirms that carnosine supports male reproductive health by attenuating oxidative damage, preserving mitochondrial integrity, and sustaining hormonal and spermatogenic homeostasis under stress conditions (Fig. 6).

Although endometriosis represents a different disease related to women, the oxidative and immune pathways implicated in its pathogenesis show a notable overlap with those involved in male infertility. This overlap suggests that carnosine, due to its broad-spectrum cytoprotective actions, could be considered as a supportive intervention in both contexts.

5. Clinical Trial With Carnosine Involving Endometriosis-Related Markers

To date, no clinical trial has specifically evaluated carnosine supplementation in women with endometriosis. However, human studies in related inflammatory and ox-

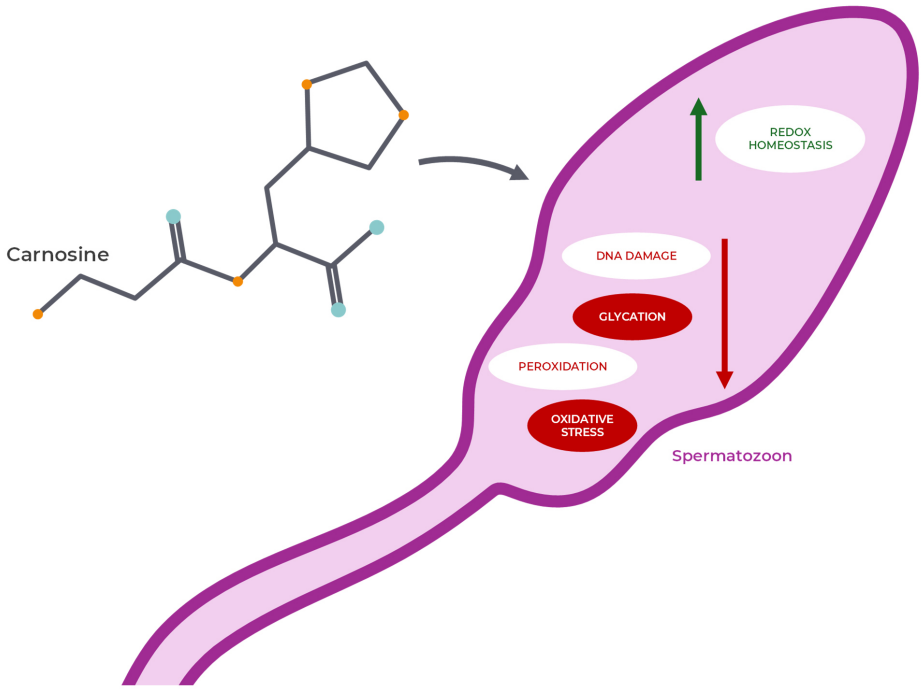

Fig. 6. Role of carnosine in male reproductive health. Carnosine has shown protective activity towards male reproductive health, decreasing DNA damage and glycation, along with oxidative stress and the related peroxidation of lipids. Overall, it also allows an improvement of redox homeostasis.

idative contexts provide translational insights. A meta-analysis of randomized controlled trials involving histidine-containing dipeptides (including carnosine) reported significant reductions in systemic oxidative markers (e.g., MDA and 8-OHdG) and inflammatory markers (e.g., C-reactive protein (CRP) and TNF-α), along with the increase in antioxidant defense parameters (e.g., CAT and SOD) [107]. In metabolic syndrome patients, carnosine combined with vitamin B complex significantly decreased immune activation markers such as neopterin, a pyrazine-pyrimidine molecule that monocytes and macrophages create in response to IFN-γ released by activated T-cells, also improving oxidative stress profiles [108]. These trials demonstrate that carnosine can reduce key inflammatory and oxidative markers implicated in endometriosis. Basing on these findings, it is possible to hypothesize the rationale for a pilot clinical trial of carnosine in endometriosis, beginning with oxidative/inflammatory biomarker endpoints and proceeding towards clinical outcomes such as pain relief and lesion size reduction.

6. Conclusions, Current Limitations, and Future Perspectives

There are numerous evidence showing that the natural dipeptide carnosine possesses a therapeutic potential in the context of human reproduction. It has shown to exert its antioxidant and potential protective effects on sperm and reproductive tissues. Additionally, carnosine has shown to play a role in several aspects of female reproduction, including ovarian health, fetal development, and potentially influencing pregnancy outcomes. In particular, studies have shown the ability of carnosine to protect ovarian follicles from damage caused by electromagnetic fields, potentially improving fertility. Furthermore, maternal supplementation with carnosine has shown promise in enhancing fetal growth and development in animal models. In addition to the above direct positive modulatory effects, carnosine has shown to be able to modulate endometriosis-related markers as well as macrophages and microglia, the latter emerging as an innovative regulator of female fertility, and in particular in the context of endometriosis.

In summary, carnosine has shown very promising results in supporting reproductive health, but further research is needed to fully understand its therapeutic potential on reproductive disorders, also strengthening the possible benefits of carnosine administration for prevention and/or treatment of endometriosis. In this context, a critical limitation of the current literature is represented by the absence of direct *in vitro* and *in vivo* studies using established endometriosis models (e.g., rodent models of endometriosis, human endometriotic stromal cell cultures), along with the lack of clinical studies focused on the role of carnosine in the management of endometriosis markers and symptoms. Carnosine's multimodal potential including antioxidant, chelating, and immunomodulatory properties is deeply reported in the literature, and systematic reviews of clinical studies on the role of oxidative stress and the potential of antioxidant therapy in endometriosis identify several candidates that have been tested, but reports on carno-

sine are still missing [109–111]. Given the absence of direct carnosine-endometriosis studies, in the present review we chose to focus on mechanistic and preclinical evidence regarding the multimodal potential of this dipeptide, and on well-established pathogenic pathways in endometriosis (iron overload, ROS, immune dysfunction) to justify the consideration of carnosine as a possible therapeutic candidate. This approach is intentionally hypothesis-generating: the conclusions drawn here are provisional and aim to motivate dedicated new *in vitro*, *in vivo*, and early clinical studies. Future research must prioritize investigating the effects of carnosine in this specific disease to validate the promising mechanisms proposed herein as well as to determine optimal dosing and delivery strategies.

Abbreviations

8-isoPGF2α, 8-isoprostane; 8-OHdG, 8-hydroxydeoxyguanosine; Aβ, Amyloid-β; BCF, Beat-cross frequency; CAT, Catalase; CHOP, Cyclophosphamide, hydroxydaunomycin, oncovin, and prednisone; cGAS–STING, Cyclic GMP-AMP synthase-stimulator of interferon genes; CRP, C-reactive protein; GnRH, Gonadotropin-releasing hormone; GPX, Glutathione peroxidase; HO-1, Heme oxygenase-1; Hsp70, 70 kDa-HSP; IFN-γ, Interferon-γ; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-10, Interleukin-10; iNOS, Inducible nitric oxide synthase; Keap1, Kelch-like ECH-associated protein 1; LPS, Lipopolysaccharide; MDA, Malondialdehyde; MAPK, Mitogen-activated protein kinases; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NKG2D, NK group 2D; NK, Natural killer; Nox1/2, NADPH oxidases; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; PCOS, Polycystic ovary syndrome; RAGE, Receptor for advanced glycation end products; ROS, Reactive oxygen species; SOD, Superoxide dismutase; TGF-β1, Transforming growth factor-β1; TNF-α, Tumor necrosis factor-α.

Author Contributions

Project administration and conceptualization of the manuscript: GCaro and GCaru; literature search: GCaro, LDP, KP, SAB, VC, AG, RM, GiuL, BT, VDP, EM, FB, AMA, GiaL, and GCaru; writing—original draft: GCaro and GCaru; preparation of the figures: GCaro, LDP, and GCaru; writing—review & editing: GCaro, LDP, KP, SAB, VC, AG, RM, GiuL, BT, VDP, EM, FB, AMA, GiaL, GCaru. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. In particular, the judgments in data interpretation and writing were not influenced by the relationship between Prof. Giuseppe Lazzarino and LTA-Biotech srl.

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