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A Comprehensive Review of the Potential Effects of *Ophiocordyceps sinensis* and *Cordyceps militaris* on Spermatogenesis

Tin Hoang Nguyen[1,2*], Phuc Le Nhu Nguyen[1], Hang Thi Thu Nguyen[1], Nhi Thi Nguyen[1], Nhan Thanh Danh[1], Dang Ngoc Anh Hua[1] and Van De Tran[1]

[1]Can Tho University of Medicine and Pharmacy, Can Tho – 900000, Vietnam; nhtin@ctump.edu.vn

[2]Department of Physiology, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho – 900000, Vietnam

Abstract

Spermatogenesis depends on coordinated endocrine regulation, intact seminiferous tubule architecture, oxidative balance, and preservation of the blood–testis barrier (BTB). Disturbance of these processes contributes to impaired sperm production and male infertility. *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) and *Cordyceps militaris* are medicinal fungi of growing interest in reproductive biology, while cordycepin, a *Cordyceps*-derived pure compound, has emerged as a major candidate mediator of these effects. Previous reviews have focused mainly on general pharmacology or Leydig-cell steroidogenesis and have not comprehensively integrated evidence across structural, endocrine, and functional aspects of spermatogenesis. This literature review provides a mechanism-oriented synthesis of the potential effects of *O. sinensis*, *C. militaris*, and cordycepin on male reproductive function. Experimental evidence indicates that these agents can improve male reproductive outcomes through multiple convergent mechanisms. At the structural level, they preserve or restore seminiferous tubule architecture, improve Sertoli- and germ-cell organisation, maintain Leydig-cell integrity, and protect BTB function. At the functional level, they enhance Leydig-cell steroidogenesis, support testosterone synthesis, improve sperm count, motility, and kinematic parameters, and may also promote sperm hyperactivation and the acrosome reaction during capacitation. The principal mechanisms implicated include adenosine receptor-dependent cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/steroidogenic acute regulatory protein signalling, sirtuin 1 (SIRT1)/forkhead box o3a (Foxo3a)-mediated antioxidant defence, suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/Mitogen-Activated Protein Kinase (MAPK) inflammatory pathways, and reduction of apoptosis and oxidative damage. *O. sinensis*, *C. militaris*, and cordycepin show multi-target potential to support both the morphology and function of spermatogenesis. However, the evidence remains predominantly preclinical, and clinical translation will require standardised preparations, pharmacokinetic characterisation, long-term safety assessment, and rigorous human trials.

Major Findings: *O. sinensis*, *C. militaris*, and cordycepin improve male reproductive function through preserving seminiferous tubule architecture, supporting Sertoli cell and Leydig cell integrity, protecting the BTB, enhancing testosterone synthesis, and improving sperm count, motility, and kinematic parameters.

Keywords: Blood–testis Barrier, Leydig Cell, Sertoli Cell, Spermatogenesis, Testis, Testosterone

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1. Introduction

Spermatogenesis is sustained by a complex microenvironmental niche involving Sertoli, Leydig, peritubular, and immune cells, tight endocrine control, redox balance, and an intact blood–testis barrier (BTB). Disturbance of any of these elements can reduce sperm output and male fertility. Spermatogonial

*Author for correspondence

stem cells (SSCs) lie at the basement membrane and are regulated by Sertoli cells [glial cell line-derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF2), retinoic acid-mediated signals] and endocrine cues [follicle-stimulating hormone (FSH), testosterone][1,2]. Interstitial macrophages, Leydig cells [insulin-like growth factor 1 (IGF1), colony-stimulating factor 1 (CSF1)], vasculature (vascular endothelial growth factor, oxygen), and peritubular myoid cells (GDNF, CSF1) critically support SSC self-renewal and differentiation[2,3]. Mast cells and other immune cells are emerging regulators and potential mediators of pathology within this niche[3]. Sertoli cells orchestrate germ-cell development, maintain the SSC niche, regulate meiosis, and form the BTB that creates a protected adluminal environment[1,2,4,5]. BTB integrity is dynamically regulated by FSH, androgens, transforming growth factor beta (TGF-β) family members, and local peptides; its disruption allows immune attack and toxicant entry, impairing spermatogenesis[4,5]. Current evidence suggests that assessing male fertility interventions only by sperm count/motility is incomplete. Robust evaluation should span steroidogenesis and endocrine profile [luteinizing hormone (LH), FSH, testosterone, intratesticular testosterone][6]; testicular histoarchitecture (seminiferous organization, SSC pool, Sertoli and Leydig cell integrity)[2,7]; redox and mitochondrial status [reactive oxygen species (ROS), antioxidant capacity, mitochondrial function][7-9]; BTB function and immune/inflammatory markers[4]; sperm functional competence [deoxyribonucleic acid (DNA) integrity, capacitation, acrosome reaction, fertilizing ability)[8,9]. As a result, agents aimed at supporting male fertility should be tested across this integrated framework, not solely on ejaculate parameters.

Across models of toxicant exposure, diabetes, ageing, and drug-induced injury, *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) and *Cordyceps militaris* (Figure 1), and especially cordycepin, act on steroidogenic signalling, oxidative stress, inflammation, BTB integrity, and sperm function. *O. sinensis* extracts stimulate testosterone production in normal mouse Leydig cells in a dose- and time-dependent manner, requiring new protein synthesis and upregulation of steroidogenic acute regulatory protein (StAR); signalling involves cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) and, in tumour cells, combined PKA/protein kinase C (PKC) activation and mitochondrial Ca^{2+} signalling[10-12]. Cordycepin itself increases plasma testosterone and Leydig cell steroidogenesis via adenosine receptors, activating the cAMP–PKA–StAR pathway[13]. Cordycepin ameliorates diabetes-induced testicular damage in mice, restoring seminiferous architecture, spermatogenesis, and BTB integrity through sirtuin 1 (SIRT1)/forkhead box o3a (Foxo3a)-driven antioxidant enzymes [manganese superoxide dismutase (Mn-SOD), catalase (CAT)][14]. In naturally aged rats, cordycepin improves sperm kinematics, spermatogenesis-related gene expression, SIRT1 and mechanistic target of rapamycin complex 1 (mTORC1) signalling, and testicular histology, supporting endocrine and redox homeostasis[15]. Another ageing model shows cordycepin reduces testicular inflammaging by down-regulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/mitogen-activated protein kinase (MAPK) signalling pathways, including c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38, and pro-inflammatory cytokines in the testis[16]. In human sperm *in vitro*, cordycepin enhances hyperactivation and the acrosome reaction during capacitation, with increased PKA activity and protein tyrosine phosphorylation, acting via all four adenosine receptor subtypes without increasing ROS or DNA damage[17]. This suggests direct effects on sperm function relevant to fertilisation. However, current data are almost entirely rodent or *in vitro*; rigorous human trials and standardised preparations are still needed before translating these findings to clinical fertility support.

Despite this growing body of work, the review literature remains fragmented. The existing dedicated review on *Cordyceps* and male reproduction has concentrated mainly on Leydig-cell steroidogenesis and cordycepin, without systematically mapping actions across the full spermatogenic continuum from spermatogonia to ejaculated spermatozoa[18]. In contrast, recent *Cordyceps* reviews have emphasised broader pharmacology or non-reproductive indications rather than testis-specific mechanisms. At the same time, most *in vivo* reproductive studies of *O. sinensis* and *C. militaris* have assessed only a narrow set of outcomes, typically hormone levels, basic testicular histology, or routine semen parameters, despite reporting diverse

effects on testosterone, seminiferous epithelium, oxidative stress, inflammatory signalling, apoptosis, and sperm quality[3,14,15,19-27]. Building on this fragmented literature, the objective of this review is to develop a comprehensive, mechanism-oriented synthesis of the potential actions of *O. sinensis* and *C. militaris* on spermatogenesis by integrating experimental evidence across hypothalamic–pituitary–testicular (HPT) regulation, Sertoli and Leydig cell function, BTB integrity, redox and inflammatory pathways, germ-cell survival, testicular histopathology, spermiogram outcomes, and sperm functional endpoints, including capacitation, hyperactivation, and the acrosome reaction. In addition, their main bioactive compounds

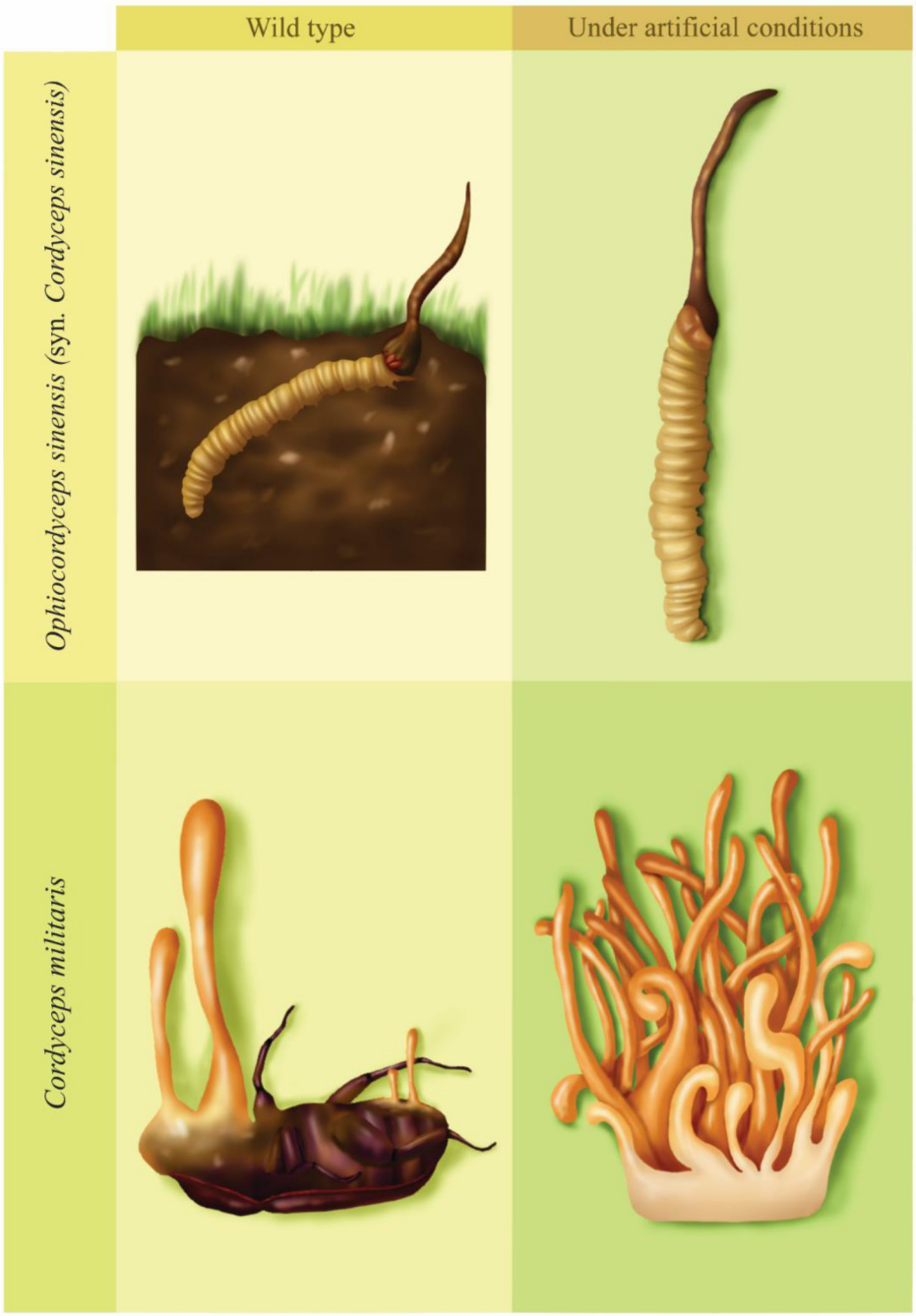


Figure 1. Comparative morphology of *Ophiocordyceps sinensis* and *Cordyceps militaris* in the wild and under artificial cultivation conditions.

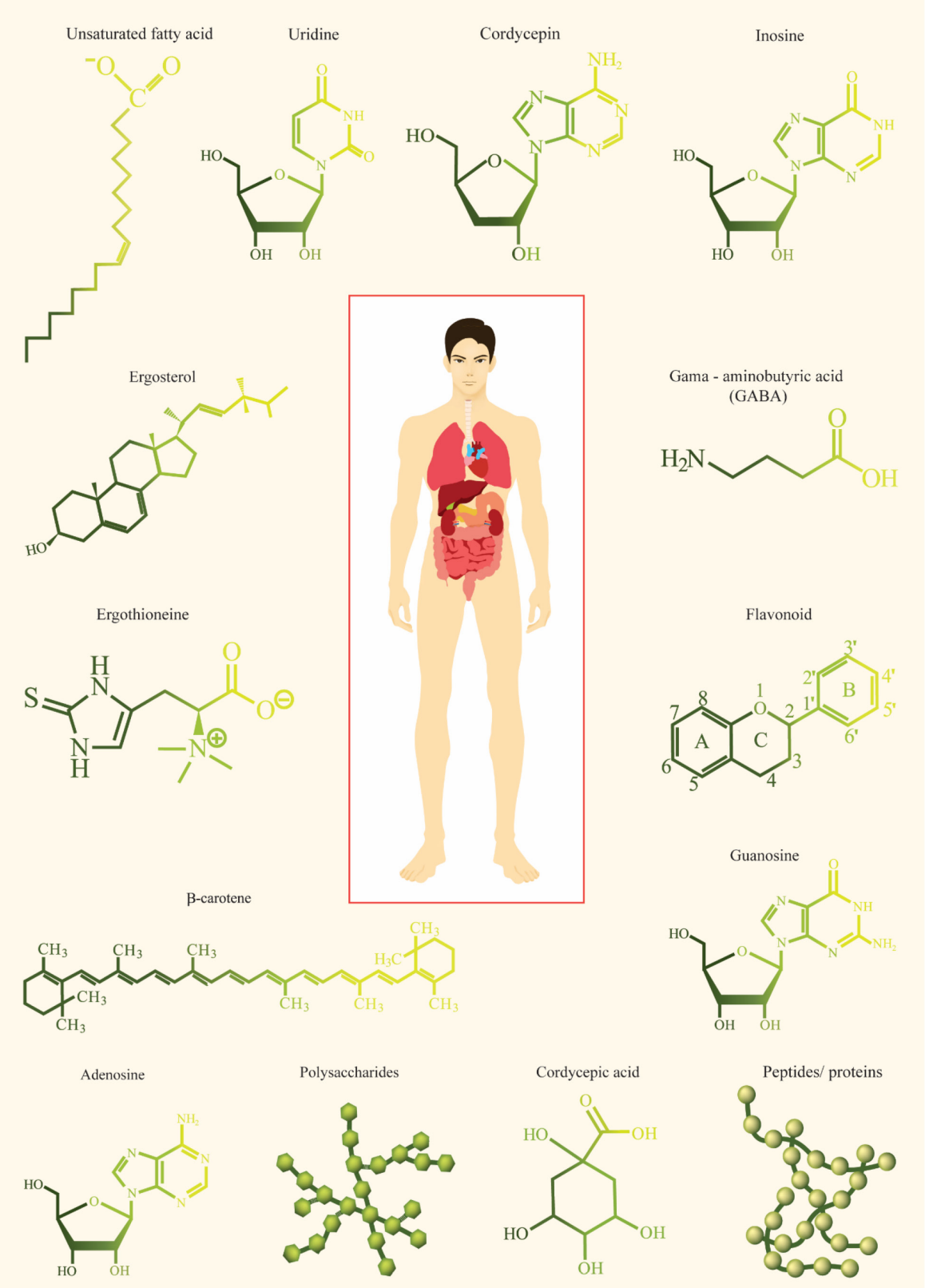


Figure 2. Major bioactive compounds identified in *Ophiocordyceps sinensis* and *Cordyceps militaris* and their potential biological effects in target tissues.

will be mentioned, and their potential for clinical translation will be discussed to provide an overview and future applications.

Wild *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) is characterised by its natural caterpillar–fungus complex, with a slender stromal structure emerging from the host larva, whereas artificially cultivated forms show variations in stromatal size, shape, and colour depending on substrate and environmental conditions. *C. militaris* typically has club-shaped, orange fruiting bodies that also vary morphologically between wild and cultivated states in terms of branching, pigmentation, and density[28-30]. Unlike *O. sinensis*, which is difficult to cultivate artificially, *C. militaris* can be grown more easily using solid-state fermentation or liquid culture methods, with cultivation conditions significantly influencing morphology and bioactive compound production, such as cordycepin[31-33]. Cultivated *C. militaris* often contains higher levels of cordycepin compared to wild *O. sinensis*, which lacks cordycepin but contains adenosine; this biochemical difference is important for their pharmacological applications[34,35]. Microbial communities associated with natural *C. militaris* also impact its development and quality, suggesting that ecological origin influences both morphology and biological properties[36]. Morphological differences between wild and cultivated *Cordyceps* sp. reflect their ecological origins and cultivation methods, which must be considered when comparing their chemical composition and therapeutic potential[37,38]. This was our original figure, which was drawn using MediBang Paint Pro (MediBang Inc.).

2. The Bioactive Compounds Involved in the Pharmacological Effects of *O. sinensis* and *C. militaris*

The pharmacological effects of *O. sinensis* and *C. militaris* cannot be ascribed to a single constituent; rather, they arise from a chemically complex matrix dominated by several major classes of bioactive molecules, as shown in Figure 2. Wild and cultured *O. sinensis* contain >200 metabolites, prominently nucleosides/nucleotides, polysaccharides, proteins/peptides, sterols, fatty acids, and amino acid–derived metabolites[39-41]. *C. militaris* similarly contains a diverse metabolite spectrum, with some constituents more abundant than in *O. sinensis*[39,42]. Across both species, polysaccharides, nucleosides (including but not limited to cordycepin), sterols, proteins/peptides, amino acids, and micronutrients collectively shape pharmacological profiles, with substantial variation driven by strain, host/substrate, and culture conditions[39,42-45]. This chemical complexity underpins their pleiotropic antioxidant, immunomodulatory, metabolic, and cytoprotective effects rather than a single active principle.

Ophiocordyceps sinensis and *Cordyceps militaris* contain several principal bioactive constituents, including cordycepin, adenosine-related nucleosides, polysaccharides, sterols, peptides, and other secondary metabolites. Polysaccharides are major components in both species and contribute significantly to immunomodulatory and antitumor activities, with *O. sinensis* containing diverse monosaccharides and *C. militaris* polysaccharides showing antioxidant, anti-ageing, and anti-tumor effects[46,47]. Cordycepin, a nucleoside analogue found abundantly in *C. militaris* but absent in *O. sinensis*, exhibits anticancer, antiviral (including potential activity against SARS-CoV-2), immunomodulatory, and ergogenic properties[32,35,48,49]. Adenosine is present in both fungi and is linked to cardiovascular benefits and sedative effects[35,47]. Both fungi also produce peptides and sterols that contribute to their pharmacological profiles, including antioxidant, anti-inflammatory, antimicrobial, and endocrine-regulating effects[50,51]. The bioactive compounds from these fungi modulate gut microbiota differently; *O. sinensis* tends to promote probiotic bacteria more effectively than *C. militaris*[52]. These constituents therefore underpin the broad therapeutic potential of both species in traditional medicine and modern pharmacology. This was our original figure, which was drawn using MediBang Paint Pro (MediBang Inc.).

2.1. Nucleosides and Related Purine Metabolites

The nucleoside fraction is the most extensively studied and pharmacologically distinctive component of both *O. sinensis* and *C. militaris*. In *O. sinensis*, adenosine is the primary marker compound and serves as a pharmacopoeial quality indicator, mediating anti-inflammatory and immunomodulatory effects through

purinergic receptor signalling[13,53,54]. In contrast, *C. militaris* is characterised by its signature metabolite cordycepin (3'-deoxyadenosine), which acts as a bioactive adenosine analogue with broader impacts on ribonucleic acid (RNA) metabolism, cellular energetics, stress responses, and inflammatory pathways[34,49,55]. Importantly, authentic *C. militaris* possesses the genetic machinery for cordycepin biosynthesis, coupled with pentostatin production that protects cordycepin from enzymatic degradation, whereas cordycepin presence in *O. sinensis* is inconsistent, and canonical biosynthetic genes have not been confirmed in this species[34,55]. Thus, while nucleoside-driven pharmacology, largely via adenosine, is shared by both fungi, cordycepin-centred activity is much more characteristic of *C. militaris* than *O. sinensis*[34,56]. This distinction supports the use of cultivated *C. militaris* as a reliable source of cordycepin for therapeutic applications compared to wild or cultured *O. sinensis*[34,57].

2.2 Polysaccharides

Polysaccharides are the principal bioactive macromolecules in both *O. sinensis* and *C. militaris*, contributing significantly to their immunomodulatory effects. In *O. sinensis*, polysaccharides constitute about 3–8% of dry weight and include both intracellular and extracellular types, while in *C. militaris*, polysaccharides are found in fruiting bodies, mycelia, and fermentation broth, with their abundance and structure influenced by substrate and culture conditions[58-60]. These polysaccharides enhance immune function by activating macrophages, promoting phagocytosis, stimulating lymphocyte proliferation, and regulating cytokine and chemokine secretion, such as nitric oxide (NO), tumour necrosis factor - alpha (TNF-α), interleukin (IL-6 and IL-10)[60-62]. Their immunomodulatory activity is linked to structural features, including molecular weight, branching degree, glycosidic linkage types, and extraction methods; for example, low-molecular-weight galactoglucomannans with high branching show strong immune stimulation[60,61]. Mechanistically, these polysaccharides activate immune cells via pathways such as MAPK and NF-κB signalling[59,60,63]. Overall, *Cordyceps*-derived polysaccharides represent a structurally diverse family of bioactives whose immunomodulatory potency depends on precise molecular characteristics rather than a single uniform entity[58].

2.3 Sterols, Carotenoids, and Other Lipophilic Metabolites

The lipophilic fraction in *Cordyceps* sp., including *O. sinensis* and *C. militaris*, contributes significantly to their pharmacological effects, particularly cytoprotection and anti-inflammation. In *O. sinensis*, sterols such as ergosterol, a fungal structural sterol and vitamin D2 precursor, and its derivatives exhibit anticancer potential, while in *C. militaris*, ergosterol is linked to antioxidant, anti-inflammatory, and immunomodulatory activities[64,65]. Additionally, *C. militaris* contains carotenoids like cordyxanthins that provide antioxidant and cytoprotective properties, contributing to its characteristic coloration[65]. Lipid metabolism modulation by *Cordyceps* involves glycerophospholipid and sphingolipid pathways, which are associated with reduced inflammatory cytokines (e.g., TNF-α, IL-8) and lung tissue protection in disease models[64,66]. Network pharmacology suggests that lipophilic compounds such as phytosterols and fatty acid esters regulate key inflammatory and oxidative stress pathways, including NF-κB and Toll-like receptor 4 signalling[67]. In short, the lipophilic metabolome likely plays a broader role in cytoprotection and anti-inflammatory effects than traditionally recognised in *Cordyceps* research, though these components are less standardised compared to nucleosides and polysaccharides[64,65].

2.4 Proteins, Peptides, and Amino Acid–derived Metabolites

Proteins, peptides, and amino acid–derived metabolites form an important but less studied bioactive fraction in *Cordyceps* sp., contributing to their pharmacological effects beyond nucleosides and polysaccharides. In *O. sinensis*, proteins and peptides are recognised as major bioactive classes, with rare cyclic dipeptides, polyamines, and nitrogen-containing metabolites identified; a fibrinolytic serine protease isolated from culture supernatant suggests roles in vascular and hemostatic regulation[41]. *C. militaris* contains proteins, peptides, γ-aminobutyric acid (GABA), and ergothioneine, which may enhance antioxidant and cytoprotective activities[41,50]. Proteomic analyses reveal species-specific differences in amino acid composition and protein quality, with *C. militaris* showing higher crude protein and essential amino acids like lysine

and methionine compared to *O. sinensis*, which adapts to hypoxia with elevated leucine and histidine levels linked to oxidative stress resistance[68]. Polypeptides extracted from *C. militaris* demonstrate antimicrobial and anticancer activities *in vitro*, indicating potential therapeutic applications[69]. Metabolomic profiling highlights the abundance of amino acids and derivatives during growth stages of *C. militaris*, suggesting their importance in development and bioactivity[70,71]. However, this protein/peptide fraction remains undercharacterized relative to nucleosides and polysaccharides, necessitating further research to distinguish pharmacologically active molecules from nutritional components[39,68].

2.5 Polyols and Small-molecule Antioxidants

The term "cordycepic acid" is now understood to primarily refer to D-mannitol, a polyol rather than an acidic compound, which is a major low-molecular-weight metabolite in *C. militaris*. D-mannitol plays roles in osmotic regulation, free-radical scavenging, and antioxidant protection, and has been linked to anti-inflammatory and metabolic effects[42,72]. Comparative metabolomics of *O. sinensis* also highlights other small polar metabolites such as trehalose, glycerol, citric acid, sugar alcohols, and organic acids that likely contribute cooperatively with nucleosides and polyols to the biological activity of *Cordyceps* preparations[73,74]. The production of D-mannitol and other bioactive metabolites in *C. militaris* is influenced by substrate choice and cultivation conditions, affecting yield and pharmacological potential[42,75]. These small molecules are part of a complex metabolome that supports antioxidant, immunomodulatory, and metabolic functions, rather than a single dominant compound driving effects[45,72]. As a result, the biological activity of *Cordyceps* sp. is best understood as arising from synergistic interactions among multiple small polar metabolites, including D-mannitol[45,72,73].

3. The Effects on Male Reproductive Organ Morphology

3.1 Gross Reproductive Organ Morphology

Cordyceps militaris and *Ophiocordyceps sinensis* preparations, as well as their active compound cordycepin, generally promote protective and restorative effects on male reproductive organs rather than causing hypertrophy. In juvenile male mice, *C. militaris* fermentation products increased seminiferous tubule area and improved reproductive maturation without significantly changing absolute testicular weight, indicating enhanced functional development rather than nonspecific organ enlargement[19]. *Cordyceps* extracts have been shown to increase testosterone production and improve sperm quality, motility, and density in various animal models, supporting androgen-like activity without consistent increases in organ size[19,22,76]. Cordycepin specifically ameliorates age-related testicular dysfunction by improving sperm parameters and regulating molecular pathways involved in inflammation and autophagy, further supporting its protective role[15,16]. These findings suggest that *Cordyceps* sp. enhances male reproductive health primarily through functional improvements rather than hypertrophic changes in reproductive organ morphology[18,19,22].

Cordyceps militaris preparations and cordycepin consistently preserve or partially restore male reproductive organ morphology under pathological conditions such as ageing, diabetes, and toxicant-induced injury. In aged rats, cordycepin attenuates reductions in seminiferous tubule size and improves germ and Sertoli cell indices while reducing inflammation via NF-κB/MAPK signalling pathways[15,16]. In diabetic models, *C. militaris* enhances reproductive performance and sperm quality, although changes in absolute organ weights may not always be dose-dependent or linear, indicating that histological and functional measures are more sensitive endpoints than gross organ weight[25]. Toxicant-induced damage models show that *C. militaris* extract and cordycepin improve sexual organ weights, seminiferous tubule size, sperm parameters, and antioxidant enzyme activities, mitigating oxidative stress and apoptosis[20,22,25]. Current evidence highlights the restorative potential of *Cordyceps* sp. in male reproductive dysfunction through antioxidant, anti-inflammatory, and hormonal regulatory mechanisms rather than hypertrophic effects[16,20,77].

Moreover, *C. militaris* exhibits tissue-selective androgenic modulation, supporting circulating testosterone and dihydrotestosterone (DHT) levels while suppressing undesirable prostate enlargement, as shown in a rat model of late-onset hypogonadism

and testosterone-induced prostate hypertrophy[78]. This selective effect contrasts with indiscriminate androgen stimulation, as *C. militaris* fruit body extract maintained androgen levels but inhibited prostate cell proliferation and androgen-regulated gene expression, partly through cordycepin's modulation of the adenosine A1 receptor[78,79]. Cordycepin also inhibits prostate cancer cell proliferation independently of some adenosine receptors, indicating complex receptor-mediated mechanisms that may contribute to tissue-specific effects[79]. The ability of *Cordyceps* sp. to enhance testosterone secretion via Leydig cell proliferation involves activation of the cAMP-PKA signalling pathway, which is crucial for steroidogenesis, further supporting its role in targeted androgen regulation[80]. This tissue selectivity aligns with the broader concept of selective androgen receptor modulators (SARMs), which aim to maximise anabolic benefits while minimising adverse effects like prostate hypertrophy, although clinical evidence for SARMs remains limited[81,82]. Taken together, *C. militaris* appears to balance androgen support with prostate safety by modulating androgen-responsive tissues differentially rather than causing uniform stimulation across all such tissues[78,79].

3.2 Testicular Histomorphology and Seminiferous Tubule Architecture

Cordyceps-derived interventions show stronger and more consistent benefits on male reproductive health when assessed by testicular histology rather than gross organ weight. Across various disease models, key reproducible effects include preservation or restoration of seminiferous tubule architecture, increased tubule size, improved organisation of Sertoli and germ cells, reduced luminal vacuolisation, and recovery of spermatogenic cell density[14,15,83]. In aged rats, cordycepin improved seminiferous tubule structure and increased spermatogonial and Sertoli cell populations, correlating with enhanced sperm motility and related parameters[15]. In diabetes and ischemia/reperfusion injury models, cordycepin ameliorated seminiferous tubular atrophy, restored orderly germ cell arrangement, and increased the presence of mature spermatozoa within the tubules[14,84]. These histological improvements are often accompanied by reductions in oxidative stress, inflammation, and apoptosis markers in testicular tissue[83,84]. Testicular histology provides a sensitive and reliable endpoint to demonstrate the protective and restorative effects of *Cordyceps* sp. on male reproductive function under pathological conditions.

Cordycepin improved seminiferous architecture, restored the BTB, reduced apoptosis, and upregulated SIRT1/Foxo3a, increasing downstream antioxidant enzymes (Mn-SOD, CAT) and spermatogenic function[14]. In naturally aged rats, cordycepin restored antioxidant enzyme systems, normalised SIRT1 and mTORC1, reduced inflammatory mediators via NF-κB/MAPK inhibition, and improved spermatogenesis-related proteins alongside better tubule structure and sperm kinematics[15,20]. *C. militaris* fermentation products increased seminiferous tubule area, sperm concentration and motility, and enhanced testosterone synthesis, likely via antioxidant pathways including SIRT1/Foxo3a and MAPKs[14,16,19,20]. *C. militaris* extract against bisphenol A (BPA) increased testicular superoxide dismutase (SOD), glutathione peroxidase (GSH-PX) and reduced glutathione (GSH), reduced malondialdehyde (MDA), and improved hormones (LH, testosterone), sperm count/motility, and seminiferous histology[25]. Cordycepin also protected BTB and spermatogenesis from nanoplastic exposure by reducing oxidative stress and restoring junctional integrity in Sertoli cells[85]. *C. Militaris* extract reversed valproate-induced losses in testis weight, testosterone, seminiferous tubule size, and sperm density, improving fertility outcomes[22]. Across diverse disease and toxicant models, *Cordyceps*-derived agents consistently couple improved seminiferous tubule microarchitecture with normalisation of endocrine, antioxidant, and anti-inflammatory pathways, indicating that their principal morphological benefit is the preservation of the microenvironment for spermatogenesis rather than simple organ hypertrophy.

4. The Effects on Spermatogenesis

As shown in Figure 3, spermatogenesis is a highly coordinated and complex biological process involving both mitotic and meiotic divisions, in which endocrine regulation plays a central role in maintaining normal germ cell development and maturation. Additionally, local autocrine and paracrine factors within the

seminiferous epithelium coordinate cellular events such as BTB restructuring and spermiation through a regulatory network involving bioactive peptides derived from laminin and collagen fragments[86,87].

Spermatogenesis occurs within the seminiferous tubules, beginning with spermatogonia that proliferate and differentiate into primary spermatocytes, which then undergo meiosis to form haploid round spermatids. These spermatids mature through spermiogenesis, involving nuclear condensation, acrosome formation, cytoplasmic remodelling, and flagellum development, ultimately releasing mature spermatozoa into the tubule lumen. Sertoli cells play a critical role by providing structural and metabolic support, maintaining the seminiferous epithelium microenvironment, and mediating signals essential for germ cell survival and maturation[86,88]. The HPT axis regulates this process hormonally: gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates pituitary secretion of LH and FSH. LH acts on Leydig cells to produce testosterone, while FSH primarily targets Sertoli cells to support spermatogenesis; both testosterone and

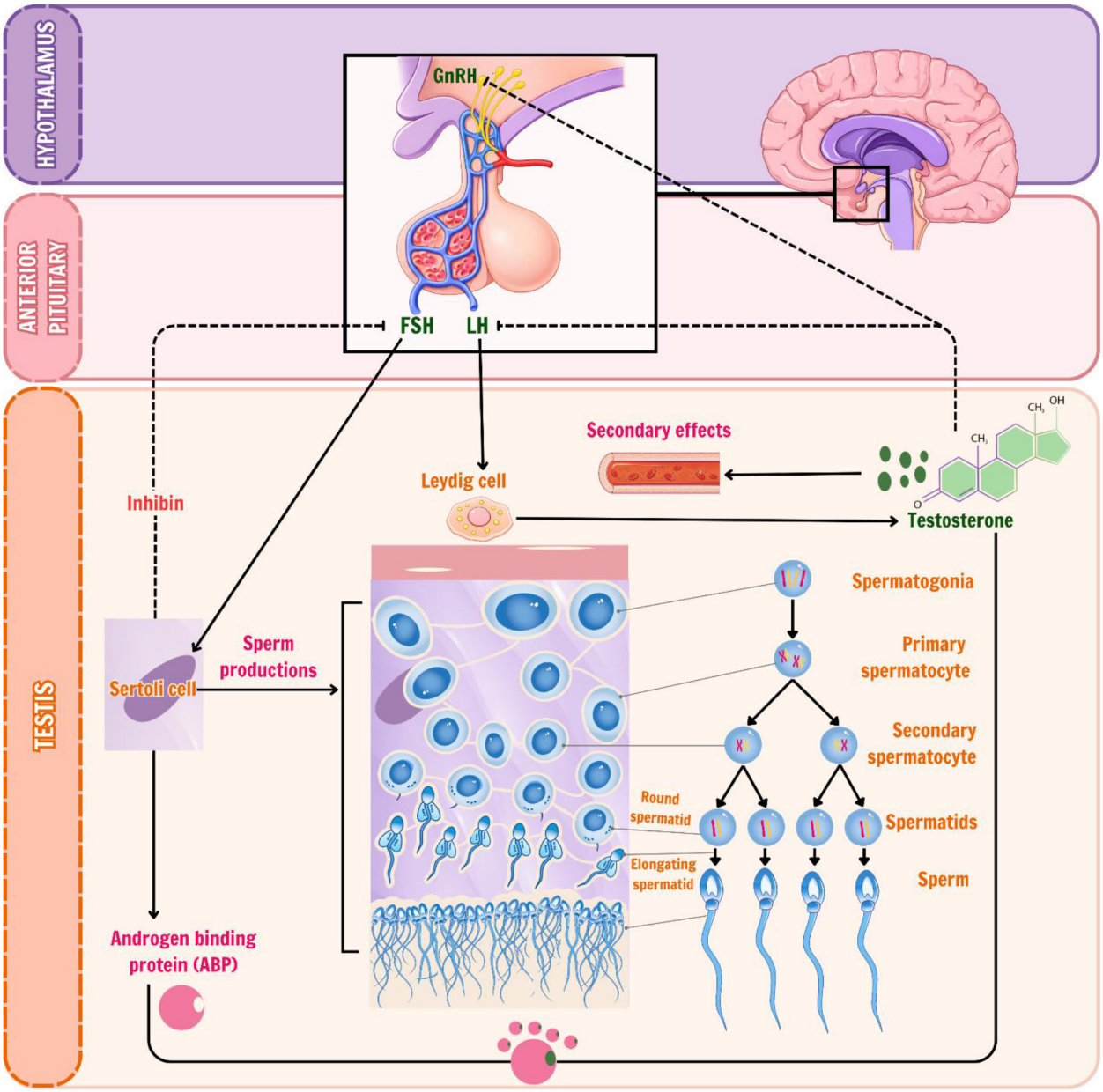


Figure 3. Spermatogenic architecture regulated by the hypothalamic - pituitary - testicular axis.

FSH-dependent Sertoli cell activity are essential for normal sperm production[89,90]. Negative feedback is maintained by testosterone inhibiting GnRH and gonadotropin release at the hypothalamic and pituitary levels, while inhibin from Sertoli cells suppresses FSH secretion to ensure endocrine homeostasis[91,92]. This was our original figure, which was drawn using Canva[93].

4.1 Effects on Testosterone Synthesis and Endocrine Regulation

Multiple *in vitro* and *in vivo* studies show that *Cordyceps* sp. preparations and cordycepin directly stimulate Leydig-cell steroidogenesis, beyond general nutritional support. Crude *O. sinensis* extracts and protein/polysaccharide fractions (F2, F3) increase testosterone production in primary mouse Leydig cells and elevate plasma testosterone *in vivo* in a dose- and time-dependent manner[12,94]. *C. militaris* fruit body extract enhances LH- or dibutyryl-cAMP–stimulated testosterone secretion in primary rat Leydig cells and maintains higher serum testosterone/DHT in castrated rats[78]. Cordycepin increases plasma testosterone in mice and stimulates testosterone production in primary Leydig cells in a concentration- and time-dependent fashion[18,95]. Cordycepin also restores testosterone in oxidative stress–exposed TM3 Leydig cells and in aged rats, indicating a context-dependent magnitude of androgenic effect[20]. Additionally, mechanistic work in Leydig models supports direct modulation of canonical steroidogenic signalling. Cordycepin upregulates A1, A2a, A2b, and A3 adenosine receptor messenger RNAs (mRNAs); adenosine receptor antagonists suppress cordycepin-induced testosterone, indicating an adenosine receptor–dependent trigger[95,96]. Cordycepin-stimulated testosterone is blocked by cAMP and PKA antagonists (Rp-cAMPS, H89, PKI) and accompanied by induction of StAR protein, demonstrating activation of the adenosine receptor–cAMP/PKA–StAR signalling axis[18,95]. *O. sinensis* mycelium and fruiting-body extracts similarly rely on cAMP–PKA signalling, with PKA inhibition (H89) attenuating steroidogenesis[11,78,80]. Multi-omics in *Cordyceps sobolifera* primary rat Leydig cells show coordinated upregulation of cAMP signalling and steroid hormone biosynthesis pathways; PKA and adenylate cyclase inhibitors blunt the testosterone increase[80]. Evidence from Leydig-cell systems shows direct, receptor- and kinase-mediated stimulation of steroidogenesis, chiefly via adenosine receptors and the cAMP-PKA axis, with androgenic potency varying by species, fraction, and physiological context.

Cordyceps-derived products most reliably raise testosterone when the reproductive axis is impaired, acting as restorative modulators rather than universal stimulants. In aged rats, chronic cordycepin (10–20 mg/kg) restores spermatogenesis-related proteins, sex hormone receptors, androgen receptor (AR), and luteinizing hormone receptor (LHR) follicle-stimulating hormone receptor (FSHR), SIRT1/mTORC1 signalling, antioxidant status, and sperm kinematics, effectively reversing age-related testicular decline and hormonal disruption[15,20]. In diabetic models, *C. militaris* and cordycepin increase serum testosterone together with improved sperm count, testicular histology, NO synthase and antioxidant enzymes, and reduced lipid peroxidation and apoptosis, indicating a coordinated repair of testicular structure and function rather than isolated androgen elevation[14,22,26]. In healthy juvenile mice, different *C. militaris* fermentation fractions show divergent endocrine profiles: extracellular polysaccharides (EPS) significantly enhance testosterone synthesis, whereas mycelia and mixed products mainly increase seminiferous tubule area, sperm concentration, and motility with less pronounced hormonal change[19]. Some *O. sinensis* fractions can even reduce human chorionic gonadotropin (hCG)-stimulated testosterone in normal Leydig cells and in hCG-treated mice, suggesting potential attenuation rather than stimulation in fully active axes[13,18]. *C. militaris* fruit-body extract in late-onset hypogonadism and benign prostatic hyperplasia (BPH) models tends to maintain rather than markedly elevate androgen levels in relatively healthy animals, while still improving reproductive endpoints[78]. *Cordyceps*-derived interventions behave primarily as context-dependent, restorative modulators of androgen synthesis under reproductive stress, instead of simple testosterone boosters in all physiological states.

On the other hand, *Cordyceps* sp. can support androgens while limiting prostate stimulation, suggesting a tissue-selective endocrine profile. In testosterone-propionate (TP)–treated rats, *C. militaris* fruit body extract maintained high serum

testosterone and DHT, yet reduced TP-stimulated prostate hypertrophy and prostate weight[78]. The same *C. militaris* extract increased testosterone and DHT secretion from primary testicular cells without upregulating steroidogenic enzyme mRNAs, while inhibiting the proliferation of prostate cell lines[78]. In testosterone-induced BPH, cordycepin alone attenuated prostate enlargement, reduced cyclin D1 and proliferating cell nuclear antigen, and exerted antioxidant, anti-inflammatory, and pro-apoptotic effects in prostate tissue[97].

Cordyceps militaris extract and cordycepin also suppressed androgen-regulated gene expression (FKBP5, TMPRSS2, KLK3) and androgen receptor phosphorylation in lymph node carcinoma of the prostate (LNCaP) cells, with cordycepin acting partly via adenosine A1 receptor–dependent modulation of androgen signalling[79]. A pilot trial in BPH patients found *C. militaris* fruiting bodies reduced prostate volume and improved urinary and sexual function, with no reported androgen-driven worsening of prostate indices[98]. Other *C. militaris* preparations can act more globally androgenically (e.g., increasing accessory gland weights in juvenile or castrated models)[19,22,99], indicating that tissue selectivity may depend on preparation, dose, and hormonal background. Therefore, *C. militaris* and cordycepin often enhance or preserve androgenic function while blunting prostate overgrowth, supporting the idea of restorative, partially tissue-selective modulation rather than indiscriminate stimulation of all androgen-responsive organs.

4.2 Effects on Sperm Production, Motility, and Sperm Functional Quality

Cordyceps-derived products most consistently improve sperm count and motility across animal models, supporting a spermatogenic benefit beyond hormones alone. Dietary *C. militaris* mycelium for 2 months significantly increased semen volume, total sperm number, and the proportion of motile, morphologically normal sperm, with effects persisting for 2 weeks after cessation[23]. In Sprague–Dawley rats, *C. militaris* mycelium (1–5%) for 6 weeks increased epididymal sperm count and the percentage of motile sperm, in parallel with higher serum testosterone and estradiol, while LH and FSH remained unchanged[21]. Different *C. militaris* fermentation products had distinct but convergent benefits; mycelia and fermentation broth increased sperm concentration, while extracellular polysaccharides, broth, and combined products increased the proportion of motile sperm; several preparations also enlarged the seminiferous tubule area and enhanced testosterone synthesis[19]. *C. militaris* fruit body extract or related *C. militaris*-derived preparations protected against sodium valproate–, BPA–, cyclophosphamide-, and diabetic damage by improving sperm density/count, motility, progressive movement, and pregnancy rates in partners, often with concurrent restoration of testicular histology and antioxidant defenses[15,25,26,100,101]. Cordycepin alone in aged rats improved detailed sperm kinematic indices (motility, progressiveness, path and straight-line velocity) and normalised spermatogenesis-related proteins and testicular structure[15]. Cordycepin enhanced hyperactivated motility and acrosome reaction during capacitation without increasing ROS or DNA damage[17]. Across these studies, increases in sperm quantity and motility/kinematics are the most reproducible findings, whereas hormonal changes (e.g., testosterone, LH/FSH) are present but more variable[15,19,21,23,25,26,100,101]. This pattern strengthens the inference that *Cordyceps*-derived interventions directly support spermatogenesis and sperm function, with formulation- and context-dependent differences in magnitude.

Across diabetic, aged, and toxicant-induced models of impaired spermatogenesis, *C. militaris* and cordycepin most robustly restore sperm production and motility when reproductive function is already compromised, acting through antioxidant, anti-inflammatory, antiapoptotic, and BTB-preserving mechanisms. In streptozotocin (STZ)-induced diabetic rats, cultured *C. militaris* reversed diabetes-related declines in sperm count, motility, viability, testosterone, and sexual behaviour, while improving testicular antioxidant status (increased SOD, GSH, CAT; decreased MDA)[26,102]. In type 2 diabetic mice, cordycepin ameliorated testicular damage, restored BTB integrity, and improved spermatogenic function through SIRT1/Foxo3a-driven upregulation of Mn-SOD and CAT, reducing oxidative stress and apoptosis[14,77]. In aged rats, cordycepin improved detailed sperm kinematics (motility, progressiveness, path and straight-line velocity), normalised spermatogenesis-related proteins, SIRT1,

Table 1. Potential effects of *O. sinensis* and *C. militaris* preparations on the male reproductive organ and spermatogenesis

Model (n per group)	Dose	Intervention Duration	Key Findings of Reproductive Effects	Comparison of Effects Among Different Doses	References
Studies on *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) Preparations					
Primary normal mouse Leydig cells *in vitro*; no *in vivo* animal grouping for the main experiment.	*O. sinensis* 0.1–10 mg/mL *in vitro*; maximal stimulation was reported around 3 mg/mL.	*In vitro:* incubation for up to several hours; no *in vivo* route.	*O. sinensis* increased testosterone production in normal mouse Leydig cells in a dose- and time-dependent manner, suggesting a direct steroidogenic effect. However, it inhibited hCG- and dibutyryl-cAMP-stimulated testosterone production, indicating a more complex regulatory effect on Leydig-cell steroidogenesis than a simple linear stimulatory action. This is best classified as mechanistic endocrine evidence rather than a full spermatogenesis study with sperm or histologic endpoints.	A clear dose-dependent increase was reported up to approximately 3 mg/mL, after which the effect plateaued or was less emphasised.	[12]
In vitro: Purified mouse Leydig cells *In vivo*: Male mice were used.	*In vitro*: Fractions up to 3 mg/mL showed stimulatory activity. *In vivo*: 0.02 and 0.2 mg/g body weight of whole *O. sinensis* or fractions.	*In vitro*: Incubation for up to several hours. *In vivo*: Up to 7 days;	Whole *O. sinensis* and particularly fractions F2 and F3 stimulated testosterone production in mouse Leydig cells both *in vitro* and *in vivo*. Fraction F1 was inactive. The study supports the concept that selected *O. sinensis* fractions enhance male reproductive endocrine function, but it remains primarily a Leydig cell/ steroidogenesis paper rather than a comprehensive spermatogenesis study.	F2 and F3 outperformed F1; higher tested concentrations/ doses showed stronger testosterone-stimulatory effects.	[94]
Immature and mature male mice; 3 groups with 5 mice per group	0.02 and 0.2 mg/g body weight of *O. sinensis* mycelium or fractions.	1-7 days	*O. sinensis* mycelium and active fractions increased plasma testosterone in both immature and mature male mice. This research is more directly relevant to male reproductive function than the pure Leydig-cell studies. Still, it emphasises endocrine stimulation rather than full spermatogenic readouts such as sperm count, motility, or testicular histology.	Both 0.02 and 0.2 mg/g were tested, with stronger endocrine stimulation generally seen at the higher dose and/or longer exposure. Active fractions appeared more effective than inactive fractions.	[76]
Studies on *Cordyceps militaris* Preparations					

Table 1. Continued...

Model (n per group)	Dose	Intervention Duration	Key Findings of Reproductive Effects	Comparison of Effects Among Different Doses	References
17 Duroc and 12 Landrace boars aged 29–40 months. Control group: Duroc n = 8, Landrace n = 6; treatment group: Duroc n = 9, Landrace n = 6.	Regular diet versus diet supplemented with *C. militaris* mycelium.	2 months of dietary supplementation.	*C. militaris* supplementation improved sperm production in subfertile boars, with enhancement evident by the end of the first month and peaking in the second month. Sperm motility and morphology also improved in a substantial proportion of animals. This is one of the most clinically relevant animal-production studies in the field because it evaluates direct semen outcomes rather than only endocrine markers.	No dose - response comparison; single treatment *vs*. control only.	[23]
Male Sprague–Dawley rats, 7 weeks old; 3 groups (control, 1% *C. militaris*, 5% *C. militaris*); about 30 rats per group	Diet supplemented with *C. militaris* mycelium at 1% or 5% of feed	6 weeks and then allowed to recover for 1 week; oral via feed	*C. militaris* increased epididymal sperm count, improved sperm motility, and elevated testosterone and estradiol-17 concentrations. Serum cordycepin also rose during supplementation. FSH, LH, and prolactin did not show major changes. This study is one of the strongest direct pieces of evidence that *C. militaris* positively affects sperm output and sperm movement *in vivo*.	Both 1% and 5% were beneficial; 5% produced higher serum cordycepin levels late in treatment, but both doses improved sperm-related outcomes. The evidence suggests a benefit with both doses rather than a sharply separated dose–response gradient.	[21]
Rat model of bisphenol A (BPA)-induced reproductive damage. 35 adult male Sprague-Dawley rats were divided into 7 groups with 5 rats per group.	BPA 200 mg/kg, with *C. militaris* extract at 200, 400, or 800 mg/kg/day.	4 weeks	*C. militaris* extract attenuated BPA-induced reproductive toxicity in rats by improving antioxidant status, restoring testosterone and LH levels, enhancing sperm parameters, and ameliorating testicular histopathology. These findings suggest a protective effect of *C. militaris* against chemically induced reproductive damage.	The protective effects against BPA-induced reproductive toxicity showed a dose-dependent pattern, with 800 mg/kg producing the greatest improvements in antioxidant status, testosterone/LH levels, sperm count and motility, and testicular histology.	[25]

Table 1. Continued...

Model (n per group)	Dose	Intervention Duration	Key Findings of Reproductive Effects	Comparison of Effects Among Different Doses	References
Male Wistar rats, castrated, 5 rats per group	*C. militaris* extract 20 mg/rat/day orally; testosterone propionate 1 mg/kg every other day in the hypo gonadism model and 3 mg/kg/day in the prostate-hypertrophy model.	*C. militaris* was given orally for 12 days in the hypogonadism model or 30 days in the prostate-hypertrophy model.	The extract decreased testosterone catabolism, maintained circulating testosterone and DHT, stimulated androgen secretion by testicular cells, and suppressed testosterone-induced prostate hypertrophy. This is a valuable androgen-homeostasis study, but it does not directly evaluate sperm count, sperm motility, or full spermatogenesis.	No dose comparison; single extract dose only.	78
Streptozotocin-induced diabetic male rats plus normal controls. Multiple groups; sperm endpoints were generally analysed with n = 10/group, while some nitric oxide synthase endpoints used n = 6/group.	Cultured *C. militaris* 0.1, 0.5, or 1.0 g/kg body weight/day; comparator sildenafil 5 mg/kg; vehicle control groups were included.	3 weeks, oral gavage for cultured *C. militaris*; sildenafil was given as a comparator before behavioural testing.	Cultured *C. militaris* improved sexual performance, erectile function, sperm count, sperm motility, testosterone, testicular oxidative status, and penile nitric oxide synthase signalling in diabetic rats. This is one of the most informative disease-model studies because it simultaneously addresses erectile physiology, hormones, and sperm quality.	The response was not purely linear. The 0.1 and 0.5 g/kg doses often performed as well as or better than 1.0 g/kg for several reproductive outcomes, suggesting a non-monotonic or plateau-like dose–response relationship, rather than a simple pattern in which higher doses consistently produce greater benefit.	26
Six-week-old Wistar rats were divided into four experimental groups, 6 rats per group.	*C. militaris* extract (100 mg/kg)	21 days, oral administration.	*C. militaris* treatment in streptozotocin-induced diabetic rats improved sexual behaviour, increased testosterone, improved epididymal sperm parameters, lowered malondialdehyde, and improved antioxidant defences.	No internal dose comparison; single-dose treatment only.	102

Table 1. Continued...

Model (n per group)	Dose	Intervention Duration	Key Findings of Reproductive Effects	Comparison of Effects Among Different Doses	References
Male Wistar rats in three experimental contexts: Androgenic assay in castrated immature male rats Protection model against valproic acid (VPA)-induced reproductive injury Rehabilitation model after VPA-induced injury The protection model used 4 groups, n = 10 rats/group.	Androgenic assay: *C. militaris* fruit body extract (CE) 0.112, 0.336, 0.560 g/kg/day Protection model: VPA 500 mg/kg/day plus CE 0.112 or 0.336 g/kg/day Rehabilitation model: after VPA injury, CE 0.112 or 0.336 g/kg/day	Androgenic assay: 10 days Protection model: 7 weeks Rehabilitation model: 10 days after the injury phase The extract was administered orally.	CE showed mild androgenic activity in the Hershberger-type assay and improved testosterone, testicular histology, seminiferous tubule dimensions, sperm density, live sperm percentage, and progressive motility in VPA-induced reproductive injury. It also showed partial rehabilitation effects after toxicant exposure had already occurred.	0.336 g/kg/day was generally more effective than 0.112 g/kg/day in both protection and rehabilitation settings. The highest androgenic-assay dose (0.560 g/kg/day) produced the strongest effects on accessory sex organ weights, but that assay was not designed as a spermatogenesis model.	[22]
Hypogonadal mouse model using Swiss albino mice (5–6 weeks old). Experimental groups were arranged with n = 8 animals per group.	*Cordyceps* water: 11.76–23.52 mL/kg body weight/day. *Cordyceps* capsule: 58.8–117.6 mg powdered material/kg body weight/day.	14 days of oral administration, once daily in mice.	Both *Cordyceps* preparations increased circulating testosterone and 17β-estradiol levels in hypogonadal mice, approaching values observed in physiological controls. The treatments increased plasma testosterone to ~2.37–2.87 ng/mL and estradiol to ~24.28–32.32 pg/mL, without affecting hormone levels in normal animals. These results suggest potential benefits for improving reproductive hormone balance and sexual function.	Both low and high doses of the two *Cordyceps* formulations increased testosterone in hypogonadal mice, with values in the approximate range 2.37–2.87 ng/mL, indicating a beneficial endocrine effect across tested doses rather than a sharply differentiated dose-response.	[108]
Juvenile male mice were divided into four experimental groups, 5 mice per group.	Diet containing 5% (weight per weight) of *C. militaris*: extracellular polysaccharides (EPS), fruiting body (FB), mycelium (MY), and combined fruiting body + mycelium (FBMY).	28 days, oral through diet.	The different *C. militaris* fermentation products promoted male reproductive development in different ways. MY increased testicular volume and seminiferous tubule area, and improved sperm concentration. EPS, FB, and FBMY improved sperm motility. EPS showed especially strong androgen-like activity, with higher serum testosterone-related indices. This study compares different fungal fractions/products rather than only one extract.	This was not a dose-escalation study. Instead, it compared different product types at the same 5% inclusion level. Broadly, MY appeared strongest for testicular growth/sperm concentration, whereas EPS was strongest for testosterone-related androgenic effects.	[19]

and mTORC1 expression, and corrected histological indices of impaired spermatogenesis[15,20,77]. *C. militaris* fruit body extract protected against sodium valproate–induced testicular toxicity, increasing sperm density, viable sperm, progressive motility, and pregnancy rate while restoring testosterone and seminiferous tubule structure[22].

Taken together, animal and limited human *in vitro* data indicate that *Cordyceps*-derived products improve both sperm output and sperm movement, offering more direct evidence for enhanced spermatogenesis than endocrine measures alone. Effects are broadly consistent but modulated by species, health status, and specific fungal formulation.

5. Discussion

5.1 Natural versus Cultivated Materials: Compositional Shift and Functional Implications

Cultivated and wild *Cordyceps* sp. share similar classes of bioactive compounds but differ significantly in their relative abundances, affecting their pharmacological profiles. In *O. sinensis*, cultivated samples generally have higher levels of amino acids, crude fat, and nucleosides like adenosine, while wild specimens are richer in metabolites such as trehalose, glycerol, citric acid, ergosterol, trace elements, and certain lipids, including linolenic acid[103-105]. These differences suggest that cultivated *O. sinensis* can replicate core nucleoside- and polysaccharide-related effects but may not fully match the sterol-, lipid-, or small-molecule-driven activities of wild material[103,104]. For *C. militaris*, cultivation serves as a controllable production platform where factors like substrate composition, pH, temperature, oxygen levels, and harvest timing can be optimised to enhance yields of cordycepin, adenosine, D-mannitol, polysaccharides, ergosterol, and carotenoids[35,106,107]. Cultivated *C. militaris* is thus preferable for standardised nucleoside-rich preparations due to its consistent metabolite profile, whereas wild *O. sinensis* offers a more complex and variable metabolite matrix[105,107]. Hence, neither source is universally superior; rather, they represent distinct chemotypes with different dominant bioactivities influenced by their origin and cultivation conditions[103,107].

5.2 *Cordyceps* Dose–response in Testicular Protection: Higher is not Always Better

Animal studies support morphology-preserving and pro-spermatogenic effects across a range of doses; however, the dose–response relationship often appears to plateau or remain nonlinear, rather than demonstrating progressively greater benefit with increasing dose.

Table 1 shows evidence in reproductive effects and dose–response patterns of *Cordyceps* sp. extracts. Higher extract doses (up to 0.336 g/kg) progressively improved organ weights, seminiferous tubule size, sperm density, and pregnancy rates, but effects tended to plateau at the top dose rather than increase indefinitely[22]. *C. militaris* at 200–800 mg/kg improved antioxidant enzymes, hormones, sperm count/motility, and histology; benefits were significant at all doses, with limited evidence of a strictly linear gradient across 200–800 mg/kg[25]. Extracts at 0.1–1.0 g/kg in diabetic rats improved sperm count, testosterone, testicular SOD, and histology, but differences among doses were modest, compatible with a plateauing or non-monotonic curve[26,102]. In type 2 diabetes mellitus mice, cordycepin and *C. militaris* extracts showed hormetic, J- or inverted-U–shaped dose–response patterns for oxidative and inflammatory markers, with low doses sometimes as effective or more effective than high doses, and little separation between high vs low groups on several endpoints[109].

The reproductive effects and dose - response patterns of Cordycepin, a *Cordyceps*-derived pure compound, were evaluated in cross-*in vivo* and *in vitro* studies, as shown in Table 2. Cordycepin at 10 and 20 mg/kg improved BTB integrity, seminiferous architecture, and sperm morphology via SIRT1/Foxo3a activation; the abstract does not clearly separate histologic efficacy between 10 *vs.* 20 mg/kg, only that both were effective[14]. Moreover, cordycepin at 10–20 mg/kg often produces the clearest recovery of spermatogenesis-related proteins, SIRT1/mTORC1 signalling, antioxidant defences, and testicular histology, with weaker or less complete changes at 5 mg/kg, indicating a partial dose–response that appears to plateau at higher doses[15,16,110]. In senile rats, 5, 10, and 20 mg/kg cordycepin all improved sperm kinematics and histology, but restoration of spermatogenesis-related proteins, SIRT1, and mTORC1

Table 2. Potential effects of Cordycepin on male reproductive function

Model (n per group)	Dose	Intervention Duration	Key Findings of Reproductive Effects	Comparison of Effects Among Different Doses	References
Male B6 (C57BL/6NCrj) mice; Control, Cordycepin-40 (n = 28 mice/ group)	Control: Saline; Cordycepin-40: 40 mg/kg	Intra-peritoneal (IP) injection for 7 days	The treatment significantly increased testis weights and plasma testosterone concentrations in mice. Regarding the specific mechanism, cordycepin binds to adenosine receptors (specifically A1, A2a, and A3) on Leydig cells. This interaction activates the cAMP-PKA signalling pathway. Consequently, this pathway induces de novo protein synthesis and upregulates the expression of the StAR protein, which ultimately stimulates steroidogenesis and testosterone production.	The 40 mg/kg dose effectively stimulated testosterone production and increased testis weight after 7 days of administration. In contrast, the lower dose of 20 mg/kg showed no *in vivo* effects. Therefore, the IP injection of 40 mg/kg is the optimal dose to enhance reproductive function in this model.	[95]
Sprague–Dawley rats, a total of 30 males: 24 middle-aged and 6 young rats allocated into 5 groups.	Vehicle, 5 mg/kg, 10 mg/kg, or 20 mg/kg cordycepin in middle-aged rats; young controls were also included.	4 months, oral administration.	Long-term oral administration of cordycepin derived from *C. militaris* improved testicular function in middle-aged Sprague–Dawley rats. Specifically, treatment increased epididymal weight, sperm motility, progressive motility, and the proportion of mature spermatozoa, while also improving the histological structure of seminiferous tubules.	This study shows dose-dependent improvement, with 20 mg/kg producing the strongest reproductive benefit.	[110]
Sprague–Dawley rats; Young control, Aged control, Cordycepin-5, Cordycepin-10, Cordycepin-20 (≈10 rats/group)	Cordycepin-5:5 mg/kg; Cordycepin-10:10 mg/kg; Cordycepin-20:20 mg/kg;	Oral administration for 6 months	The treatment improved sperm motility and sperm kinematic parameters in aged rats. The compound enhanced spermatogenesis and improved the histological structure of seminiferous tubules. It increased the expression of reproductive hormone receptors, including AR, FSHR, and LHR. The intervention elevated antioxidant enzyme activities such as glutathione peroxidase 4 (GPx4), glutathione S-transferase mu 5 (GSTm5), and peroxiredoxin 4 (PRx4). In addition, it regulates signalling pathways associated with reproductive function, including SIRT1 and mTOR.	The 20 mg/kg dose produced the strongest restoration of spermat ogenesis-related molecular markers and testicular function, indicating a dose-responsive improvement across the 5–20 mg/kg range.	[15]

Table 2. Continued...

In vitro: hydrogen peroxide-exposed TM3 Leydig cells. *In vivo*: naturally aged Sprague–Dawley rats were divided into three groups (n = 6).	*In vitro*: 1, 5, and 10 µg/mL *In vivo*: 20 mg/kg cordycepin in aged rats	Long-term aged-rat treatment; oral administration in the *in vivo* arm; *in vitro* exposure to cordycepin in TM3 cells.	Cordycepin improved Leydig-cell viability under oxidative stress, reduced lipid peroxidation, restored redox-related and spermatogenesis-related proteins, improved testosterone output, and attenuated oxidative/apoptotic signalling in aged testes. This is a strong mechanistic bridge study connecting redox control, steroidogenesis, and age-related testicular damage.	*In vitro* effects were dose-dependent, with the strongest restoration at 10 µg/mL. The *in vivo* arm used a single 20 mg/kg dose.	[20]
Naturally aged Sprague–Dawley rats were divided into five groups (n = 10): young control, aged control, and 3 treated aged rat groups.	Cordycepin from *C. militaris* at doses of 5, 10, and 20 mg/kg.	Long-term aged-rat treatment; oral administration.	Cordycepin mitigated inflammaging-associated testicular injury by reducing inflammatory cytokines and suppressing NF-κB/MAPK signalling. Although the study is more inflammation-focused than semen-focused, it remains relevant to male reproductive biology because chronic testicular inflammation is closely linked to impaired spermatogenesis.	The anti-inflammatory and testis-protective effects were strongest at 20 mg/kg, indicating a dose-responsive pattern.	[16]
Type 2 diabetic male C57BL/6 mice induced by high-fat diet plus streptozotocin; n = 8/group.	10 mg/kg and 20 mg/kg cordycepin.	After diabetes induction, mice were treated orally for 8 weeks.	Cordycepin ameliorated diabetes-induced testicular damage, improved spermatogenic function, reduced apoptosis and oxidative stress, and restored BTB integrity through the SIRT1/Foxo3a pathway. These results link metabolic injury, redox control, barrier integrity, and male reproductive rescue.	Both of the cordycepin doses (10 and 20 mg/kg) improved diabetes-induced testicular injury, spermatogenic function, and antioxidant signalling. The 20 mg/kg group generally showed stronger restoration of molecular and histological markers, suggesting a dose-responsive protective effect.	[14]
The study recruited 20 healthy donors, and each experiment used pooled semen from at least 3 donors.	20, 100, and 500 µM cordycepin; additional inhibitor groups were used for mechanistic confirmation.	3-hour *in vitro* capacitation incubation	Cordycepin improved hyperactivation and acrosome reaction during human sperm capacitation, increased PKA activity and tyrosine phosphorylation, and acted through adenosine receptors.	The effect was dose-dependent, with 500 µM showing the strongest effect, 100 µM intermediate, and 20 µM the weakest.	[17]

was most clearly reported for 20 mg/kg, suggesting a partial dose–response with an apparent ceiling at the high dose[15]. Biochemical and inflammatory readouts improved across 5–20 mg/kg, yet detailed mechanistic work (NF-κB/MAPK) was carried out only at 20 mg/kg, so the superiority of higher doses for testicular endpoints cannot be generalized[16].

Overall, *Cordyceps*-derived interventions genuinely preserve spermatogenesis and protect sperm, but the magnitude and profile of benefit depend on fungal species, fraction (nucleosides *vs.* polysaccharides/mycelia), injury model, and dose. The available evidence does not support a straightforward pattern in which higher doses consistently confer greater benefit across all preparations and disease contexts.

5.3 Limitations and Barriers to Clinical Translation

Animal and human *in vitro* data suggest that cordycepin's reproductive relevance now spans both testicular protection/spermatogenesis and post-testicular sperm functional competence, though only the latter has been directly shown in human cells and requires *in vivo* confirmation. Mechanistically, human sperm express all four adenosine receptor (A1, A2A, A2B, A3) subtypes, and pharmacologic blockade of these receptors markedly reduced cordycepin-induced hyperactivation and acrosome reaction, consistent with an adenosine receptor–mediated cAMP/PKA pathway. Molecular docking supported the direct binding of cordycepin to these receptors[17]. These data align with broader capacitation literature showing that small molecules can selectively modulate hyperactivation and/or acrosome reaction without affecting spermatogenesis (e.g., progesterone, pentoxifylline, F4-neuroprostanes)[111-114]. The human data are entirely *in vitro* on ejaculated sperm, so they do not demonstrate enhanced spermatogenesis, testicular structure, or *in vivo* fertility. Nonetheless, they indicate that cordycepin can improve post-testicular functional competence, particularly capacitation-associated hyperactivation and acrosome reaction, complementing animal evidence on testicular protection and sperm output[14,15,19,22,110].

For male infertility, *Cordyceps*-derived interventions are still at an exploratory stage: encouraging preclinical and limited clinical signals exist, but the absence of robust human trials, standardisation, and long-term safety data are the main barriers to clinical translation and inclusion in guidelines. There are 3 key barriers to clinical translation in male infertility. Firstly, the broader Traditional Chinese medicine (TCM) for male infertility literature is dominated by small, non-blinded, low-quality domestic studies with heterogeneous outcomes and poor adverse-event reporting[115,116]. World Health Organisation (WHO)- and guideline-level reviews conclude there are insufficient data to recommend herbal therapies for male infertility, emphasising the need for large, placebo-controlled randomised controlled trials (RCTs) with live-birth outcomes[117-119]. Secondly, *Cordyceps* sp., extraction methods, doses, and combinations (e.g., with other herbs in complex prescriptions) vary widely, making reproducible dosing and safety assessment difficult[18,115,116]. Human pharmacokinetics, bioavailability, and long-term safety of cordycepin and related actives in infertile men remain poorly characterized[16-18]. Thirdly, major evidence-based guidelines, such as the WHO, European Association of Urology (EAU), and others, do not endorse herbal/TCM therapies due to very low-quality evidence[118-121]. Lack of standardised, registered *Cordyceps* products tested in rigorous male-infertility trials prevents regulatory approval and integration into routine care.

5.4 Future Perspective

Cordyceps-derived interventions, including *O. sinensis*, *C. militaris*, and cordycepin, have the potential to evolve from general nutraceuticals into mechanism-informed adjunct therapies for male infertility if current barriers like evidence quality, product standardisation, pharmacokinetics, and long-term safety are addressed. Preclinical studies demonstrate effects on steroidogenesis, seminiferous tubule integrity, sperm count and motility, BTB protection, and redox homeostasis, which are relevant to oxidative-stress–predominant idiopathic infertility, metabolic or diabetes-related reproductive dysfunction, testicular ageing, high sperm DNA fragmentation, and subclinical Leydig-cell insufficiency[14-16,18-20]. Cordycepin enhances human sperm hyperactivation and acrosome reaction during capacitation via adenosine receptor-mediated pathways without increasing DNA damage or ROS *in vitro*[17]. These findings suggest *Cordyceps*-derived

compounds could serve as pre-assisted reproductive technology (ART) optimisation tools to improve sperm molecular quality before intrauterine insemination (IUI) or *in vitro* fertilisation/intracytoplasmic sperm injection (IVF/ICSI) in selected patients with oxidative damage or elevated sperm DNA fragmentation, a factor recognised by the EAU as clinically relevant in unexplained infertility and ART failure. However, their role in *in vitro* maturation (IVM) of oocytes remains speculative due to limited preclinical evidence[17]. Overall, *Cordyceps* interventions are unlikely to replace established infertility treatments but may complement them by targeting specific molecular dysfunctions underlying male infertility[22].

Combining *Cordyceps*-derived compounds with traditional medicinal plants like liquorice (*Glycyrrhiza* spp.), *Morinda officinalis*, and goji berry (*Lycium barbarum*) holds promise for enhancing male reproductive health through complementary mechanisms such as reducing oxidative stress, improving mitochondrial function, modulating endocrine balance, and preventing germ-cell apoptosis. *M. officinalis* and *L. barbarum* coupled-herbs have been shown to alleviate apoptosis, reduce oxidative stress, and promote male reproductive function via key pathways including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling and androgen receptor modulation[122,123]. *L. barbarum* polysaccharides specifically protect against reproductive toxicity by activating antioxidant responses [the nuclear factor erythroid 2–related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) signalling pathway] and suppressing apoptosis, thereby restoring spermatogenesis[124]. *Cordyceps* polysaccharides also improve sperm quality and hormone levels by stimulating the HPT axis and inhibiting apoptotic pathways[27], while cordycepin from *C. militaris* enhances testosterone synthesis and testicular development[15,19]. Clinical evidence supports polyherbal formulations' ability to significantly improve sperm concentration, motility, semen volume, and regulate serum hormones in oligospermic males, suggesting synergistic spermatogenic effects[125,126]. However, rational design of such combinations requires detailed pharmacologic, toxicologic, pharmacokinetic studies, and systems biology approaches to optimise composition, dose ratios, safety, and efficacy before clinical application[18].

Combining *Cordyceps* pharmacology with clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 (CRISPR-associated protein 9) gene editing, multi-omics, and artificial intelligence (AI) holds significant promise for advancing male infertility treatment over the next two decades. CRISPR/Cas9 is already transforming spermatogenesis research by identifying causal genes and regulatory pathways, with animal models demonstrating restored sperm production in some knockout cases, suggesting gene editing could clarify which infertility subtypes are amenable to drug-based versus gene-based therapies[127,128]. Multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, are redefining male infertility as a set of molecular endophenotypes rather than a single diagnosis, enabling biomarker-guided patient stratification to identify those most likely to benefit from *Cordyceps*-derived compounds[129]. AI can integrate diverse clinical and molecular data, such as semen analysis, sperm DNA fragmentation, endocrine profiles, imaging, and multi-omics signatures, to standardise diagnosis, optimise sperm selection for IVF/ICSI, predict treatment response, and personalise dosing or formulation choices[128,130]. Future *Cordyceps*-based therapies may shift from empirical herbal mixtures toward chemically standardised, mechanism-driven combinations targeting complementary pathways like oxidative stress and mitochondrial dysfunction; this precision approach could enhance natural conception and serve as adjuncts in assisted reproductive technologies such as IUI and IVF/ICSI[130]. However, the role of *Cordyceps* in IVM or laboratory media optimisation remains speculative and requires dedicated translational studies before clinical application can be recommended[128].

6. Conclusion

In conclusion, *Cordyceps* and its bioactive constituents, particularly cordycepin, may improve male reproductive function through multiple complementary mechanisms. These proposed mechanisms include stimulation of steroidogenesis, likely through the adenosine receptor–cAMP/PKA–StAR pathway, modulation of endocrine homeostasis, attenuation of oxidative stress and inflammation, reduction of germ-cell apoptosis, preservation of

testicular architecture, and support of spermatogenesis and sperm quality. However, the available evidence is still largely restricted to heterogeneous animal studies, with substantial variability in species, disease models, formulations, doses, and treatment duration, and with limited mechanistic standardisation and no robust clinical confirmation. Therefore, although the findings are promising, they should be interpreted cautiously and cannot yet be directly extrapolated to human male fertility. Future research should focus on standardised *Cordyceps*-derived preparations, clearer dose–response characterisation, deeper mechanistic validation, long-term safety assessment, and adequately powered clinical studies to determine translational relevance.

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Author Contribution

Conceptualisation: T.H.N. and P.L.N.N.; Methodology: T.H.N., P.L.N.N., and D.V.T.; Data Curation: H.T.T.N.,

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