



# MOTS-c peptide in metabolism, disease and therapy: a comprehensive review

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**Abstract.** MOTS-c (mitochondrial open reading frame of the 12S rRNA type c) is a mitochondria-derived peptide (MDP) that has emerged as a key regulator of metabolic homeostasis, stress response, and aging-related processes. This comprehensive review synthesizes current knowledge on the discovery, molecular mechanisms, physiological roles, and therapeutic potential of MOTS-c, with particular emphasis on its role in metabolism, disease modulation, and translational medicine. MOTS-c acts as a retrograde signaling molecule linking mitochondrial function to nuclear gene expression, primarily through AMPK activation and modulation of multiple signaling pathways, including Nrf2, NF- $\kappa$ B, PI3K/AKT, and mTOR. Preclinical evidence demonstrates that MOTS-c exerts broad protective effects across multiple organ systems, improving insulin sensitivity, glucose metabolism, lipid utilization, and reducing inflammation, oxidative stress, and apoptosis. These properties position MOTS-c as a promising candidate for the treatment of metabolic disorders, cardiovascular diseases, inflammatory conditions, neurodegeneration, and certain cancers. Despite robust data from animal and cellular models, clinical translation remains limited. Human studies are largely observational, highlighting associations between circulating MOTS-c levels and metabolic or age-related diseases, without conclusive evidence from controlled clinical trials. Key challenges include peptide stability, bioavailability, species-specific differences, and incomplete understanding of receptor-mediated mechanisms. Overall, MOTS-c represents a novel and biologically significant mitochondrial signaling peptide with substantial therapeutic potential. However, further well-designed clinical studies are required to validate its efficacy, safety, and applicability in human medicine.

**Key Words:** aging, AMPK signaling, cardiovascular disease, inflammation, insulin resistance, metabolism, mitochondrial-derived peptides, MOTS-c, obesity, therapeutic peptides.

**Introduction.** MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c) is a 16-amino-acid peptide encoded by a short open reading frame within the mitochondrial 12S rRNA gene. It is now recognized as a mitochondria-derived peptide (MDP) that acts both as an intracellular stress signal and a circulating hormone-like factor, with wide-ranging roles in metabolism, inflammation, aging, cardiovascular and other diseases (Lee et al 2016; Kim et al 2017; Mohtashami et al 2022; Wan et al 2023; Zheng et al 2023).

The aim of this study is to provide a comprehensive and up-to-date review of the mitochondrial-derived peptide MOTS-c, focusing on its molecular mechanisms of action, physiological roles in metabolic regulation, involvement in disease pathogenesis, and potential as a therapeutic agent, while critically evaluating current preclinical and clinical evidence and identifying key challenges for its translational application.

**Peptide therapies for obesity and anti-aging: recent advances and societal impact.** Peptide drugs have rapidly changed obesity treatment and are being explored for broader "healthy aging" effects. Most evidence focuses on incretin-based peptides (semaglutide, tirzepatide, retatrutide), with earlier-stage data for GHK-Cu and MOTS-c in aging-related conditions.

## Incretin-based peptides for obesity (semaglutide, tirzepatide, retatrutide)

**Semaglutide (GLP-1 agonist).** Weekly 2.4 mg causes ~15-17% weight loss over 68-104 weeks in people with obesity, plus better blood pressure, lipids, liver fat, and quality of life (Bailey et al 2023; Bergmann et al 2023; Bailey et al 2024; Melson et al 2025). GI side effects are common but usually mild-moderate (Bergmann et al 2023; Bailey et al 2024) (Table 1).

**Tirzepatide (dual GLP-1/GIP agonist).** Produces up to ~22-23% weight loss in phase 3 obesity trials and often more weight loss than semaglutide, with similar GI tolerability (Alkhezi et al 2023; Bergmann et al 2023; Tan et al 2023; Xie et al 2024; Melson et al 2025) (Table 1).

**Retatrutide (triple GLP-1/GIP/glucagon agonist).** Phase 2/early data show ~20-24% weight loss and strong metabolic benefits; phase 3 trials are ongoing (Bailey et al 2023, 2024; Xie et al 2024; Bailey et al 2025; Kokkorakis et al 2025; Melson et al 2025; Petrescu-Mag & Dăescu 2025) (Table 1).

Real-world studies show substantial but somewhat smaller weight loss than in trials, high early discontinuation (20-50%), and no strong signal of severe long-term toxicity so far (Pickart & Margolina 2018; Bailey et al 2024; Drucker 2025; Thomsen et al 2025).

Table 1  
Relative weight loss with leading incretin peptides (summarized by Consensus, 2026)

Peptide (typical trial dose)	Mean weight loss (%)	Key notes	Citations
Semaglutide 2.4 mg weekly	~15-17%	Approved obesity Rx	(Bergmann et al 2023; Bailey et al 2024; Melson et al 2025)
Tirzepatide 15 mg weekly	~20-22%	Dual agonist	(Alkhezi et al 2023; Tan et al 2023; Xie et al 2024; Melson et al 2025)
Retatrutide 8-12 mg weekly	~20-24%	Triple agonist, in trials	(Bailey et al 2023, 2024; Xie et al 2024; Bailey et al 2025; Melson et al 2025)

## Anti-aging and tissue-protective peptides (GHK-Cu, MOTS-c)

**GHK-Cu:** A natural peptide-copper complex that promotes collagen, elastin, blood vessel and nerve growth, improves repair of skin, bone, lung, liver, and has antioxidant, anti-inflammatory, and DNA-repair-related actions (Pickart & Margolina 2018; Dou et al 2020). Considered a candidate anti-aging peptide, but human clinical aging trials are still limited (Dou et al 2020).

**MOTS-c:** A mitochondrial peptide that declines with age; in models, improves muscle metabolism, insulin sensitivity, and multiple age-related diseases (diabetes, CVD, osteoporosis, postmenopausal obesity, Alzheimer's) (Lu et al 2019; Mohtashami et al 2022; Zheng et al 2023). In ovariectomized mice, MOTS-c prevents weight gain, reduces inflammation, and activates brown fat via AMPK, suggesting promise for menopausal metabolic dysfunction (Lu et al 2019). Clinical application remains experimental (Mohtashami et al 2022; Zheng et al 2023).

## Impact on human and animal health

**Human societal impact.** Incretin peptides can approach bariatric-surgery-like weight loss and improve cardio-renal outcomes, potentially reducing obesity-related morbidity and healthcare burden (Bailey et al 2024; Bailey et al 2025; Drucker 2025; Kokkorakis et al

2025; Melson et al 2025; Østergaard 2026). High costs, access barriers, long-term safety (e.g., bone, cognition, lean mass), and need for lifelong treatment are major challenges (Bailey et al 2024; Drucker 2025; Melson et al 2025; Thomsen et al 2025; Østergaard 2026).

**Animals.** The available abstracts mainly report animal data for MOTS-c (menopause model) and preclinical anti-obesity food-derived peptides (Lu et al 2019; Aguiar et al 2024; Hajfathalian et al 2025). There is not yet clear societal-level evidence for veterinary “anti-aging” peptide use.

Modern incretin-based peptides (semaglutide, tirzepatide, retatrutide) provide unprecedented, surgery-approaching weight loss with broad metabolic benefits but require chronic use and careful management of GI effects, access, and long-term safety. GHK-Cu and MOTS-c show promising anti-aging and metabolic effects in preclinical and early studies, yet robust human aging data are still limited. Overall, peptide therapeutics are reshaping obesity care and may soon expand into targeted “healthy aging”, pending further long-term and clinical research.

**MOTS-c: discovery and initial functional concept.** MOTS-c was identified around 2015 by an in silico search for short open reading frames (sORFs) in the human 12S rRNA region of mtDNA. A 51-bp sORF with a strong Kozak consensus was found and shown to encode a bioactive 16-amino-acid peptide, termed MOTS-c (Lee et al 2016; Ran et al 2025). This followed the earlier discovery of another mtDNA-encoded peptide, humanin, and suggested that mitochondria encode a broader repertoire of signaling microproteins than the canonical 37 mtDNA genes (Lee et al 2016; Kim et al 2017).

Early work showed that MOTS-c is expressed in multiple tissues (notably skeletal muscle, heart, kidney) and is detectable in plasma, indicating both local (cell-autonomous) and endocrine-like roles (Lee et al 2016; Wan et al 2023; Zheng et al 2023). Initial functional studies established that MOTS-c:

- enhances skeletal muscle glucose uptake and redirects glucose into the pentose phosphate pathway, while suppressing mitochondrial respiration (Lee et al 2016);
- increases lipid utilization by upregulating carnitine shuttles and  $\beta$ -oxidation intermediates, with reduced intracellular fatty acids (Lee et al 2016);
- activates the folate-AICAR-AMPK pathway, leading to AMPK activation and broad metabolic reprogramming (Lee et al 2016; Kamiński et al 2023; Wan et al 2023).

Because of these effects, the initially proposed role of MOTS-c was as a mitochondrial signal that regulates muscle and fat metabolism, insulin sensitivity and energy homeostasis, with implications for obesity, diabetes, exercise capacity and longevity (Lee et al 2016; Kim et al 2017; Mohtashami et al 2022).

**Mechanism of action and signaling of MOTS-c.** MOTS-c is synthesized in the cytoplasm from mtDNA-encoded transcripts. Under metabolic or oxidative stress, it translocates to the nucleus in an AMPK-dependent manner, where it binds nuclear DNA and cooperates with transcription factors (e.g., Nrf2) at antioxidant response elements to regulate stress-response and metabolic genes (Wan et al 2023; Zheng et al 2023; Ran et al 2025). This establishes MOTS-c as a key component of retrograde mitochondrial-nuclear communication.

At the cellular level, major mechanisms include:

- inhibition of folate cycle and de novo purine synthesis, raising AICAR, which activates AMPK (Kamiński et al 2023; Wan et al 2023);
- activation of AMPK in many tissues, leading to improved insulin sensitivity, enhanced fatty-acid oxidation, reduced inflammation and oxidative stress (Lee et al 2016; Yin et al 2020; Zhong et al 2022; Wu et al 2023; Fang et al 2025; Wu et al 2025);
- modulation of additional pathways, including ERK1/2, NF- $\kappa$ B, Nrf2/ARE, TGF- $\beta$ /Smad, PI3K/AKT, mTORC2 and PTEN, which link MOTS-c to inflammation, fibrosis, cell survival and endocrine regulation (Kamiński et al 2023).

Plasma MOTS-c levels are detectable in humans and decline with age, consistent with a role in healthy aging and age-related disease susceptibility (Mohtashami et al 2022; Wan et al 2023; Zheng et al 2023).

**Development as a putative pharmaceutical product.** Given its strong metabolic and cytoprotective actions in preclinical studies, MOTS-c is being explored as a drug candidate rather than a traditional “supplement” (Mohtashami et al 2022; Kamiński et al 2023; Zheng et al 2023; Fang et al 2025; Ran et al 2025). Key envisioned indications include:

- metabolic diseases: obesity, insulin resistance, type 2 diabetes and diabetic complications (especially cardiomyopathy) (Lee et al 2016; Mohtashami et al 2022; Fang et al 2025; Wu et al 2025);
- cardiovascular diseases: heart failure, ischemia–reperfusion injury, atherosclerosis and sepsis-related cardiomyopathy (Zhong et al 2022; Lu et al 2023; Wu et al 2023; Ran et al 2025; Wu et al 2025);
- inflammatory/immune-mediated diseases: inflammatory bowel disease, sepsis-associated organ injury, acute lung injury, colitis, and neuropathic pain (Yin et al 2020; Jiang et al 2023a, b; Lu et al 2023; Wu et al 2025; Bai et al 2026);
- aging and age-related disorders: osteoporosis, postmenopausal obesity, neurodegeneration, age-related macular degeneration (AMD) (Mohtashami et al 2022; Zheng et al 2023; Mohtashami et al 2025);
- cancer: particularly ovarian cancer, where MOTS-c appears to act as a tumor suppressor (Yin et al 2024);
- viral hepatitis: chronic hepatitis B (CHB), where it has both biomarker and antiviral promise (Lin et al 2024).

So far, development focuses on injectable peptides and, in some work, engineered analogues with improved stability and oral bioavailability, such as a MOTS-c–cell-penetrating peptide fusion for oral treatment of colitis (Jiang et al 2023a). MOTS-c is also listed by the World Anti-Doping Agency as a banned substance, reflecting perceived performance-enhancing potential in sports (Bień et al 2025).

**Current stage of testing and clinical translation of MOTS-c.** Despite extensive animal and cellular data, no approved MOTS-c drug exists yet, and large, registered phase II–III clinical trials have not been reported in the literature up to 2025. Reviews consistently note that:

- MOTS-c has shown strong therapeutic effects in multiple rodent disease models (metabolic, cardiovascular, inflammatory, neurologic, infectious) (Mohtashami et al 2022; Kamiński et al 2023; Wan et al 2023; Zheng et al 2023; Fang et al 2025; Ran et al 2025);
- effective clinical application methods have not yet been established, and MOTS-c is still used rarely in human disease treatment, mainly within research contexts (Mohtashami et al 2022; Zheng et al 2023; Ran et al 2025);
- challenges include peptide stability, bioavailability (especially oral), cost of synthesis and the absence of identified cell-surface receptors (Jiang et al 2023a; Kamiński et al 2023; Zheng et al 2023).

Some human data exist as observational or mechanistic studies, not large interventional trials, notably in HBV infection and cardiac surgery-associated lung injury, where circulating MOTS-c was measured and exogenous peptide used in preclinical models (Lu et al 2023; Lin et al 2024). Over-the-counter MOTS-c injections marketed online are not supported by formal clinical trial data, and safety, purity and dosing are not established in peer-reviewed research.

**Effects in animal models: broad spectrum of actions.** The utilization of mammals as model organisms in pharmacology and toxicology is fundamentally important, since their physiological, metabolic, and genetic resemblance to humans enables a more reliable prediction of drug efficacy, safety profiles, and possible adverse effects, thus offering crucial insights prior to clinical application (Petrescu-Mag et al 2020; Proorocu et al 2022; Petrescu-Mag 2023a, b, c; Daescu & Oroian 2024; Petrescu-Mag 2025a).

Preclinical studies in rodents (mice and rats) dominate and show consistent metabolic, anti-inflammatory, antioxidant and anti-apoptotic benefits of MOTS-c.

In metabolic regulation and diabetes, exogenous MOTS-c improves glucose tolerance, insulin sensitivity and body-weight control in diet-induced obesity and models of insulin resistance, largely via AMPK activation and improved lipid and glucose handling (Lee et al 2016; Mohtashami et al 2022; Wan et al 2023; Fang et al 2025). In streptozotocin-induced type 1 diabetic mice, continuous subcutaneous MOTS-c for 12 weeks ameliorated diabetic cardiomyopathy, improved cardiac function and structure, restored AMPK signaling and reduced cardiac inflammation (Wu et al 2025).

In cardiovascular disease, MOTS-c attenuates pressure overload-induced heart failure in mice; subcutaneous administration via osmotic pump slowed development of cardiac dysfunction and dilation, reduced inflammatory cytokines and upregulated antioxidant genes in the heart, with AMPK activation (Zhong et al 2022). MOTS-c also protects against LPS-induced septic cardiomyopathy by decreasing inflammatory cytokine expression, limiting mitochondrial dysfunction and oxidative stress, reducing cardiomyocyte apoptosis, and activating AMPK/AKT/ERK while inhibiting JNK/STAT3 (Wu et al 2023). Mitochondria-derived peptides, including MOTS-c, are therefore considered promising microproteins for cardiovascular therapy, though clinical translation remains early (Ran et al 2025).

In neurologic and pain models, intrathecal MOTS-c in mice with spared nerve injury produced dose-dependent antinociceptive effects, linked to AMPK activation in the spinal cord, decreased microglial activation, reduced proinflammatory cytokines and lower neuronal oxidative damage, with minimal opioid-like side effects (Jiang et al 2023b). Systemic MOTS-c also showed antinociceptive and anti-inflammatory effects in the mouse formalin test, reducing second-phase pain behavior, lowering inflammatory cytokines and modulating spinal MAPK and c-Fos signaling via AMPK (Yin et al 2020). In sepsis-associated encephalopathy induced by LPS, MOTS-c pretreatment improved survival, reduced neuroinflammation, preserved blood–brain barrier (BBB) ultrastructure and permeability, decreased glial activation (GFAP, Iba-1, MMP-9) and enhanced neurotrophic factor expression (Bai et al 2026).

In pulmonary and systemic inflammation, MOTS-c suppressed ferroptosis and alleviated acute lung injury caused by myocardial ischemia–reperfusion in rats. It reduced histological lung damage, modulated ferroptosis-related genes and acted through PPAR $\gamma$  signaling in vivo and in hypoxia–reoxygenation-treated lung epithelial cells (Lu et al 2023). Previous work in sepsis-related ALI similarly supports anti-inflammatory and anti-ferroptotic roles (Lu et al 2023).

In gastrointestinal inflammation, intraperitoneal MOTS-c markedly improved dextran sulfate sodium–induced colitis in mice, reducing weight loss, diarrhea, colon shortening and histologic injury, while suppressing pro-inflammatory cytokines, myeloperoxidase, macrophage activation and neutrophil recruitment and showing anti-apoptotic effects via modulation of AMPK and MAPK pathways. Native MOTS-c was ineffective orally, but an engineered MOTS-c-(PRR)5 fusion (MP) with improved epithelial penetration and longer half-life was effective when given orally, highlighting the potential for orally active MOTS-c analogues (Jiang et al 2023a).

In cancer, serum and tumor MOTS-c levels are reduced in ovarian cancer patients and correlate with poor prognosis. Exogenous MOTS-c inhibits ovarian cancer cell proliferation, migration and invasion, induces cell-cycle arrest and apoptosis, and, mechanistically, binds LARS1 and promotes its ubiquitination and degradation by competing with deubiquitinase USP7, thereby limiting oncogenic LARS1 signaling. In xenograft mouse models, MOTS-c significantly inhibited tumor growth without evident systemic toxicity on heart, liver or kidney histology or standard serum biochemistry (Yin et al 2024).

In viral infection, MOTS-c levels are inversely correlated with HBV DNA load in patients with chronic HBV, and have high diagnostic performance to distinguish chronic hepatitis B from healthy controls and inflammatory versus inactive carrier states. In HBV-infected mouse and cell models, MOTS-c inhibited viral replication by about 50-70%, improved liver function and showed no obvious toxicity. Mechanistically, it promoted

mitochondrial biogenesis, enhanced MAVS-mediated antiviral signaling and regulated MYH9-actin-dependent mitochondrial dynamics and homeostasis (Lin et al 2024).

In eye disease, MOTS-c improved survival and stress responses of retinal pigment epithelial cells (ARPE19) and patient-derived cybrid cell lines relevant to age-related macular degeneration, with dose-dependent effects on apoptosis, mitochondrial biogenesis and AMPK signaling, particularly at lower doses (500 nM). This suggests potential for AMD therapy, though effects were complex and dependent on cell differentiation status and mitochondrial background (Mohtashami et al 2025).

**Specific data in pigs and small rodents.** In a detailed *in vitro* study of pancreatic islets from rats and pigs, MOTS-c significantly modulated endocrine function and cell survival. In isolated islets, MOTS-c reduced insulin and glucagon secretion while enhancing cell viability and reducing cell death. The peptide's secretion patterns and regulatory responses differed between rat and pig islets, likely reflecting species-specific differences in peptide sequence, islet architecture and hormone regulation. Importantly, the study emphasizes that MOTS-c in pigs differs structurally and functionally from that in rats and that pigs may provide a more physiologically relevant large-animal model for human translation. The authors note that these discrepancies in animal data are particularly concerning given the widespread, largely unregulated use of MOTS-c in humans, and highlight that WADA has banned MOTS-c in sport (Bień et al 2025).

**Human data and observed effects in patients.** Human evidence remains limited and is mostly associative or mechanistic, with very early translational steps.

In metabolic and aging contexts, circulating MOTS-c levels are lower in individuals with obesity and in older people, and have been linked to insulin resistance and age-related pathologies such as diabetes, cardiovascular disease, osteoporosis, postmenopausal obesity and Alzheimer's disease (Mohtashami et al 2022; Kamiński et al 2023; Wan et al 2023; Bień et al 2025; Fang et al 2025). These associations support a role for endogenous MOTS-c deficiency in disease risk, but do not yet prove therapeutic benefit of supplementation.

In cardiac surgery and lung injury, patients undergoing off-pump coronary artery bypass grafting who developed postoperative acute lung injury had reduced circulating MOTS-c and increased oxidative stress marker malondialdehyde. Preclinical rat models of myocardial ischemia-reperfusion-induced lung injury show that exogenous MOTS-c can attenuate ferroptosis and lung damage via PPAR $\gamma$  signaling, suggesting a possible future perioperative therapy, although no interventional human trial is reported (Lu et al 2023).

In chronic HBV infection, a large cohort (404 HBV-infected patients and 85 healthy controls) showed strong negative correlations between serum MOTS-c and HBV DNA, and useful diagnostic performance metrics for disease staging. In HBV-infected mice treated with MOTS-c, viral replication fell by 50-70% with improved liver function and no clear toxicity (Lin et al 2024). This points to MOTS-c as both biomarker and potential antiviral therapeutic, but again, formal human treatment trials are not yet described.

In ophthalmology, MOTS-c was tested *in vitro* on human RPE-derived cells and patient-derived cybrids, not yet in patients, but the work suggests possible benefit in AMD through metabolic and gene-expression regulation (Mohtashami et al 2025). More broadly, reviews emphasize MOTS-c's potential to ameliorate age-related loss of muscle homeostasis and physical capacity, with implications for sarcopenia and frailty, though clinical trials are still lacking (Mohtashami et al 2022; Wan et al 2023; Zheng et al 2023).

No paper in this set reports controlled clinical administration of MOTS-c to human patients with outcome data (e.g., randomized trials). Thus, any subjective "effects in patients" outside these mechanistic or biomarker studies would currently be anecdotal and not supported by peer-reviewed data.

**Therapeutic potential and future perspectives.** Across systems, a coherent picture emerges: MOTS-c is a stress-responsive mitochondrial microprotein that activates AMPK, modulates multiple downstream pathways and coordinates metabolic and inflammatory adaptation across tissues (Table 2). Potential advantages as a therapy include:

- multi-organ protection: cardiovascular, endocrine, immune, nervous system, lung, gut and eye (Mohtashami et al 2022; Kamiński et al 2023; Wan et al 2023; Zheng et al 2023; Ran et al 2025);
- broad mechanisms: metabolic reprogramming, anti-inflammatory, antioxidant, anti-ferroptotic and cytoprotective effects (Yin et al 2020; Zhong et al 2022; Jiang et al 2023a, b; Lu et al 2023; Wu et al 2023; Wu et al 2025; Bai et al 2026);
- disease-modifying potential in chronic conditions such as diabetes, heart failure, IBD, chronic viral hepatitis, neurodegeneration and age-related decline (Mohtashami et al 2022; Lin et al 2024; Zheng et al 2023; Fang et al 2025; Ran et al 2025);
- anti-tumor properties at least in certain cancers (e.g., ovarian cancer) (Yin et al 2024).

However, several limitations and open questions slow translation:

- lack of identified receptor and incomplete understanding of tissue-specific signaling (Kamiński et al 2023; Bień et al 2025);
- peptide instability, poor oral bioavailability and manufacturing cost; although analogues like the orally active MP for colitis suggest viable strategies (Jiang et al 2023a);
- species-specific differences (rat vs pig MOTS-c) that complicate extrapolation to humans and may impact efficacy, dosing and safety (Bień et al 2025);
- sparse human interventional data and unknown long-term safety, especially if used chronically or at supra-physiological levels.

Taken together, MOTS-c offers a promising but still experimental therapeutic avenue. The most realistic near-term perspectives include development of:

- injectable MOTS-c or analogues for high-risk indications (e.g., diabetic cardiomyopathy, heart failure, sepsis-related organ injury, HBV-related liver disease, neuropathic pain);
- orally bioavailable analogues for chronic inflammatory and metabolic diseases (e.g., IBD, type 2 diabetes, obesity);
- MOTS-c-based biomarkers for disease staging and prognosis (HBV, cardiovascular and metabolic risk).

Any clinical use outside of trials should be considered unproven and potentially risky, particularly given interspecies differences and the peptide's potent systemic actions.

Table 2

Major preclinical disease models where MOTS-c shows therapeutic promise (summarized by Consensus, 2026)

<i>Disease area/model</i>	<i>Main observed MOTS-c effects</i>	<i>Citations</i>
Obesity, insulin resistance, T2DM, aging	Improves glucose metabolism, insulin sensitivity, lipid utilization; levels fall with age	(Lee et al 2016; Kim et al 2017; Mohtashami et al 2022; Kamiński et al 2023; Wan et al 2023; Zheng et al 2023; Fang et al 2025)
Heart failure, diabetic and septic cardiomyopathy	Improves cardiac function and remodeling; reduces inflammation/oxidative stress via AMPK, AKT, ERK	(Zhong et al 2022; Wu et al 2023; Ran et al 2025)
Neuropathic and inflammatory pain	Antinociceptive, anti-inflammatory; activates AMPK, reduces microglial activation and MAPK-c-Fos	(Yin et al 2020; Jiang et al 2023b)
IBD/colitis	Ameliorates DSS colitis; reduces cytokines, immune cell infiltration; oral analogue effective	(Jiang et al 2023a)
Acute lung injury (MIR, sepsis)	Inhibits ferroptosis, reduces lung damage via PPARγ; protects BBB in SAE	(Lu et al 2023; Bai et al 2026)

Cancer (ovarian)	Decreases proliferation, migration, invasion; LARS1 degradation; in vivo tumor suppression without toxicity	(Yin et al 2024)
Chronic HBV infection	Serum levels inversely correlate with HBV DNA; suppresses HBV replication and improves liver function in models	(Lin et al 2024)
Pancreatic islet function (rat, pig)	Modulates insulin/glucagon secretion, enhances islet cell viability; species-specific differences	(Bień et al 2025)
AMD and retinal degeneration	Modulates apoptosis, mitochondrial biogenesis and AMPK in RPE and cybrids	(Mohtashami et al 2025)

**Conclusions.** MOTS-c has emerged as a critical mitochondrial-derived signaling peptide with wide-ranging effects on metabolism, cellular stress responses, and age-related pathologies. Its ability to activate AMPK and modulate multiple downstream pathways underpins its pleiotropic protective actions observed in numerous preclinical models, including metabolic, cardiovascular, inflammatory, neurological, and infectious diseases.

The available evidence consistently demonstrates that MOTS-c improves metabolic homeostasis, enhances insulin sensitivity, reduces inflammation and oxidative stress, and exerts cytoprotective and anti-apoptotic effects. These findings support its potential as a disease-modifying therapeutic agent across a broad spectrum of chronic conditions. In addition, its role as a circulating biomarker in disorders such as chronic hepatitis B and metabolic diseases further highlights its clinical relevance.

However, translation into clinical practice remains in an early stage. The absence of large-scale randomized controlled trials, uncertainties regarding optimal dosing and delivery, peptide stability, and interspecies variability represent significant limitations. Furthermore, the lack of a clearly identified receptor and incomplete understanding of tissue-specific signaling mechanisms continue to constrain therapeutic development.

In conclusion, while MOTS-c represents a highly promising candidate in the field of peptide therapeutics and mitochondrial biology, its clinical utility remains to be established. Future research should prioritize well-designed human trials, development of stable and bioavailable analogues, and deeper mechanistic insights to fully harness its therapeutic potential.

**Conflict of interest.** The authors declare that there is no conflict of interest.

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