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Review Article

Leveraging mitochondrial stress to improve healthy aging

Abril Gorgori-Gonzalez[a,d], Silvana Soto-Rodriguez[a,d], Eva Tamayo-Torres[a], Esther Garcia-Dominguez[a,b], Vicente Sebastia[c], Juan Gambini[a,b], Gloria Olaso-Gonzalez[a,b], Maria Carmen Gomez-Cabrera[a,b,*]

[a] Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, Fundacion Investigacion Hospital Clinico Universitario/INCLIVA, 46010, Valencia, Spain
[b] CIBER de Fragilidad y Envejecimiento Saludable (CIBERFES) ISCIII, 28029, Madrid, Spain
[c] Clinica Ypsilon de medicina física y rehabilitación, Valencia, Spain

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ABSTRACT

Aging is characterized by a progressive decline in physiological function, driven by intrinsic mechanisms (primary aging) and modifiable factors (secondary aging), ultimately leading to multimorbidity, disability, and mortality. Mitochondrial dysfunction, a major hallmark of aging, plays a central role in the loss of muscle mass and strength observed in frailty and sarcopenia. With age, mitochondrial quality control processes, including biogenesis, mitophagy, and dynamics, become dysregulated, impairing energy metabolism and muscle homeostasis.

Mitochondrial dysfunction correlates with clinical biomarkers of sarcopenia and frailty, such as the decrease in walking speed and muscle strength, making it a therapeutic target for mitohormesis-based strategies aimed at preserving functional capacity. Mitohormetic agents induce reversible mitochondrial stress, triggering adaptive responses that enhance function. Among these interventions, physical exercise, particularly endurance and resistance training (RT), has been reported to be among the most effective, as it may modulate mitochondrial biogenesis, dynamics, and mitophagy through increases in proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) expression, mitochondrial deoxyribonucleic acid (mtDNA) copy number, and mitochondrial content. Chronic RT can also elevate fusion and fission markers, potentially as a compensatory mechanism to mitigate mitochondrial damage.

Apart from exercise, mitohormetic compounds such as harmol and piceid are emerging as promising supplements in the aging field. By modulating mitochondrial bioenergetics and dynamics, they may complement lifestyle-based interventions to improve mitochondrial fitness and extend health span.

1. The concept of healthy aging

Aging is a universal, progressive, intrinsic, and deleterious time-dependent process that leads to a decline in physiological function, accompanied by an increased vulnerability to disease and death.[1,2]

Aging can be viewed as a balance between the ongoing accumulation of physiological damage and the body's compensatory repair mechanisms.[3] Over time, the accumulation of molecular and cellular damage exceeds the capacity for repair, resulting in a gradual decline in physical and cognitive function, increased susceptibility to disease, and ultimately, death.[4]

Current demographic projections suggest that while life expectancy will rise modestly, the burden of disability is expected to increase substantially, placing greater pressure on healthcare systems and sustainability costs. According to the World Health Organization (WHO), by 2030, one in six people worldwide will be aged 60 years or older, and by 2050, this number is expected to double. Furthermore, the number of individuals aged 80 and above is projected to triple between 2020 and 2050.[5]

Two forms of aging have been described. Primary aging is the progressive and inevitable process of bodily deterioration during adulthood. It is an unavoidable decline in cellular integrity and function that occurs regardless of environmental influences, illness, or lifestyle

* Corresponding author. Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, Fundacion Investigacion Hospital Clinico Universitario/INCLIVA, 46010, Valencia, Spain
E-mail address: carmen.gomez@uv.es (M.C. Gomez-Cabrera).
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[d] These two authors contributed equally to this work.

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Abbreviations list

aat-1	amino acid transporter
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
ANT	Adenine nucleotide translocator
Atg	autophagy protein 5
ATP	Adenosine triphosphate
Bcl2 –	B-cell lymphoma 2
BNIP3	Bcl2 and adenovirus E1B 19-kDa-interacting protein 3
C. elegans	*Caenorhabditis elegans*
DAMPs	Damage-associated molecular patterns
Deptor	DEP domain-containing mTOR-interacting protein
DNA	Deoxyribonucleic acid
Drp1	Dynamin-related protein
EGCG	Epigallocatechin-3-gallate
eiF5A	eukaryotic translation initiation factor 5A
ET	Endurance training
ETC	Electron transport chain
FIS1	Fission protein 1
FNDC5	Fibronectin type III domain 5
FOXOS	Forkhead box O proteins
FRTA	Free Radical Theory of Aging
FTO	*Fat Mass and Obesity-Associated*
FUNDC1	FUN14 domain-containing protein 1
GTPases	Guanosine triphosphatases
HO-1	Heme Oxygenase 1
IGF-1	Insulin-like growth factor 1
Il-10	Interleukin 10
IMM	Inner mitochondrial membrane
LAMP2	Lysosome-associated membrane glycoprotein 2
LC3	Microtubule-associated protein 1A/1B-light chain 3
MAP	Mitogen-activated protein
Mfn1	Mitofusin 1
Mfn2	Mitofusin 2
mLST8	Mammalian lethal with SEC13 protein 8
mRNA	Messenger ribonucleic acid
mtDNA	Mitochondrial deoxyribonucleic acid
mTOR	Mammalian target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
NAD^+	nicotinamide adenine dinucleotide
NQO1	Quinone oxidoreductase 1
Nrf2	Nuclear factor erythroid 2–related factor 2
Opa1	Optic atrophy 1
OxPhos	Oxidative phosphorylation
PGAM	Phosphoglycerate mutase
PGAM5	PGAM family member 5
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PGC-1β	Peroxisome proliferator-activated receptor gamma coactivator 1-beta
PINK1	PTEN-induced putative kinase
PRAS40	Proline-rich Akt substrate of 40 kDa
PRDX-2	Peroxiredoxin 2
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
Raptor	regulatory-associated protein of mTOR
ROS	Reactive oxygen species
RT	Resistance training
SA-β-gal	Senescence-associated β-galactosidase
Sirt1	Sirtuin 1
SIRT3	Sirtuin 3
Skn-1	Skinhead-1
TFAM	Mitochondrial transcription factor A
TFEB	Transcription factor EB
Ulk1	Unc-51-like kinase 1
UPRmt	Mitochondrial unfolded protein response
VDAC	Voltage-gated anion channel
WHO	World Health Organization
YY1	Yin–Yang 1
ΔΨm	Mitochondrial membrane potential

factors.[6,7] Efforts to slow primary aging extend the maximum lifespan in various species. However, no current interventions have been proven to reverse this type of aging in humans.[8] It is believed that the genetic makeup of a species determines its maximum potential lifespan.

Secondary aging refers to additional deleterious structural and functional age-related changes caused by diseases and lifestyle factors. It results from external factors and health conditions, including smoking, disease, and sedentariness.[6,7] This form of aging impacts average life expectancy but does not affect the biological ceiling of lifespan. A significant portion of the older adult population lives with multiple chronic conditions, a state known as multimorbidity. These conditions commonly include cancer, diabetes, cardiovascular disease, stroke, and arthritis, all of which can lead to reduced quality of life, increased healthcare utilization, and greater risk of disability or mortality.[9] The high prevalence of these coexisting diseases underscores the need for integrated care approaches and preventive strategies explicitly tailored to the aging population.

The WHO defines healthy aging as "the process of developing and maintaining the functional ability that enables well-being in older age". This definition highlights the idea that healthy aging is not just about preventing illness but about enabling older adults to lead meaningful, active, and engaged lives. A health-oriented approach is crucial for addressing the aging process.[5]

Lifestyle modifications that promote health, well-being, and functional capacity can help minimize disease development and, consequently, slow the progression of secondary aging. While aging is unavoidable, the rate and extent of functional decline associated with it can be significantly modulated by lifestyle factors, particularly exercise. For instance, relative maximal oxygen consumption begins to decline in the third decade of life because of primary aging. However, this decline can be modulated by lifestyle, with regular aerobic activity slowing the process and sedentary behavior accelerating it, reflecting the effects of secondary aging.[8]

A determinant of functional capacity and autonomy is the integrity of the neuromuscular system.[10] With age, various components of this system fail, leading to a loss of muscle mass and function, as well as a decreased ability to remain physically active. The underlying mechanisms involved in the loss of muscle mass and function associated with aging have been the subject of intense investigations.[11,12] We now know that the accumulation of mitochondrial abnormalities are potential causes of aging in the muscle cells. Among these abnormalities, we can highlight: i) impaired mitochondrial dynamics, ii) reduced organelle biogenesis, iii) reduced quality control via mitophagy, iv) accumulation of mitochondrial deoxyribonucleic acid (mtDNA) damage, v) respiratory chain defects, and vi) oxidative stress.[10,13] The Johns Hopkins Americans Center has identified mitochondrial function decline as one of the biological domains where intervention development should move forward due to its potential relevance for the prevention or treatment of frailty (Fig. 1).[14]

The "Hallmarks of Aging", a major reference paper in biogerontology[1] has been revisited in 2023.[15] In this landmark paper, the

authors highlight the role of mitochondrial dysfunction in aging and discuss how lifespan can be improved through a hormetic response ("mitohormesis") compromising mitochondrial function.[15]

The decrease in mitochondrial oxidative capacity is the only biological marker of aging that has consistently and mechanistically been associated with two robust functional biomarkers, i.e. the decrease in walking speed and muscle strength, which convey critical information on the individual's health status and predict the risk of frailty in older adults.[16,17]

2. Mitochondria, aging, and frailty

Frailty is an age-associated biological syndrome characterized by decreased biological reserves, which puts an individual at risk when facing minor stressors and is associated with poor outcomes.[18,19] Frailty further increases the risk of adverse outcomes, such as disability, hospitalization, and mortality in the older adult population.[20,21]

Approximately, one-quarter of people aged 85 and older are estimated to be frail. Frailty often precedes disability and a consequent loss of independence in old individuals.[21] In geriatrics, disability is considered to have a significantly greater impact on a patient's quality of life than the disease itself.[22] Additionally, it is known that most health expenditure is used to address disabilities rather than specific illnesses. Health expenditure is multiplied by five when the level of disability in older adults goes from mild to serious and this expense is maintained until the death of the subject.[11,12]

Interestingly, not all individuals experience the same trajectory of aging. While some older adults maintain high levels of physical function and independence, others exhibit a steady decline in functional capacity despite the absence of clinically diagnosed diseases.[2] Thus, the development of interventions to reduce the severity of this decline will bring significant benefits to both the individual and their family members, as well as to society.[23]

In this context, molecular profiling approaches offer valuable insights into the biological underpinnings of these divergent aging trajectories. Several evidences support the role of mitochondria in age-related muscle deterioration.[24] Mitochondria exhibit cell-type-specific phenotypes, perform multiple interconnected functions, and undergo dynamic, often reversible, physiological recalibrations.[25] Five key levels of analysis have been proposed to characterize mitochondrial biology systematically: 1) Cell-dependent properties, including mitochondrial content, mtDNA copy number, and spatial distribution within the cytoplasm and perinuclear region; 2) Static molecular features, such as protein composition, membrane lipids, mtDNA integrity, cristae density, and quantifiable morphological traits; 3) Single-enzyme activities, including citrate synthase, pyruvate dehydrogenase complex, oxidative phosphorylation (OxPhos) complexes, and individual inner mitochondrial membrane (IMM) transporters; 4) Organelle-level functions, such as calcium homeostasis, lipid synthesis, adenosine triphosphate (ATP) production, and mitochondrial interaction with other organelles (e.g., steroidogenesis, iron/sulfur cluster synthesis); and 5) Mitochondrial dynamics, including motility, fusion-fission dynamics, biogenesis, and mitochondrial-nuclear signaling via metabolites, ions, and proteins.[25]

During aging, many of these mitochondrial behaviors become dysregulated, contributing to impaired skeletal muscle homeostasis.[26]

2.1. Mitochondria energy production in aging

Our mitochondria have an undeniable metabolic role through the generation of most cellular ATP, but they also participate in cell signaling via the production of reactive oxygen species (ROS), contribute to inflammation through the release of damage-associated molecular patterns (DAMPs), regulate cytosolic calcium homeostasis, and support essential biosynthetic processes.[27,28]

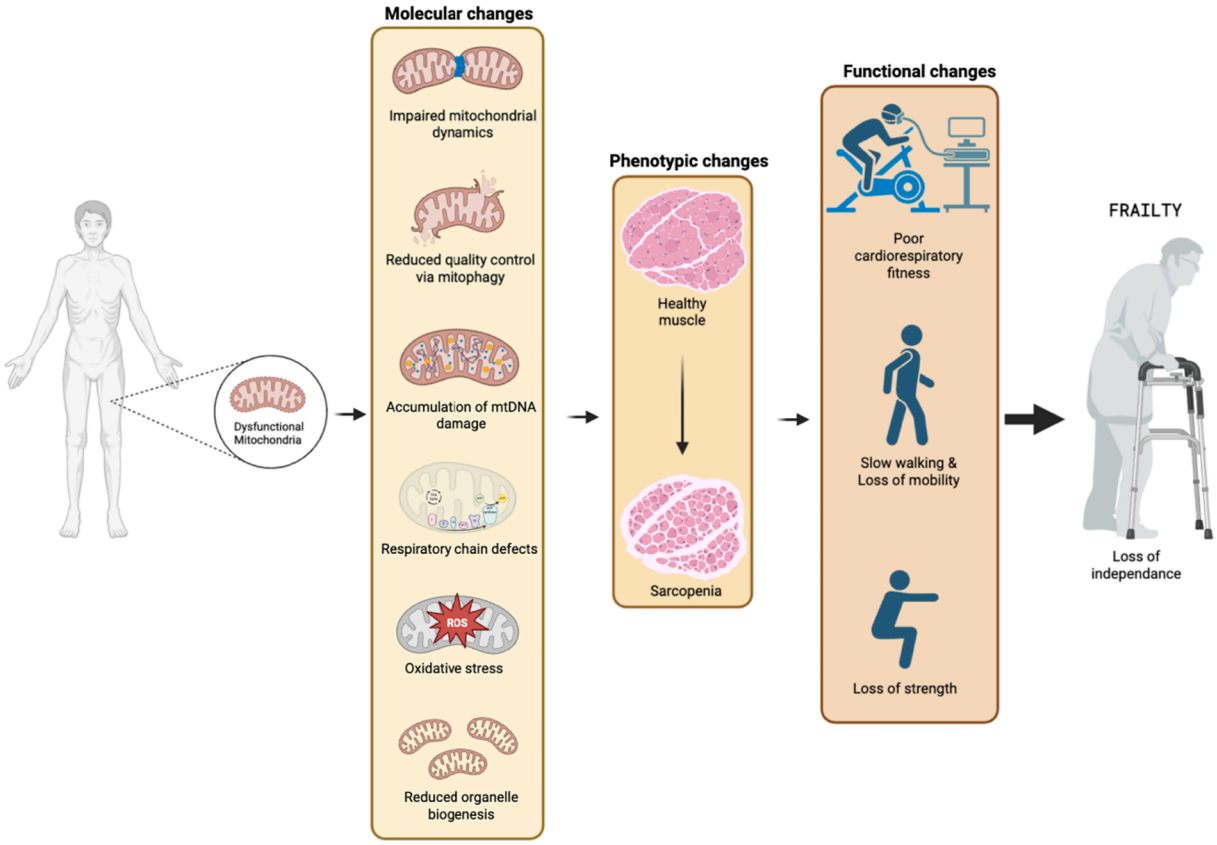

Fig. 1. Mitochondrial dysfunction as a central driver of frailty: from molecular alterations and structural changes to functional decline. Figure created by Biorender.

One of the most accepted physiological frameworks to explain frailty is characterized by mitochondrial dysfunction, oxidative stress, and energy imbalance leading to an energy collapse.[15,18] It has been demonstrated that age-associated downregulation of the electron transport chain (ETC) and oxidative phosphorylation is common among mice, rats, rhesus monkeys, and humans when studied at three stages along their lifespan (young, middle-aged, and old).[29] Numerous studies have described damage to mitochondria in aged cells and organisms, including in human samples.[30] Mitochondrial dysfunction is widely recognized as a major contributor to organismal damage. Cells with high energy demands, such as those in the muscles, are more susceptible to the reduced energy output of defective mitochondria and are consequently more strongly affected by mitochondrial impairment.[31]

As previously mentioned in this review, different research teams have demonstrated that the age-related decline in mitochondrial oxidative capacity is associated to insulin resistance, decreased muscle strength, and reduced walking performance, with some evidence suggesting a causal relationship.[13,32] Moreover, it has been suggested that the age-associated reduction in mitochondrial respiration in human muscle biopsies is related to mobility loss and lower cardiorespiratory fitness.[13,33] Thus, emerging evidence suggests that reduced muscle oxidative capacity and efficiency underlie the etiology of mobility loss in older adults.[13] However, there is little longitudinal data that connects age-related changes in mitochondrial dysfunction with phenotypic and pathological changes in aging (Fig. 1).

Mitochondrial energy production in response to skeletal muscle movement decreases during activity at a faster rate in frail older adults compared to non-frail older adults.[34] This suggests that frailty involves a reduced ability to generate energy when needed because of mitochondrial dysfunction. Work on an interleukin 10 (Il-10) knockout mouse model of frailty also suggested a mitochondrial link to frailty. This mouse develops accelerated chronic inflammation, exhibits lower ATP production at older ages compared to age-matched controls, and has a decreased ability to clear damaged mitochondria, suggesting abnormally slow mitophagy.[35] The fact that insulin resistance and mitochondrial dysfunction appear in both men and women from the third to the fourth decade of life suggests that before the onset of skeletal muscle loss, cellular and metabolic biomarkers must first appear.[36] Thus, mitochondrial dysfunction has been proposed as the driving force underlying both musculoskeletal aging and sarcopenia, as well as other age-related diseases. The Baltimore Longitudinal Study of Aging assessed the relationship between the decline in mitochondrial oxidative capacity and impaired walking performance in men aged 24–97 years. Mitochondrial oxidative capacity was evaluated noninvasively using *in vivo* phosphorus magnetic resonance spectroscopy of skeletal muscle, which measures post-exercise phosphocreatine recovery kinetics as a marker of mitochondrial ATP production. The findings demonstrated that the reduction in mitochondrial capacity directly impacted both muscle strength and mobility (Fig. 1).[37]

2.2. Mitochondrial biogenesis and mitophagy in aging

Mitochondrial biogenesis is significantly affected by aging because the signaling pathways involving key transcription factors and transcriptional coactivators are downregulated in the skeletal muscle of older individuals.[38] Specifically, the activities of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and sirtuin 3 (SIRT3) are reduced, accompanied by a decrease in the protein levels of mitochondrial transcription factor A (TFAM), an important regulator of mtDNA replication and transcription.[39]

Mitophagy is a specialized form of autophagy that targets, removes, and recycles damaged or depolarized mitochondria.[40] Mitophagy efficiency declines with aging leading to the accumulation of dysfunctional mitochondria, increased oxidative stress, and impaired cellular energy metabolism. Mitophagy occurs through ubiquitin-mediated and receptor-mediated pathways.[41] In the ubiquitin-mediated pathway, phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-induced putative kinase (PINK1) and Parkin play central roles. Under normal conditions, PINK1 is rapidly degraded at the inner mitochondrial membrane. When mitochondrial membrane potential ($\Delta\Psi m$) decreases, PINK1 accumulates on the outer membrane, recruiting cytosolic Parkin, which ubiquitinates outer membrane proteins, marking them for degradation or recognition by autophagy adaptors.[42,43] This pathway also promotes mitochondrial fission and prevents fusion, isolating damaged mitochondria from the healthy network.

Receptor-mediated mitophagy involves proteins like Bcl2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) and NIX, especially under hypoxic conditions.[41,44] FUN14 domain-containing protein 1 (FUNDC1), an outer membrane protein, acts as a receptor during hypoxia or mitochondrial uncoupling. Its interaction with microtubule-associated protein 1A/1B-light chain 3 (LC3), involved in autophagosome formation and maturation, is regulated by phosphorylation; PGAM5 dephosphorylates FUNDC1, enhancing its binding to LC3 and promoting mitophagy. Under oxidative stress conditions, phosphoglycerate mutase (PGAM) family member 5 (PGAM5) activity increases, also contributing to mitochondrial fission and mitophagy.[41,44,45] Additionally, lipid-mediated and other ubiquitin ligase-dependent mitophagy pathways exist.[41]

Aging is associated with decreased transcription of lysosome-associated membrane glycoprotein 2 (LAMP2), an essential component of autophagic machinery. Furthermore, there is an accumulation of lipofuscins, non-degradable aggregates of oxidized proteins and lipids that disrupt autophagic flux and impair the clearance of dysfunctional mitochondria. These changes collectively contribute to the progressive decline in mitochondrial quality control observed during aging.[46,47]

2.3. Mitochondrial dynamics in aging

Mitochondrial dynamics, a process that occurs in equilibrium in healthy mitochondria, refers to their ability to exist in various dynamic morphological states depending on environmental and cellular physiology. This process allows mitochondria to transition between large, elongated networks and small, individual spheroid organelles and vice versa.[48] It involves the continuous fusion and division of organelles, which both maximize the adaptability and efficiency of OxPhos and eliminate damaged mitochondrial components.[40]

Mitochondrial fusion is mediated by three key guanosine triphosphatases (GTPases): mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2), which regulate outer mitochondrial membrane fusion, and optic atrophy protein 1 (Opa1), which facilitates fusion of the inner mitochondrial membrane. Mitochondrial fission is primarily orchestrated by the cytosolic GTPase dynamin-related protein 1 (Drp1), which is recruited to the mitochondrial surface by adaptor proteins such as fission protein 1 (Fis1).[49]

Aging is associated with impaired mitochondrial dynamics, marked by an imbalance between fusion and fission.[48] In skeletal muscle, fission allows the segregation of dysfunctional mitochondria for removal via mitophagy and supports their replacement through biogenesis.[50] Age-related declines in key fusion proteins, such as OPA1, disrupt this balance and have been associated with reductions in skeletal muscle mass.[51] Age-related loss of Mfn2 contributes to metabolic alterations and sarcopenia.[52] Furthermore, overexpression of Mfn2 in skeletal muscle from young and old mice has been shown to induce mild, non-pathological hypertrophy, which could mitigate age-associated muscle atrophy.[53] Old mice also exhibit reduced Drp1 activity and altered mitochondrial morphology in neurons, skeletal muscle, and oocytes.[54]

3. From hormetic stress to healthy aging: the role of mitochondria

3.1. Hormesis

Paracelsus is quoted as saying, "all things are poison, and nothing is without poison; only the dose makes a thing, not a poison".[55] Paracelsus paved the way for the modern threshold concept and the definition of hormesis. Hormesis is a process whereby exposure to a low dose of a potentially harmful stressor promotes adaptive changes to the cell that enable it to better tolerate subsequent stress.[56] These harmful conditions encompass not only toxic substances but also any environmental stimulus (mild stress) with potentially deleterious consequences for the organism, such as temperature fluctuations, fasting, hyperoxia, etc.

Hormesis represents an evolutionarily conserved mechanism of biological adaptability that enables organisms to survive and even benefit from moderate adversity. The term "hormesis" was introduced in the 19th century following observations that low concentrations of toxic agents could stimulate growth in organisms such as yeast and plants.[57] A well-known example of the principle of hormesis is vaccination, where controlled exposure to a pathogen elicits an immune response that strengthens the body's defenses.[58]

When evaluating the impact of hormetic agents, the resulting response typically follows a biphasic curve. This can be visualized on a graph that plots the biological effect against the dose, producing a characteristic U-shaped curve (Fig. 2A). Initially, as the dose increases from very low to moderate levels, the curve dips downward (blue line), representing a beneficial adaptive response to mild stress. However, as the dose continues to rise, the curve ascends, reflecting the onset of harmful effects associated with excessive exposure.[59] This biphasic pattern contrasts with the conventional linear dose-response model (Fig. 2B), where greater exposure to a stressor leads directly to proportionally increased harm.[60]

Toxicology studies have shown that low doses of toxic substances can have stimulatory effects on our cells.[61] Mildly stressing our cells does not cause them to die. They become stronger because their stress response reinforces their ability to adapt to even more stress.[59] The process of enhancing cellular resilience through hormesis yields several health benefits. In this paradigm, prior stressor exposures lead to enhanced protective responses, compared to naïve unexposed controls who are exposed for the first time.[62]

Hormesis studies were initially mainly developed in invertebrates and have been considered of potential interest in aging research very recently, with the development of studies in rodents and humans.[63,64]

3.2. Hormesis and aging

The dose and intensity of the stressor determine in part whether the organism responds with positive physiological changes or impairments. This is a relatively novel concept in the aging field, which has led to questioning certain dogmas, such as the one established by the Free Radical Theory of Aging (FRTA).[65,66] This theory postulated that the endogenous production of ROS represents a key damaging factor in cell aging.[67] *In vitro* approaches showed that disproportionate and supra-physiological ROS levels exert harmful effects on various types of cultured cells. Antioxidants, which counteract the actions of the excess of ROS, prevented these effects in cultured cells. Oxidative stress was then linked to disease development and accelerated aging, prompting professionals in the biomedical field to suggest the use of antioxidants to prevent or even reverse age-associated conditions.[68–70] However, these approaches were not successful in animal and human studies, where physiological ROS levels do not necessarily promote chronic diseases.[58] The FRTA, although initially widely accepted by the scientific community, has been questioned by multiple observations,[65] because we now know that ROS are signaling molecules that, instead of being detrimental, mediate essential cell processes and adaptations promoting protective mechanisms within the cell that prevent cellular damage.[71,72] Experimental and clinical evidence has shown that high doses of antioxidants do not have a favorable effect on aging or age-associated diseases, casting doubts on the validity of this theory.[68,73,74] Moreover, relevant evidence has suggested a beneficial role for ROS in extending lifespan under stress conditions. However, the mechanism by which this is mediated and regulated within the cell is not fully understood. This implies that different concentrations of the same agent, in this case ROS, may exert a nonlinear U-shape hormetic response.[73]

3.3. Mitohormesis

In recent years, the concept of hormesis has been explicitly applied to mitochondria (mitohormesis), suggesting that in response to a perturbation, mitochondria can initiate and transduce signals to the nucleus (including ROS) that coordinate a transcriptional response. This results in mitochondrial and non-mitochondrial adaptations that return and maintain cellular homeostasis, increase fitness, and confer resistance to subsequent stresses.[74] There is compelling *in vitro* support showing that mild mitochondrial stress can enhance cellular resistance to oxidative damage. For instance, low-dose hydrogen peroxide preconditioning in neuronal PC12 cells preserves mitochondrial membrane potential and protects against subsequent lethal oxidative insults.[75] Similarly,

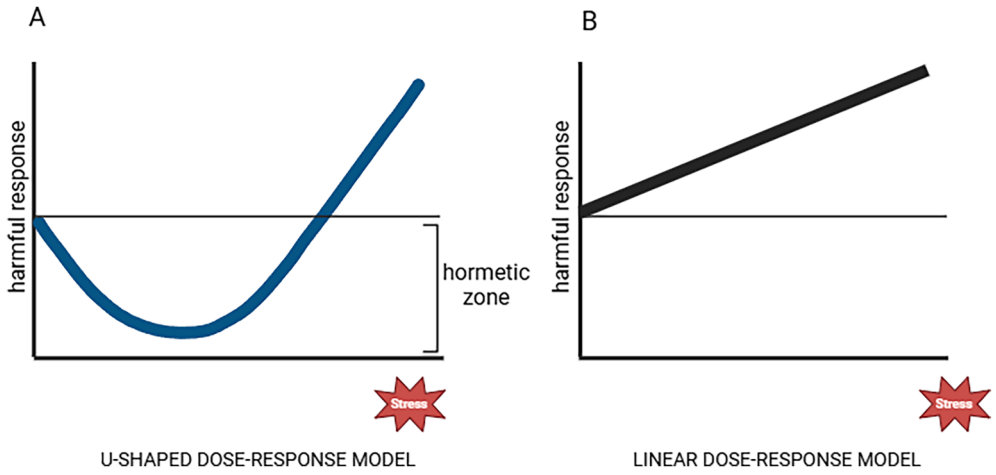

Fig. 2. Characteristic U-shaped curve proposed for the hormetic effect (A) and dose-response curve (B). Figure created by Biorender.

mitochondrial translation stressors such as doxycycline activate the mitochondrial unfolded protein response (UPRmt), which enhances mitochondrial proteostasis and improves cell survival after oxidative challenge.[76] Moreover, mild increases in mitochondrial ROS activate nuclear factor erythroid 2–related factor 2 (Nrf2) signaling in fibroblasts, upregulating antioxidant defenses and conferring resistance to further oxidative injury.[77] These findings have also been confirmed in invertebrate models. Pioneering studies in *Caenorhabditis elegans* and *Drosophila melanogaster* first demonstrated that mild mitochondrial perturbation can extend lifespan in both organisms.[78]

The concept of mitohormesis provides a mechanistic approach to better delineate the potential benefits of activating cellular stress response pathways in aging. It suggests a common feature likely shared by diverse health-promoting interventions.[79] ROS act on redox-sensitive transcription factors, which in turn can transcriptionally upregulate genes involved in cellular stress response (chaperone proteins, endogenous antioxidants, growth factors and mitochondrial proteins), resulting in a net positive outcome for the organism despite the initial mitochondrial perturbation.

Mitohormesis and, in particular, the general importance of ROS as mediators of intracellular stress response signaling are well supported by experimental evidence and might explain why physiologically prompting an endogenous ROS defense effectively contributes to the extension of health span, whereas doing so exogenously using antioxidant supplements may not have the same beneficial effect.[80]

Mitohormesis is also a central concept explaining how physical activity and/or some nutritional interventions counteract age-related decline.[81] These strategies will be discussed in more detail in the following paragraphs.

3.4. Exercise as a mitohormetic intervention

Physical activity is itself a form of stress that, when performed consistently, triggers hormetic responses, such as improved mitochondrial function, increased antioxidant capacity, and enhanced cellular repair mechanisms. Over time, these adaptations contribute to improved physical performance and greater resistance to injury or fatigue. While hormesis was first described *in vitro* and in invertebrate models,[63] it has since gained attention in aging and exercise research, with increasing evidence from rodent and human studies highlighting its role in promoting health span and functional resilience.[64]

Early investigations by Dr. Chepinoga documented an increase in oxygen consumption and succinate dehydrogenase activity in trained rabbit muscles.[82] Hearn and Wainio later found that moderate training did not improve mitochondrial function.[83] Dr. Holloszy, in 1967, showed that high-intensity exercise training could more than double oxygen consumption and trigger major enzymatic and protein mitochondrial adaptations in the skeletal muscle,[84] laying the foundation for modern exercise physiology.

Today, we know that the ability of mitochondria to adapt to muscle contraction is essential not only for performance but also for healthy aging, and that understanding how exercise enhances mitochondrial function offers valuable insights into strategies for preserving muscle health over time.[85]

While endurance training (ET) is traditionally considered more effective for mitochondrial adaptations, recent research indicates that resistance training (RT) can also induce positive effects on mitochondrial function and is a key intervention against sarcopenia.[86] Interestingly, RT has also been associated with a phenomenon termed "mitochondrial volume dilution," which occurs when muscle hypertrophy outpaces mitochondrial biogenesis, so new muscle proteins are synthesized faster than new mitochondria are produced.[87] Importantly, this does not imply a loss of mitochondria or impaired function, as overall oxidative capacity and specific mitochondrial functions may be maintained or even enhanced through functional adaptations induced by hormetic signaling. Although "mitochondrial volume dilution" itself is not a hallmark of aging, in older adults, it may become more pronounced because age-related impairments in mitochondrial biogenesis can limit the compensatory response to muscle hypertrophy.

Long-term RT in younger adults increases mtDNA copy number, mitochondrial content, and both messenger ribonucleic acid (mRNA) and protein levels of PGC-1α. However, findings in older adults remain inconsistent.[88,89] Parise and colleagues reported that 12 weeks of unilateral RT in older adults produced no difference in citrate synthase activity between trained and untrained legs, consistent with another study showing no change after training.[90,91] Likewise, no changes in mitochondrial biogenesis markers (PGC-1α, TFAM, total OxPhos) or mRNA expression have been observed after 8–12 weeks of RT in the vastus lateralis in older adults.[91,92] Together, these findings suggest a potential age-related attenuation in the capacity of skeletal muscle to stimulate mitochondrial biogenesis in response to RT despite the known benefits of such training on muscle mass and strength.

Resistance training in older adults has been shown to increase ADP sensitivity along with maximal respiration (state 3) and complex I adaptations.[93,94] With aging, an "adenosine diphosphate (ADP) insensitivity" develops, limiting maximal coupled respiration, partly due to S-glutathionylation of cysteine residues in key proteins for ADP/ATP transport and synthesis, including adenine nucleotide translocator (ANT), the voltage-gated anion channel (VDAC), creatine kinase, and ATP synthase.[95] Because ADP sensitivity improves rapidly after acute exercise, regulation is likely post-translational rather than transcriptional. Notably, RT enhances ADP sensitivity and state 3 respiration without altering ANT or VDAC content,[93] suggesting that the mechanism involves functional modifications rather than increased protein abundance, though the precise process remains unclear.

Resistance training also increases complex IV activity[96] , which may indirectly reduce oxidative stress by enhancing electron transfer efficiency, minimizing electron leakage, and thereby lowering ROS production.[97,98] Electron leakage from the ETC can directly interact with oxygen, resulting in increased ROS. However, when complex IV transfers electrons efficiently, it ensures that oxygen is completely reduced, preventing electron leakage and decreasing ROS generation.

The role of RT in mitochondrial dynamics has also been studied. RT increases fibronectin type III domain 5 (FNDC5)/irisin via PGC-1α, promoting mitochondrial fission and mitophagy, which attenuates myopathy in models of critical limb ischemia in aged muscles.[99] Chronic resistance training (> 10 weeks) upregulates both mitochondrial fusion proteins (MFN1, MFN2, OPA1) and the fission protein DRP1, suggesting a compensatory remodeling response. In this context, fusion may serve to dilute damaged mitochondrial components by merging them with intact organelles, while fission enables quality control through segregation of dysfunctional mitochondria.[92]

3.5. The mammalian target of rapamycin (mTOR) and its role in mitochondrial adaptations

mTOR is a central nutrient and energy sensor that regulates cell growth, protein synthesis, and metabolism. Beyond its role in muscle hypertrophy, it may play a role in exercise-induced mitochondrial remodeling in skeletal muscle.[100] However, the precise contribution of mTOR remains controversial, as both stimulatory and inhibitory effects on mitochondrial biogenesis have been reported depending on the context.

Recent studies have shown that an RT-driven mTOR complex 1 (mTORC1) activation may enhance mitochondrial biogenesis via PGC-1α, possibly through the Yin–Yang 1 (YY1) transcription factor, which stimulates genes involved in mitochondrial oxidative metabolism.[101,102] Inhibition of mTORC1 blocks these adaptations, whereas its activation upregulates peroxisome proliferator-activated receptor gamma coactivator 1-beta (PGC-1β) and oxidative enzymes such as succinate dehydrogenase. Beyond biogenesis, mTOR also influences mitochondrial dynamics by promoting fusion, an effect lost when mTORC1 is inhibited.

Moreover, mTOR regulates genes such as Fat Mass and Obesity-Associated (FTO), which contribute to the maintenance of mitochondrial content and overall organelle health (Fig. 3).[103] Together, these hypothetical mechanisms highlight the central role of mTOR not only in muscle growth but also in coordinating metabolic adaptation, mitochondrial quality control, and skeletal muscle health. As previously mentioned, the role of mTOR in mitochondrial biogenesis remains controversial: while acute activation appears to support oxidative adaptations, chronic or excessive activation may interfere with adenosine monophosphate (AMP)-activated protein kinase (AMPK)-PGC-1α signaling and impair mitochondrial remodeling, suggesting that mTOR acts as a context-dependent regulator rather than as a simple binary switch. Although current findings provide initial clues about the role of mTOR in mitochondrial function induced by RT, the evidence remains limited and warrants further investigation.

3.6. *Mitochondrial stressors, role of diet and dietary compounds*

Dietary restriction and phytochemicals have been explored as mitohormetic strategies to promote health span and lifespan.[104,105] The low energy status, reflected by elevated AMP levels, activates AMPK, which phosphorylates mitochondrial fission factor to regulate fission and Unc-51-like kinase 1 (Ulk1) to initiate mitophagy.[106,107] AMPK also enhances nicotinamide adenine dinucleotide (NAD^+) levels, thereby stimulating sirtuin 1 (SIRT1), which deacetylates and activates PGC-1α; in addition, AMPK directly phosphorylates PGC-1α, leading to the induction of nuclear respiratory factors that drive mitochondrial biogenesis.[108]

Additional hormetic mechanisms involve transient metabolic impairments and redox signaling. For example, chemical inhibition of glycolysis transiently increases ROS production, which activates AMPK and induces catalase expression, enhancing stress resistance.[109] Similarly, reduced insulin/insulin-like growth factor 1 (IGF-1) signaling can elevate ROS, which are sensed by p38 mitogen-activated protein (MAP) kinase and Nrf2, triggering endogenous antioxidant defenses that improve stress resistance and extend lifespan.[110] Together, these pathways illustrate how dietary and metabolic stressors engage AMPK, mTOR, and ROS-dependent signaling to drive adaptive mitochondrial remodeling and promote longevity.

A diet rich in fruits and vegetables has been associated with improvements in life expectancy.[111] These benefits were once attributed to their antioxidant properties. However, many studies have failed to confirm this, and some suggest the opposite. In the context of hormesis, antioxidants may blunt beneficial responses, particularly ROS signaling. The current focus has shifted toward promoting acute ROS production and other hormetic responses through phytochemicals.[105,112]

Phytochemicals contribute to plant growth and development and serve defensive roles, protecting plants from predators.[113] Based on their chemical structure, phytochemicals can be classified into nitrogen compounds, terpenoids, phenolic cpounds, alkaloids, and sulfur compounds. Among these, polyphenols are the most extensively studied.[114]

Among the compounds that induce reversible mitochondrial stress and thereby enhance mitochondrial function are metformin, epigallocatechin-3-gallate (EGCG), glucosamine, spermidine, and urolithin A.[115]

Metformin, a widely used antidiabetic drug, exerts beneficial effects on health span and lifespan partly through mitohormesis. By mildly inhibiting mitochondrial complex I, metformin increases the AMP/ATP ratio and activates AMPK, leading to enhanced respiration and a controlled rise in mitochondrial ROS. Rather than causing damage, these ROS function as signaling molecules that induce adaptive stress responses. A central mediator in this process is the peroxiredoxin 2 (PRDX-2), which translates ROS signals into downstream pathways. Oxidized PRDX-2 dimers activate MAP kinase cascades, culminating in skinhead-

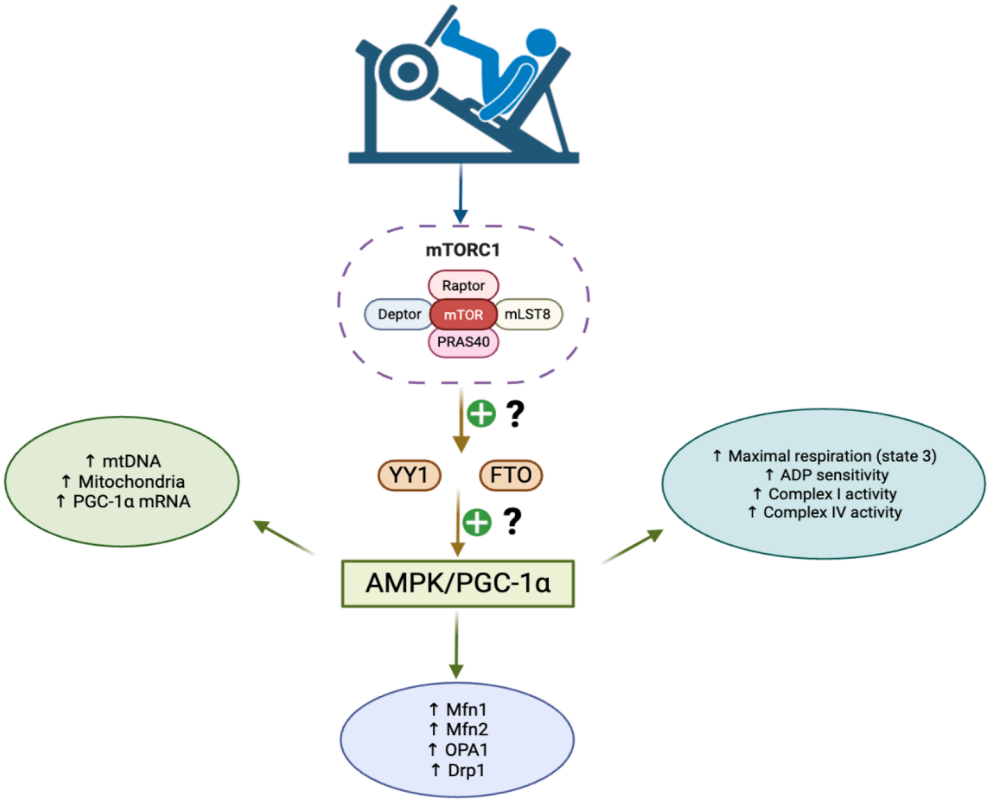

Fig. 3. Resistance training enhances mitochondrial health in adult skeletal muscle, potentially via mTOR complex 1 (mTORC1) activation, which may promote biogenesis, dynamics, and respiratory function. mTOR: mammalian target of rapamycin; mLST8: mammalian lethal with SEC13 protein 8; PRAS40: proline-rich Akt substrate of 40 kDa; Deptor: DEP domain-containing mTOR-interacting protein; Raptor: regulatory-associated protein of mTOR; YY1: Yin–Yang 1; FTO: Fat Mass and Obesity-Associated; ADP: adenosine diphosphate; AMPK: AMP-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Mfn1: mitofusin 1; Mfn2: mitofusin 2; OPA1: Optic atrophy 1; Drp1: Dynamin-related protein; mtDNA: mitochondrial deoxyribonucleic acid; mRNA: Messenger ribonucleic acid. Figure created by Biorender.

1 (Skn-1), the *Caenorhabditis elegans* (*C. elegans*) ortholog of mammalian NRF2, that improves stress resistance. Thus, metformin promotes longevity by coupling mitochondrial stress to pro-survival signaling, a mechanism that appears evolutionarily conserved and may underlie some of its health benefits in mammals.[116] EGCG, a polyphenol found mainly in green tea, also has mitohormetic properties extending the lifespan of *C. elegans* by inhibiting complex I. EGCG induces a transient increase in ROS generation, activating the AMPK and Sirt1 axis, and a posterior activation of forkhead box O proteins (FOXOs), a family of transcription factors for antioxidant genes.[117,118]

Glucosamine is involved in cartilage and connective tissue structure and is commonly used as a supplement for joint health. Glucosamine is another mitohormetic compound shown to extend lifespan in *C. elegans* and aged mice by inhibiting glycolysis and enhancing amino acid turnover. Its effects depend on SKN-1 mediated transcriptional activation, and it specifically induces expression of the amino acid transporter gene (*aat-1*). This dual action highlights glucosamine's capacity to couple metabolic stress with adaptive transcriptional programs that promote longevity.[119]

Spermidine is a ubiquitous polyamine derived from ornithine via the polyamine biosynthetic pathway. Present in all living cells, it supports growth, gene regulation, and stress responses, and is particularly abundant in rapidly dividing tissues as well as dietary sources such as cheese. Spermidine is necessary to obtain a modification and posterior activation of the eukaryotic translation initiation factor 5A (eIF5A), essential to stimulate autophagy.[120]

Urolithin A is a gut microbiota-derived metabolite formed from the conversion of ellagitannins present in pomegranate and certain berries. It exerts its pro-longevity effects primarily by activating mitophagy. Preclinical studies in *C. elegans*, rodents, and humans have shown that urolithin A supplementation can improve muscle function, extend lifespan, and support healthy aging.[121]

In the following sections, we will discuss two phytochemicals in more detail: piceid (also known as polydatin) and harmol (a plant-derived alkaloid). These compounds are found in fruits and vegetables and can also be administered as nutritional supplements.

3.6.1. Piceid

Among the most studied polyphenols in the field of aging and mitochondrial biology, resveratrol stands out. Its action is primarily exerted through the activation of the SIRT1/AMPK pathways, leading to the induction of PGC-1α and, consequently, an increase in mitochondrial biogenesis and OxPhos capacity. It also attenuates ROS accumulation, regulates mitochondrial dynamics, and preserves the integrity of mitochondrial respiration in aging.[122] Its derivative, piceid, a natural resveratrol glycoside with greater metabolic stability and bioavailability, is being modeled as an agent with the ability to reproduce and enhance the effects of resveratrol in preserving mitochondrial function.[123,124]

Piceid is a potent single-crystalline natural stilbenoid polyphenol.[123,124] It is mainly isolated from the rhizome and root of *Polygonum cuspidatum*.[125]

Recent studies have described the protective effects of piceid at a mitochondrial level and against cellular aging, mainly through the restoration of $\Delta\Psi m$, the reduction of mitochondrial ROS production, and the activation of the antioxidant pathway NRF2/Heme Oxygenase 1 (HO-1), which increases the expression of enzymes such as HO-1 and quinone oxidoreductase 1 (NQO1), mitigating DNA damage.[126] Likewise, its impact on the decrease in the activity of senescence markers such as senescence-associated β-galactosidase (SA-β-gal), p16 and p21 has also been reported, slowing the progression of cellular aging.[126]

At the skeletal muscle level, a study examined polydatin in human myoblasts under differentiation conditions, finding it non-toxic and without effects on viability or cell cycle. It increased myogenic regulatory factors, elevating myogenin and creatine kinase mRNA, markers of muscle differentiation. These findings suggest polydatin may promote skeletal muscle maturation and potentially protect against muscle aging, though further research is needed to confirm its hormetic role and efficacy.[127] Furthermore, it would be of particular interest to explore its use as a complement or adjuvant to RT, evaluating possible synergistic effects on muscle health and mitochondrial function.

3.6.2. Harmol

Based on its chemical structure, harmol is classified as an alkaloid due to its heterocyclic nitrogen ring. Together with harmine, harmaline, harmalol, and harmane, it belongs to the β-carboline family.[128] The main dietary source of harmol in the human diet is coffee. Harmol mitohormetic action is linked to mitophagy. In C2C12 myotubes and mouse liver, it induces transient mitochondrial membrane depolarization via monoamine oxidase B and gamma-aminobutyric acid receptors, activating the compensatory AMPK pathway.[115]

Harmol is an autophagy inducer in cancer cell lines and,[129,130] in both *in vitro* and *in vivo* Parkinson's disease models.[131] It has been shown to promote α-synuclein clearance by activating the autophagy-lysosome pathway through the AMPK-mTOR-transcription factor EB (TFEB) axis.[131] In another study, treatment of α-synuclein–overexpressing neuronal cells with harmol led to protein degradation and autophagy via the autophagy protein (Atg)5/Atg12-dependent pathway.[132] Given its ability to modulate mitophagy and autophagy-related pathways, harmol may hold potential as a therapeutic agent to preserve skeletal muscle quality and function during aging.

CRediT authorship contribution statement

Abril Gorgori-Gonzalez: Writing – original draft. **Silvana Soto-Rodriguez:** Writing – original draft. **Eva Tamayo-Torres:** Writing – review & editing. **Esther Garcia-Dominguez:** Writing – review & editing. **Vicente Sebastia:** Conceptualization. **Juan Gambini:** Writing – review & editing, Conceptualization. **Gloria Olaso-Gonzalez:** Writing – review & editing. **Maria Carmen Gomez-Cabrera:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

Maria Carmen Gomez-Cabrera is an editorial member for *Sports Medicine and Health Science* and was not in the editorial review or the decision to publish this article. Otherwise the authors declare no competing interests. The authors confirm that AI-assisted technology, based on OpenAI's GPT-4 architecture, was used solely to enhance the readability and language of the work in specific paragraphs in the manuscript. This technology was not employed to replace tasks such as generating scientific insights, analyzing and interpreting data, or drawing scientific conclusions. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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